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EMERGING ISSUES IN THE MANAGEMENT OF STIS: RECENT TRENDS IN DISSEMINATED GONOCOCCAL INFECTIONS

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Emerging Issues in the Management of STIs: Recent Trends in Disseminated Gonococcal Infections
[video transcript]

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Hey, thanks very much. I

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think we're, we're still like a little bit early 829. But we'll go ahead and get started. I find it's a little hard to keep things to 30 minutes. So today I'm going to talk about disseminated gonococcal infections. And as just pointed out, one major learning objective is to characterize the epidemiologic characteristics associated with CGI infections that have been recorded in the recent literature and will also discuss the diagnosis and treatment of disseminated gonococcal infection which I will likely call DGI several times to be sure to read during the talk today. I have no disclosures. And just just background so disseminated gonococcal infection is as the name implies, it's the consequence of the spread of Neisseria gonorrhea a largely through spread through bacteremia. The initial infection is typically some untreated mucosal infection. So either genital or extra genital, and DGI results in a variety of different signs and symptoms, but generally is divided into sort of the usual syndromes, and then some more rare, less common manifestations. Within the usual syndromes are the manifestations of arthritis and arthralgias, tenosynovitis, and dermatitis or rash, and then more rarely is the dissemination leading to an infection of the heart valves called endocarditis, or Frank meningitis as can be seen with

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neisseria meningitidis.

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So why does the organism disseminate sometimes when when we all know we see mucosal gonorrhea very, very frequently without this kind of dissemination, and it's probably the interaction of two different factors. There's host factors so one would be a delayed diagnosis of mucosal gonorrhea. Another that's been associated has been missed recent menstruation, pregnancy has been in association and some immunologic factors such as terminal complement

deficiency, C, five through C A. So either a congenital or acquired terminal complement deficiency, such as this makes one more susceptible to invasive Neisseria infections, both gonococcal and Yukako. And we see this terminal complement deficiency now, with the use of eggless lism AB, which is a immune modulator that's often used with some rheumatologic conditions. So that induces a C five inhibition and can lead to dissemination and because of gonorrhea, lupus, systemic lupus has also been associated in some studies with an increased risk of dissemination. But it's not all on the host side, there do seem to be some specific organisms that contain various factors that favor dissemination. And when those organisms cycle into a community, there have been reports of local clusters of infections with higher rates of dissemination. So what about the symptoms This is from up to date so that the major signs and symptoms are as I said, are arthritis or arthralgias. So migratory poly arthralgias is seen in a high percentage of patients. Tina synovitis, also seen in a high percentage of patients and rash so all of those are in about two thirds. Fever also reported and about two thirds. Rank arthritis is less common and is usually separated from that first grouping of arthralgias, synovitis and dermatitis. But a frank septic arthritis is seen in about 40% of the patients, and these are typically a mono articular arthritis or an oligo articular arthritis meaning very few joints. And about 25% of patients in this older report had genital urinary symptoms at the time of presenting with the dissemination. So usually though 25% had symptoms but you Usually there are no symptoms of mucosal infection, and the patient feels well until their DGI symptoms began. So as I said, dermatitis tenosynovitis, parli arthralgias are one presentation period and septic arthritis. Another presentation, then more rarely endocarditis or meningitis which prevent presents like any other meningitis with photophobia, headache, neck stiffness, and occasionally there'll be reports of abscess somewhere else. There's been laryngeal abscess pericarditis, Frank osteomyelitis, but they're quite rare. Typically, the dermatitis tenosynovitis. arthralgias syndrome, which is the most commonly reported occurs two to three weeks after mucosal infection that is untreated. As I said, you may have fever and malaise and flu like illness, the poly arthralgias tends to be migratory and it can be large or small joints, usually multiple joints but not typically symmetric. The Tino synovitis is unusual and not really seen in other conditions. It's usually Fingers, toes are ankles, occasionally wrist, and you'll have sort of a palpable swelling along the tendon, and tenderness along that tendon. Rash is common. It's usually the singular or pastula tends to be distal. So it can look like an embolic kind of rash. And it's generally transient, not usually tender, and generally, there are a few lesions and they're scattered often, as I said, distal, so below the elbows and below the knees. Occasionally, you'll see it on the head and neck scalp has been reported but not typical. Most of those that I've seen have been less than, say 20 lesions. So you really have to look for them because they're not necessarily tender. So the patient may not notice them.

