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# EMERGING ISSUES IN THE MANAGEMENT OF STI: TRENDS IN ANTIBIOTIC RESISTANT GONORRHEA

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**Emerging Issues in the Management of STI: Trends in Antibiotic Resistant Gonorrhea [video transcript]**

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And for this session, we're going to be focusing on trends and antibiotic resistant gonorrhea or gonococcal infections. My name is Daniela Margaux. I'm an assistant professor of medicine in the infectious diseases Division at the University of Rochester. And I also participate in care at the Monroe County sexual health clinic. I have no financial relationships, as I mentioned, and we have two specific learning objectives for today's session versus to describe recent trends in antibiotic resistant gonorrhea records. And then to identify management strategies when antimicrobial resistance on a cockle infection is suspected. So here's why we're here today, the purpose of the talk these news lines and web images that you might have seen about drug resistant gonorrhea as being an urgent public health issue. And some of you may have just heard about this now in relation to the Massachusetts Department of Health, Health Alert. However, this topic has really been of importance for several years. And these images themselves were actually from several years ago. And still we have this ongoing public health issue related to this. So what do we know so far about antibiotic resistance, this is just kind of a bird's eye view. And we're gonna delve into some of the history and the specifics surrounding this issue. And what you can do it in your clinical work, and in your public health work to address this. So antibiotic resistance, again, is not new for gonorrhea, about 25 to 35% of isolates are resistant to penicillin, doxycycline and quinolones. That is pretty much across the US, though there is some geographic variability. Resistance to as a through Meissen is lower than that, but certainly rising, and probably faster than some of these other antibiotics. We'll talk about azithromycin has a low threshold for development of resistance, which is part of the issue. And then, again, similar to these other antibiotics, there's geographic variability. When we're looking at cephalosporins, which are really the mainstay of treatment of this point, we see resistance or what we technically referred to as an elevated NIC. I'll talk more about what that means later. But we're seeing that for many years in several countries, in particularly Southeast Asia and the Asia Pacific region, but also in emerging in the UK, in Europe as a whole. And there have been sporadic reports in Canada, Australia, less than five cases have reported in the US for elevated Mi c. There have been no case reports. In New York State. When we think about suffixing, specifically, which is our oral cephalosporin. We have been seeing reports of treatment failures in several countries as well, some of the same areas I mentioned. But something to also keep in mind. There is a program run by CDC called the just for the gonorrhea Iseult surveillance project that collects a bout I believe, 25 of the first urethral gonococcal specimens per month from various central health clinics that participate across the country. And I'll show you where they are. And they obtained culture and susceptibility testing on these to identify patterns of resistance. And in 2021, they actually started doing molecular testing on these as well, which becomes important when detecting resistance mutations or mutations

