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ECHO: DISSEMINATED GONOCOCCAL INFECTION

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[video transcript]

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None of the planning committee has any. Any sort of disclosures and I as the speaker also, so don't have any disclosures. So we're just going to talk about disseminated gonococcal infection, what are the clinical features and go through diagnosis and treatment and sort of the current literature. So I had to add this slide in since yesterday, the CDC just released the latest reported cases of gonorrhea. And you can see way back in the in the mid to late 70s. And even in the early 80s, we had much more gonorrhea than we did in the 2000s. But we have a fairly steep slope going up in 2020, despite the occurrence of the pandemic and we know that radically impacted testing. If you look at rates, rates and cases, you can see how from 2011 through 2020, that the darker colors are higher case rates. And those higher case rates, which back in 2011, were really concentrated. Just in in sort of the Mid South Louisiana, Alabama, Mississippi, have spread widely across the US. And while disseminated gonococcal infection is a relatively rare event. Of course, when gonorrhea becomes more common, even rare events happen more frequently. So to go through sort of background so disseminated gonococcal infection, which I'll just call the PGI throughout the talk is really the consequence of bacteremic spread of the organism. And so the initial infection is almost universally an untreated mucosal infection. So pharyngeal, genital rectal, potentially potentially even conjunctival. And the dissemination can can result in a variety of symptoms. But the usual syndromes are are a arthritis, arthralgia, tenosynovitis, were rash. And some combination of those less commonly, you may see endocarditis, and so actual infection on the heart valve, or meningitis, and even more rare than that, occasionally osteomyelitis or deep tissue abscesses. So why do some organisms or you know why do some cases end up with dissemination and it does seem like there's there's an effect on particular to the host of whoever has the the mucosal infection, and likely organisms specific effects as well. So the host, it's really delayed diagnosis of mucosal Gonorrhea. And you can argue there, there might be lots of reasons for that. Some might be that some are organisms don't produce very symptomatic purulent infection. We know that most urethritis, in cis men, is frankly purulent. But there are a small percentage maybe about 10% Where there's there's minimal or even some with no symptoms. Cis women with so infections of female reproductive organisms tend to be less symptomatic, so they may be untreated for a longer period of time. We do know from studies that recent menstruation is associated with dissemination and and that actually has been associated with some changes in the organism itself that that might make it more resistant to the immune system. Pregnancy has been associated with dissemination. And the thing that's always on board kinds of questions are compliment deficiency that are either congenital or acquired, or induced by medications that are now used, particularly eculizumab which can be used for P and H, I believe mostly in the pediatric young population. Lupus, systemic lupus has also been associated with a risk of dissemination, although not other autoimmune diseases, particularly, the organism also seems to matter. So there are specific clades of organisms that contain a variety of virulence factors that favor dissemination. And these virulence factors in general, favor the organism in some way that allows it to avoid the immune system. There have been multiple different factors described. I'm not going to go into it's not sort of this level of microbiology today, but but there are several

different factors, some of which are well described, and others that are just postulated. But recently, when we get into the epidemiology, there have been certain clades found in geographic locations where they seem to have Have a cluster of cases. So it does seem like

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particularly or particular organisms are definitely more likely to disseminate. I can say personally I trained in residency in Philadelphia in the late 80s, early 90s. And that was still in a period when there was a tremendous amount of gonorrhea. And we, at that time had someone on our medicine service always with disseminated gonorrhea there was that much disseminated gonorrhea, it didn't seem rare. So we clearly had organisms that had a propensity to disseminate. This is from up to date. So just sort of like a textbook overview of the major symptoms and signs of dissemination, and most common is sort of a migratory poly arthralgia, followed by a Tenosynovitis. So inflammation of the tendons and I'll go into this in a bit more detail in a minute, and rash. So all of those are symptoms that might make you think of this condition and so are seen in about two thirds of the cases. Fever is also quite common, and a little bit less frequent is a frank purulent. Arthritis, like a septic arthritis. And when that occurs, they tend to be few joints or just one joint and genital urinary symptoms. So actually having mucosal infections at the time you're presenting with the dissemination is relatively uncommon. So usually you find no no signs of mucosal infection, and the patient will have felt relatively well and then the signs of dissemination begin. The most frequent presentation is the mix of dermatitis tenosynovitis, and polyarthralgias. There is also the presentation of the septic arthritis where you may or may not have those other findings. And then as I had mentioned earlier endocarditis, meningitis, which looks like any bacterial meningitis. Additionally, there are reports of myositis, pericarditis, osteomyelitis, or deep tissue abscess, and all of those present like other organisms causing those conditions. It's just that when you get the culture back, you're surprised that it's caused by gonorrhea. The dermatitis tenosynovitis. arthralgias, which is the most frequent typically occurs two to three weeks after untreated mucosal infection, they may indeed have a flu like illness with fever and malaise. The polyarthralgia tends to be a mix of large and small joints, usually multiple joints. And the tenosynovitis is really the most helpful finding and you can actually sort of palpate along the tendon, it's generally below the elbows and below the knees and you have, you know, discreet tenderness of the tendons, sometimes just a single tendon, but often multiple, so a couple of fingers and the wrist may be and you can feel some swelling, there's usually a little bit of erythema overlying that the involve tendons. And patients definitely noticed this and it's uncommon in other syndromes, so it should cause you to think about gonorrhea. The rash is also quite frequent. It's, you might think it would be like meningococcus. And some of the individual lesions might look like meningococcus, but it's much, much less impressive. Of a rash, it's usually starts as of the vesicular or pustular rash, generally, also distal below than the elbows and below the knees. Not typically tender, but it's few and scattered lesions. Occasionally scalp has been reported. And sometimes you have to really do a very, very careful exam. So you have a patient that comes in with maybe swelling in the wrist, and a sore couple of joints. And you really have to do a careful exam to find, you know, sort of less than 10 lesions. The Arthritis if you have a frank purolent arthritis that looks like other septic arthritis, so it's typically mono or all go articular. It's asymmetric. So it doesn't look like you know, where you have matching arthritis with two risks or two knees. It may not be febrile, but maybe febrile but but a fever is not necessary. And if you do if you tap the joint,