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And they they are transient. The purulent

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arthritis as I said, usually mono or oligos articular. You may not have fever, but it can look like a frank septic arthritis with synovial fluid with a high white count can be virtually any joint but it's generally below the elbows and below the knees again. Spine, the axial skeleton is not typical. And very occasionally, you'll also have skin lesions and tenosynovitis. But but as I mentioned earlier, that are typically the poly arthralgia that's migratory to have a frank septic arthritis is more typically without those other bindings. Here's some some pictures of the rash. So you can see it looks a little bit like an belie and sort of a circular lesion that gradually becomes looks hemorrhagic and ultimately forms and eschar.

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So the diagnosis is often

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a clinical diagnosis. So you have to really consider the diagnosis in the in the appropriate clinical settings. So that requires a good history, including a good sexual history, and a careful exam looking for mucosal gonorrhea in case you might find that in that 25% will be per rash, joint effusions. tenosynovitis may be a cardiac murmur and findings of meningitis. The laboratory diagnosis is often entirely negative. That's why you end up with this clinical diagnosis. You would consider if someone had a murmur or positive blood culture and echocardiogram and certainly if someone looks like they have meningitis, she would do a lumbar puncture. It is recommended to do blood cultures. These are sometimes positive in that dermatitis arthralgia syndrome, and they're more likely to be positive in that syndrome than Imperial in arthritis. And of course, they're generally always positive in endocarditis. If you do have a frank arthritis where there's synovial fluid that you can aspirate, you do a cell count as you would with any septic arthritis. It does look septic, so you'd have a lot of white cells in the synovium usually around 20,000 When it's gonorrhea, as opposed to 50,000, which you might see with other common causes of septic arthritis like staph aureus, or even higher than 50,000 in Staph aureus. Septic arthritis, it is recommended to do STI testing at all possible mucosal sites. And that testing is preferred over culture because of the increases sensitivity. And as with anyone when you screen for one STI you screen for others. I did note in the 2021 as TD guidelines, the CDC recommends not testing of possible involve sites including joint fluid or CSF course this is not FDA approved, so it might be hard to actually To find a lab that's willing to do that, but I'll show you a study that suggests that this might be higher yield. skin lesions, occasionally, you'll

get a positive Gram stain or culture or not, if you could get a lab to do that, if you have a particular lesion, and you can get a little bit of pus out of that lesion, you can sometimes actually see the organism in that lesion. So this is a study that was released, just about a year ago, in March of 2022. It comes out of a group in Manitoba, Canada, and they looked at using AP does not test on their isolates from potential DGI sites. And so what they did was, they found that in those that were culture positive, from from a site usually join, or GC, they were also 100%. net positive using XML. For those that were culture negative, but seemed likely that they had probable DGI. They had nine of those. And they in those nine, they were able to do sequence analysis, and confirm that seven of the nine actually were due to GC, and three of the nine actually had positive gnats from your genital sites. So they concluded that Nat was significantly more sensitive as a test for synovial fluid than culture which, which I suppose is not surprising. They did also look at other causes of septic arthritis where the culture was positive, where a different organism like staph, strep or E coli or some other bacteria, and they did not have any false positive nets, or G GC from these other causes of septic arthritis. So it does seem that at least from this single study that that used for synovial fluid might be higher yield. And so maybe at some point that will

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be FDA approved. When you do see someone with CGI, and

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the differential diagnosis is, as you might imagine, sort of other causes of inflammatory arthritis, like other causes of septic arthritis, maybe Lyme arthritis, other causes of endocarditis, with this sort of migratory arthralgias and rash. You think of other acute viral infections, as shown here. Maybe Brian, rheumatic fever, reactive arthritis or rheumatologic, conditions like lupus, the treatment of DGI hasn't really changed other than the changes associated with resistance and a reluctance to use put a lens for instance. So the recommended treatment for the dermatitis arthritis syndrome is septra axon, a given potentially so IV or Iam for at least two days, at

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or until improved. And then continue