associated with resistance or treatment failures. And there's also an expansion of the program called the Aegis, where they started collecting cervical specimens and extra genital specimens as well. These are the health department jurisdictions across the US that participate in this program. So there's a pretty widespread, but there is a gap, as you see in Montana and some of the surrounding states. I referred earlier to something called the Mi see this is the minimum inhibitory concentration of antibiotic needed to inhibit growth, if you will. This in sort of plain terms is the amount of antibiotic need to really kill the bacteria and eliminate infection. This is determined by different different methods of lab testing. And in the US, there's a standardized organization called clinical and laboratory Standards Institute or CLSI. That provides us with what we describe as breakpoints when something is susceptible to any antibiotic, the concentration at which it might be intermediate susceptibility and the concentration at which it may be resistant. For certain antibiotics, we don't have These breakpoints for resistance. And so you'll see that referred to as elevated MICC, which you can see for the first three antibiotics here. But for some we have breakpoints for resistance, Ciprofloxacin as an example. And you see that listed here on the right hand side. The European version of CLSI eucast, has breakpoints that are similar to ours, some cases exactly the same. So for subtract zone you can see here, and this is from CDC that it's when the NIC is less than 0.125. We consider it to be susceptible. But we really don't have any resistance breakpoint, we just know that above that concentration, we consider the MICC to be elevated. And you can see some different examples here with suffixing. With this with her myosin, and ciprofloxacin, for example, if the MSE is less than one, we consider that susceptible. But more than one here is noted as resisting the mechanisms of resistance Barry, and now with the molecular testing that's available, that can be a bit more described more in detail. So here you can see that for different antibiotics, we have different mutations, different alleles associated with resistance. And it's important to note that we don't have a great understanding of how much the mutation alone with the as you see 23 S RNA for macrolides. For example, the DNA Gyrase for quinolones, how much does the detection of that connect to treatment failure, we don't have a great understanding, because sometimes these mutations can be detected, for example, the pen a allele, but you still might actually be able to have successful treatment with a dose of Setra axon but maybe a higher dose. So these are the mutations that are known and being investigated. But we don't have a great understanding about how much they connect to, frankly, treatment failure. The history of antibiotic resistance is interesting to evaluate. And this slide was presented by Dr. Khalil ghanim, from Hopkins, but is from me, published in 2011, originally, and the details here you can see and review independently. But the themes are really important. And here what you notice is, each time an antibiotic is introduced, sometimes very quickly over a matter of a few years. And sometimes over a matter of several years. Resistance to that antibiotic eventually develops and eventually becomes relatively widespread to the point where that antibiotic is no longer recommended for gonococcal treatment. And so you see that that happened for tetracycline AIDS for quinolones. For penicillins, etc. And even back in 2011 and 2012. When

this was created, they have these notations of possible untreatable gonorrhea in the future, as soon as possible, you know, super bug status, and in 2010, and 2011 is really when we started to see the cephalosporin resistance being more well described, including in a molecular way. And the concern started to become a bit more widespread in terms of emerging cephalosporin resistance and treatment failure. This is a little bit of a different way to look at these resistance patterns specific to the antibiotics since 2000. And going up to 2021. You can see that the antibiotics that are no longer recommended Cipro, tetra, ciprofloxacin, tetracycline and penicillin have a relatively high prevalence of resistance to Recycling's or doxycycline around 20%. Ciprofloxacin around 35%. Our go twos as the through myosin suffix seem soundtracks own for the past 10 years or so. They remain relatively low in terms of resistance prevalence, but you can see that on this graph from CDC where we look at these three drugs separately, we have had increasing prevalence of elevation of MICC for us through Meissen being detected by the just for the last several years, really since 2011, and 2012. So fixing and stuff try axon however, at least in the US have still less than 1% prevalence of elevated NIC.

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And this is another graph by CDC that looks at men who have sex with men and men who have sex with women only and compare it to the prevalence of resistance for as her Meissen and subtract zone in these two groups as analyzed by the just so you can see here by this comparison that among men who have sex with men, we do seem to have a higher prevalence of resistant gonococcal infection overall for both cephalosporin and for a through Meissen, but for is it through Meissen, it's actually quite high and approaches even 10 Excuse me 10%. So thinking about that graph, kind of expanding to other factors associated with antibiotic resistance. So male to male sexual contact does seem to be a factor associated with resistance, pharyngeal isolates with significantly higher cephalosporin MICC compared to enter general isolates has been described in 2021. When comparing these two, but when you look at azithromycin, in the elevated MICU, or resistance, prevalence does not seem to vary by sight. But there is within those who have male to male sexual contact, generally higher prevalence of resistance for both of these, as we saw on the previous graph, another group would be those who participate in sex work. And then anyone with a sex partner from higher prevalence area of the world, which would be that Asia Pacific region. One of the factors that's really it's not on this slide, and it's less so a factor associated with drug resistance, but more particular site of concern for evolving resistance to antibiotics. Is that fair next. So pharyngeal gonococcal infection is a concern, or decreased penetration of certain antibiotics, particularly as a third isin and cephalosporins. For this issue, the fair next is not well penetrated by several antibiotics. And with repeated exposures at lower concentrations, it's possible that this represents a mechanism for GC antibiotic resistance to develop. So thinking about the timeline, I'm going to kind of take you forward from that 2012, year to now. So we saw some changes there of the cases where we started to see reports of resistance or elevated NIC and treatment failure.

Work closer to home, I should say, we had these reports from the UK. So first, you see on the left hand side a case of gonorrhea with high level resistance to us and three months after X zone. This was a heterosexual male who had acquired infection through travel to Southeast Asia. It was a urethral infection but also pharyngeal infection. The person received a gram of subtract zone and spectinomycin, which is not available in the US. And ultimately, the pharyngeal mucosal site was still positive, and they required three days of ertapenem but had successful treatment with that. On the right hand side, you teach C to heterosexual women a little bit of a different susceptibility pattern and no pharyngeal infection here. The first individual was cured with the usual treatment now in the US, which is 500 of iossef tracks on but they also received as a throw at that time. The second patient actually failed to treatments combination SEC tracks on an ESA through Meissen, but also gentamicin and as a through Meissen, and they actually also had to receive her dependent and work here with that medication. So that in addition to some of the historical information I described, the CD excuse me, the UK to change their gonorrhea treatment guidelines in 2019. And they've since been further updated. So the UK actually recommends a gram of subtract zone for all gonococcal infections. Ciprofloxacin can be used only if susceptibility testing is available. No co treatment with a through Meissen is recommended unless they actually have chlamydial infection. A test of cure is recommended for everyone. They do extra dental testing for all who have possible resistant GC. And anyone who has confirmed ceftriaxone resistant gonococcal infection or general infection that was acquired abroad is recommended to have pharyngeal testing. This one year later, the CDC released an alert, this is March of 2020. So sort of before the shutdowns associated with a COVID pandemic. There wasn't a case of elevated NIC to Secretary axon in Nevada, and you can see this was the first chip just isolate where the NIC was over one. However, this I was still susceptible to is through my son. And at this time during that year as if through Meissen plus subtraction was still the standard of care for GC infection. No partner testing was available at that time. This was a male patient who had three recent female partners that were not able to provide information for partner services. The patient was symptomatic with your arthritis and treated with the usual regimen of soundtracks known as a thorough with complete resolution of symptoms. And subsequent surveillance did not detect any further resistant or isolates with high MIT for set tracks. I'm in that region. Later that year, in December of 2020, the CDC released their updated treatment guidelines which introduced the concept of weight based SEF Triax zone dosing. They also release recommended safe tracks on for all pharyngeal infections due to lack of evidence, other medications are efficacious. And they also recommended a test of cure for pharyngeal infections, you know, really emphasizing this concern that that's where we're seeing the evolution of resistance. So some of the rationale behind these changes in terms of removal of this code treatment for chlamydia or CO treatment for GC with an anti colonial agent, or seeing more as a through myosin resistance with a lot of other infections, some are STIs, and some are not. We're seeing the azithromycin resistance I mentioned by the just but also doing some mouse modeling, it did appear that a

higher dose of subtraction was needed to get to that target. Am I see for depending on a person's body weight, and the CDC published sort of this compendium of evidence that guided their decision here for anyone who's interested. And so here, we get to the more recent updates or alerts in 2019 2023, from the Massachusetts Department of Health, and this was released on January 19 of this year, where they describe multi drug resistant RIA or they describe it as not susceptible, again, because we don't have that resistant concentration breakpoint. Both cases were detected in Massachusetts through enhanced surveillance in that state. So they had reduced susceptibility to subtractions in vaccine, Minnesota through and were resistant to Cipro, tetracycline, and penicillin. They detected the Penn a 60 allele, which I'll talk more about shortly. The first isolate sequence type with this molecular testing was originally identified in the Asia Pacific region, though this person had not noted any travel and detection, again was through molecular surveillance with CDC. Despite this resistance mutation detection, again, they have this microbiologic cure with 500 milligrams five M soundtracks on which is the standard of care. So there's this you know discordance about what do the mutations mean in terms of outcomes and treatment success. So here, this is a they describe the first case in detail with the susceptibility repair information, as you see. The clinical specimen, again, a male patient with your arthritis, elevated MICC for multiple drugs, CDC did the molecular testing, which detected the penny 60. The this was the first documented case of resistance to six out of the seven drugs tested as part of the just standard. And notably, as I mentioned, this was locally acquired, though, like the other case in Nevada, they couldn't really get information from the partners. There was no clinical information provided for case two, but they did describe a similar susceptibility pattern. So moving from there, now we have three cases in the US with this penny 60 detection, two in Massachusetts, one in Nevada, and at the same timeframe. Between 2019 and now, several cases were reported out of the UK. So eight cases with the same sequence as that first Massachusetts isolette were first detected in the UK, between the