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to give daily at a dose of 500 milligrams I am or an oral agent based on susceptibility testing. So here, you could use a quinolone. If you had a susceptible culture to complete seven days total. For purulent. Arthritis, the recommendation is to go out potentially to 14 days, endocarditis you

treat as with other causes of endocarditis for four to six weeks with my dose, IV subtract zone. And similarly, IV stuff try axon at meningeal dose at q 12 hours for 10 to 14 days. And then I wanted to get into a little bit what's new in DGI. And mostly what's newer, you can see here, this is from PubMed, and this little blip of papers, is back in the late 70s, early 80s, then you see we don't have a lot published. And then we have a little bit of a flurry of activity, really since about 2019.

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And most of this is sort of questioning the classic description of epidemiology and the current reports. So classically DGI has been reported in one to 3% of gonococcal infections. So this is what you would find in a textbook. Historically, it's been in those recorded as female, much much higher than those recorded as male, and, and more likely to be young females and with that association of menstruation, and pregnancy, and women with gotten a copy of infection were less likely to have accurate diagnosis a timely diagnosis more likely to be minimally symptomatic than a man with period. Right so they were less likely to be diagnosed, and that was thought to be some of the reason that they were more likely to present with dissemination. However, as the epidemiology of mucosal GC has changed with higher numbers of asymptomatic extra genital infections, particularly in men who have sex with men, there have been some changes in the epidemiology of DGI through these reports that have come out. And there have been a smattering of reports from locations in both the US and Canada, and some from Europe as well as shown here. So one example is from the nm WR that was published in 2020. And this described an ongoing cluster of highly related DGI infections in southwest Michigan that was noted in 2019. So this came about because of three simultaneous hospitalizations were cases have disseminated gonococcal infection and Kalamazoo on the same day, this generated an investigation of 27,000 cases of GC from the prior 18 months, and led to published health alerts and public notifications and medical record reviews. So they ended up coming up with a case definition of a confirmed DGI case with a sterile site with a positive test for GC. So that was blood joint fluid or CSF or a probable DGI case. So they had a positive Nat from a mucosal site, and DGI symptoms such as Timo synovitis, or poly arthralgias. So after those three, three cases, they ended up with 13 confirmed cases, and three probable cases through just over this four month period. So really a very short time to have that many cases of DGI. And they found that the eighth The median age was 39. There were 56% were reported as male versus 44%, reported as female, they were overwhelmingly confirmed cases. So they had positive test results. They were largely in this southwest Michigan area. And they had some associations of, for instance of homelessness. And if you look down at the bottom here and associations with drug use, you can see here the initial clinical manifestations were septic arthritis tenosynovitis. They had two cases of osteomyelitis, and one case of mitral valve

endocarditis. They also had quite a high rate of concurrent gonococcal infections had mucosal sites so 50% at your agenda, it'll 31 at pharyngeal and 6% at rectal. So all of these were quite unusual features compared to what is classically reported. So more men than women, a higher median age range of 3039, this association with lack of housing, and with drug use, especially methamphetamine, they were able to look for partners and they found no link partners among 27 drug use contacts. So it didn't seem to be a sexual network within the drug abuse. Drug using population. There were also very high rates of concurrent urogenital infection. And they didn't do molecular analysis of the organisms, and they were quite highly related molecularly. So it did seem to be a particular organism that had entered the community and was more likely to disseminate. So that was reported in 2020, in 2022, so just a few months ago, the CDC released a surveillance data about TGI us and this is related to infections 2015 to 2019. So just before that got this cluster in Michigan, and they found that between 2015 and 2019, they found 77 DGI cases, this ended up to be a case rate of point one three per 100,000 population, and really much lower than then the classically reported one to 3%, point o 6%. Of all reported cases of gonorrhea. They were disproportionately male, they were disproportionately non Hispanic black. And the age range was quite large, with a higher median age range, similar to what was reported in Michigan. They found blood and joint fluid were the most common sterile sites, and I've included some of the details over here that they had high rates of hospitalization, and they give you length of hospitalization, which range from really seven to greater than 15 days.