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end of 2021 in the first half of 2022. And the UK eventually published a case series where they had looked at these cases of resistant infection. So they had 10 Ceph tracks on resistant cases and 2022. And that's a big increase compared to nine that they had in the previous six years. Nine out of 10 of those had the penny 60 allele. And all of these were associated with travel to the Asia Pacific region. All of these were heterosexual individuals and all of these were successfully treated with the UK standard of care, which again is one gram of I am subtract zone. So despite that detection, again, that resistance associated mutation with a higher dose of scepter X, and they were able to overcome that. And again, similar to these other cases, not all partners were traceable. And for the UK analysis, they did perform that whole genome sequencing and suggested that these cases were similar or identical to strains of gonorrhea circulating in the Asia Pacific region. The Massachusetts alert led to sort of review and alert

from New York state as well, and really just emphasizing to for providers to be aware of this and on, you know, on the lookout for this issue, particularly, there's a JC treatment failure or a case and a person who's traveled, but also emphasizing that we haven't seen any cases in New York State. Yep. But certainly people travel and we know this is a something that we should expect to see. So at this point, New York State just recommends that we train for CDC guidelines. We that we retest in three months due to high reinfection rates of GC and these other STIs in line with CDC guidance that we requested a test of cure for pharyngeal infections. And if resistance is suspected, we can send specimens to your lab for culture and susceptibility testing, it's available, but if not Wadsworth is also performing this and New York State is also launching their own surveillance program. So what about managing treatment failure if you're concerned about resistance, so if you are worried about resistance, either because someone has traveled or because you have treated them and they're returning with persistent symptoms, that's a person you'll want to send a culture and susceptibility testing. If you have confirmed or suspected GC resistance, definitely consider a consultation with an expert. If that's available to you, at the CEA online, you're always welcome to call them as clinicians and pH PHR is we can provide some assistance, or some guidance in how to approach your challenging cases. But these, again, are cases where culture and susceptibility testing is recommended. You can report cases of cephalosporin resistance to your local health department or your state health department. There are alternative regimens to consider including higher dose septra axon, an alternative medication, if you have confirmation of susceptibility, like Ciprofloxacin or doxycycline. And then ertapenem, we have some emerging data for that test of cure after these situations is recommended. So if you're worried about resistance, or you do have resistance, you treat them definitely obtain a passive cure. And then CDC actually has a consultation and report form that you can use if you'd like to report these. Some of the new developments are here, as you see a point of care test that has some resistance assay associated with it. This is already being used in other countries, and so seems natural that we would be able to get that as soon as it's FDA approved, that might help provide different options, right at the point of care. There are some new antibiotics being evaluated, as I mentioned, and you see those here. One of the interesting things is a completely new class of antibiotics console for reasons I'll talk about that, that inhibits a DNA Gyrase excuse me, that is a DNA Cherisse inhibitor so it inhibits DNA synthesis, gentamicin. Really we need a bit more data we know. You know, it's really still inferior to subtract zone but it remains an alternative option ertapenem looks like it might be a great option for those who have documented resistance and treatment failure with set tried axon. But we don't clearly understand again, how much those pen a mutations might actually impact the carbapenems as well. And then, of course, there's still higher dose of trioxide, which does appear to be effective for some of these cases, even when resistance mutations are detected. So looking at ertapenem, they actually did a randomized control trial in the Netherlands among adults who had either you know, recolor, your genital gonococcal infection, and just over 2020 Excuse me, just over 2000 participants.