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So

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the next thing that happens sort of chronologically is right. Right after this is this is case reports up to 2019 and 2020. California issues a Dear Colleague alert referring to this Michigan outbreak and that they're seeing a similar rise in cases among their population. They follow As up in Orange County with another alert in 2021, and another in 2022. And in this one and 2022 they call attention to these cases have an association of illicit drug use, especially methamphetamine. And they call on clinicians to screen for gonorrhea and all sites of exposure. For those who who report by using methamphetamine. They then publish a very recently a characterization of these outbreaks. So they like Michigan, we notice six cases of DGI in a short timeframe at two very closely, close geographic hospitals. And that led to a review of, of their reported cases of DGI, beginning in July of 2020. They show sort of their outbreak curve here. And they do a really pretty thorough, detailed case investigation starting in November of 2020. So in that next year, they find 149 confirmed or probable DGI cases, which is much, much more

than previously reported, again, a higher median age, the age range, and those reported as female with median was 36 versus 45. And those reported, it's now that half of their cases were male, they were less likely to be among men who have sex with men, and are more likely to be among terrorists, those reported as heterosexual. They did find similar to the Michigan record about 23% with homelessness in the prior year, and 36%. With drug use, overwhelmingly methamphetamine, they had some associated comorbidities of diabetes, Hep C, HIV and some other forms of immune suppression, including chemotherapy kinds of drugs or immune modulating kinds of drugs. The main days, a time to diagnosis was three days, but the interquartile range was one to seven days, and most people had no urogenital sentence within the prior month. At the time of this report, they actually also had two deaths, which increased to four deaths when they gave A later report. So they ended up with point two 4% of their cases of gonorrhea resulting in DGI. So that's lower than that textbook, one to 3%. But much, much higher than the report from the CDC the year earlier and point oh 6%. So about four times higher, they think the difference so that so this lower range is likely related to the original estimates in the textbooks really relying on culture diagnosis of gonorrhea. So our denominator of who has gonorrhea has vastly expanded with our use of not testing that's more sensitive. And the use of extra genital testing, which has really increased the numbers, the amount of gonorrhea that's diagnosed, many of those extra genital infections are asymptomatic. It does seem that older age and a higher rate among males compared to classic risks both in the Michigan report and this California report. And there's been an association with illicit drugs in compromising conditions as other possible factors. The California group then just this about a week ago, did an early published ahead of grant report in STD STD journal called Lessons learned from this ongoing public health investigation. So they've now expanded that report from July of 20, ending in July of 2021. Going out to May of 2022. They are now up to more than 200 cases, including four deaths. And as mentioned, this is an ongoing investigation. The age range is older than the classic so 30 to 50. Largely heterosexual men more than women and and often with a complete lack of your genital symptoms. They've expanded some of the descriptions, they don't give actual case, individual case descriptions but sort of a paragraph sort of description of some atypical things that have happened. And while that early report said, diagnosis within three days here, they've said that there had been a number of atypical symptoms and misdiagnosis with inappropriate treatment. People given steroids nonsteroidals or other antibiotics to treat septic arthritis, not due to gonorrhea. They've had sort of misdiagnosed as cellulitis. DJD, sort of acute musculoskeletal injuries Gout is People misdiagnosed as lupus, rheumatoid arthritis or reactive arthritis. And they call attention to this older age group being sometimes not in the generally recommended GC screening population. So maybe not, providers are not considering gonorrhea when someone who's older without your genital symptoms comes in with these symptoms. So they give some best practices for

clinicians. And they particularly point out that the people are presenting to Eds urgent cares, ortho room, and PCPs, and so not sexual health clinics. So really, we need an awareness of DTI and awareness that current cases are not following the classic textbook descriptions. And they recommend that in individuals with gonorrhea, even with mucosal gonorrhea to inquire about symptoms, and DGI, again, of course, good practice to test all sites of exposure, if you are able to get a culture to do susceptibility testing. And to be sure to look for partners, they found enough a number of situations where partners were not treated in individuals who had DGI. And they strongly recommend the use of the DPT. They also talked about their outbreak investigation and have noted that the DI D is have their interviews, identified a number of individuals who were inappropriately treated for DGI. I've got very short courses of therapy, and they've been able to get people back into care. They've had some patients unwilling to be hospitalized and the local health departments have had to initiate daily I am parental injections to treat the disseminated infection. And then one last report out of Manitoba. So that same group that did the synovial fluid analysis, also looked at their DGI cases. And you can see here, these are rising in the recent years. And they went up 2.16%. So, so higher than that CDC report of point, Oh, 6%. And even in that the timeframe of their investigation, it actually increased to over 1%

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in 2020.

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There, there is a little bit different, they had more isolates among females. But what they do note that within the males, there was an older age group, and they do a molecular investigation and identify a common allele that is in the poor B area. And they they postulate that this is the virulence factor that is leading to the rise in dissemination in their geographic area. So in conclusion, DGI remains a bit hard to diagnose, you need to have a high index of suspicion, need to look for the classic clinical manifestations that we discussed. Post host and organism factors appear to be important. There are these increasing reports of clusters of cases in some locations, like California and Michigan, Georgia and South Carolina have also recorded some clusters. It's important to do a culture and Nat testing. And it may be that do diagnostic techniques and synovial fluid will have a higher yield. There are case report forms that you can submit cases to Wodsworth. They are interested in receiving these cases. And the California group has published a an FAQ document where providers are not familiar with DGI. That goes through some some of these weeks, well and there and see if there are any questions. So one thing that California has noted is that there were reports that were being issued for, for their cases. And when they got that report of 66 cases in a short period of time, they went back and

found out that in the the in the California State system, they had 72,000 reports of gonorrhea cases. So it was sort of buried in there these DGI cases and so as as gonorrhea has, has really gone up in the last few years with our use of NAT testing and extra dental testing and likely just, you know, higher spread of infection that the sheer numbers sort of overwhelmed the public health system. So they had to be sure that reports from sites other than the coastal sites were flagged as especially so that they could investigate those DGI cases. So it it kind of got lost in this just 72,000 cases. So just lost in the overwhelming number of mucosal

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gonorrhea cases. That QR code again

30:00
Just as put the link in the chat for ordering the cards. There is a question that just came in. How many DGI cases have you seen in your years of practice? Because I've only investigated two.

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When I trained I traded Philadelphia at a time when there were a lot of GPS DGI cases. So we had an organism locally. And so when I was a resident, pretty much always I had a DGI case on my service. So I saw really every joint, even mandible. So I saw a lot in residency. When I moved to Rochester, I would say we would see one to two per year, maybe so nothing like I saw in Philadelphia. Over the last couple of years, we maybe have a local blip where we've seen a few more. We had a two cases of endocarditis in the last four years and occasions where we had more than one septic arthritis say in a quarter selected more sporadic than in Philadelphia, but definitely,

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I've seen it

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we don't have any other questions. I see a question in the q&a.

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I mentioned a PT, how is that done with DGI. So if you tape is expedited partner therapy, where you give the patient medicine medication to give to their partner or give them a prescription to give to their partner. So the recommendation would be to give suffixing 800 milligrams to give to the partner who's presumably asymptomatic and the partner doesn't have DTI. But that

patient has DTI that the partner may be incubating infection with that same organism that has a propensity to disseminate. So 800 milligrams of suffixing is the recommended oral regimen.

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If we suspect a case, is it best to refer to the ER, rheumatology or infectious disease, many of our patients are uninsured.

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In that setting, then it's probably best to refer to an ER with with an alert to the triage in the ER that of suspected DGI. I think ers this is part of emergency medicine, education. So hopefully they're familiar with that. And because of an era cannot turn someone away for lack of insurance. So I think that would be the best solution to refer to an era and they are quite familiar with tapping joints also.

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Providers at

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Planned Parenthood and urgent care and they'll be asking further screening questions.

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Um,

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you know, as I was reading this, it did make me think that maybe we should be a little bit more proactive about interviewing our patients with gonorrhea in the way that we interviewed syphilis patients for visual symptoms. It might be smart to interview a gonorrhea cases for arthritis kind of symptoms. So I think that might actually yes, but that's probably good practice. It doesn't seem that that these organisms are spread universally throughout the country. It does seem like there's clusters of infections happening, but it's, it does seem from the reports that it can sort of linger below the surface. We're a bit before you realize you have a cluster

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not seeing anything else come in. So thank you Dr. Erwin for that presentation.

[End Transcript]