Most of the participants were male, and most of those male were males were men who have sex with men. They were randomized to receive one of four options. So 1000 milligrams of intramuscular dependent 500 milligrams of iossef trioxide, a weight based dose of gentamicin with a max of 400 milligrams, or six grams of oil fosfomycin. The primary endpoint was microbiologic cure, one to two weeks. The fosfomycin are arm was actually terminated early due to poor efficacy in the interim analysis. So we'll focus on the others here. Each of these other three arms being ertapenem SEPTA axon and gent had over 90% of patients with clearance of infection. The ertapenem was notably non inferior to Senator axon. However, they did have a higher proportion of adverse events in that group. gentamicin monotherapy did not meet non inferiority criteria when compared to subtract. So that's not new for us to know. We have seen in previous smaller studies that gentamicin even pluses through Meissen has not really been comparable and sort of an equivalent way to subtraction. And that's why it really repeats and alternative. Notably, these groups, as there are so many different arms are small. So all, all the treatment arms had about 100 participants except for fosfomycin, which only had 38. And again, was stopped early due to the interim analysis. So ertapenem Possibly an option for those. And I shouldn't say possibly, I think ertapenem is an option for those with CF triaxial resistant infection, who have no options on susceptibility testing, for example, it's also quinolone resistant and tetracycline resistant, you're really left with or dependent at that point, and it does appear to be successful. For zolfo, Deason, this is still in clinical trial phase. And I'll share with you some of the early data. So here they looked at 179 participants with symptomatic uncomplicated infection, they were randomized to receive either two or three grams of the soulful Jason or 500 milligrams of set Triax zone. They did a test of cure at one week. Similar to the other study, they had, again, mostly males with only 12 females, they had noted microbiologic here and again over 90% of those who received either dose of the solar flare basin, but still a little bit higher with scepter axon at 100%. There were 15 rectal infections. Again, all of these were cured as well. One thing to note about this new medication, which is you know, a little bit of a frustrating factor considering what we're worried about and when we might want to use it is that it had lower cure rates for pharyngeal infection. So we may not be getting that great penetration to the pharyngeal tissue. It was only 50% at the two gram dose and 82% of the three gram dose. And that compares to 100% here with saturate axon 500 milligrams. So now this is currently in phase three, where they're studying the higher dose three grams comparing that to subtract some pluses are through Meissen. So in addition to that, so we have these two alternative antibiotics or depending on which looks promising for multi drug resistant gonococcal infection where cephalosporin has failed. And there are no other, you know, oral options available. We have the solar flip basin, but not for pharyngeal infections still in the clinical trials are dependents really available at this point. But we also have enhanced surveillance to try to describe a bit better the geographic variation, the patterns of resistance, and even the molecular test, as well. So nationwide surveillance programs are already underway. And you're familiar now with the just the interest. The STD surveillance

network participates in all of this. The there are a couple of other programs that are noteworthy and strengthening the program called strengthening the United States response to resistant gonorrhea or surge is also listed here. But New York state, as I mentioned before, is also doing their own surveillance, in collaboration with Wodsworth. And if you don't have culture and susceptibility testing available to you, you can actually request testing at Wadsworth.

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So just to summarize, if you have a GC treatment failure or suspected or confirmed cephalosporin resistance, send a culture and susceptibility testing in addition to your usual GC Nat, report the cephalosporin resistant cases to your health department. And in cases of treatment failure without we exposure, consider retraining them with subtraction at the same dose or a higher dose while you're waiting for this culture and susceptibility testing. And depending on the outcome and your susceptibility results, you can then decide whether you need a different medication or whether treatment has been successful. So I'll stop there and here's our podcast information for anyone who's interested in our STI treatment cards as well. And again, mentioning just the CEI mine, you can call with your challenging STI cases as a clinician helpline for many different services as you see HIV, Hep C, Drug User Health, PEP and PrEP, and sexually transmitted infections, and any training you might need. Our website is here. So thanks everyone.

[End Transcript]