there'll be many, many white fells although typically less than with something like staph aureus. And again, generally below the elbows and below the knees and the spine is not typically involved.

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So here's some pictures of the rash. These are all taken from visual DX, and you can see sort of a pustular lesion With an erythematous base, here, you see a close up on the second one a little bit closer, you can see. And sometimes that becomes sort of necrotic or hemorrhagic. This one might have some, the bottom left might have a little bit of associated joint fluid. If you look at that middle top one, I haven't seen this as an attending. But when I was training, in residency and fellowship, I saw a few like this where you were kind of lucky enough as the practitioner to see it when it was still pustular. And you could use a TB syringe and get a little pus out and see actually see the organism on Gram stain. Here's a picture from bone and spine.com, of just showing a septic arthritis, which really isn't distinguished, you can't distinguish that from other causes of inflammatory arthritis. And this is a very old graphic that shows the frequency of the joint involvement and sort of the lack of the involvement of the axial spine. And as I mentioned, when I saw so many in residency, I saw all of these including the jaw, so they all can happen. The diagnosis is often clinical. And and I would have said before, before actually reviewing this literature for this talk, that it would be almost always a clinical diagnosis with negative mucosal tests and, and you are lucky if you get it out of blood or out of the joint. So you do still need to think of the clinical syndrome. So a sexually active a person who's sexually active, you need to know the background of GC in your in your area, do you have a lot of cases with the appropriate clinical syndrome, you need to consider the diagnosis. laboratory testing in the recent literature is is positive a little bit more often. blood cultures are more likely to be positive when you have that sort of febrile illness with dermatitis and all of those manifestations that's thought to be if you think of this sequentially as to happen before the septic arthritis develops, if you do get synovial fluid the cell count is Frank arthritis is generally high. For GC, it tends to be around 20,000. Whereas for other causes of septic arthritis like staph aureus, tends to be over 50,000 But officially 20,000 could be could be due to really any bacteria. It's recommended to do STI testing at all exposed mucosal sites. And now that we have naats, it seems that testing might be positive a bit more often and dissemination then, in the earlier literature, although a negative test in the appropriate clinical syndrome doesn't rule out the diagnosis. So you want to test all sites. So pharyngeal rectal, your urethra roll or cervical, and, in some recommendations, even conjunctiva if you have a test that's approved for that site, skin lesions are generally low yield, although as I said, if you happen to get that dollop of pus, sometimes you can see it. And then of course, if somebody has Frank meningitis, you need to do an LP, or if they have signs of endocarditis, or even murmur, you might want to consider an echocardiogram. This is a slide again, from up to date that looks at the differences between a non inflammatory arthritis like an osteo arthritis, inflammatory arthritis like rheumatoid arthritis, septic arthritis and hemorrhagic arthritis. So you can see really mostly what you're looking at is this inflammatory arthritis, you can get up to 20,000 cells septic arthritis tends to have more than 20,000. And they are predominantly neutrophils. And you might be able to see the organism on gram stain or potentially have a positive culture. The differential is sort of as you would imagine, sort of any other arthritis, septic arthritis from other bacteria. Lyme arthritis is something you would need to consider often young, young people, any other cause of endocarditis, and because of that sort

of flu like illness with an associated rash, or maybe arthralgias. There are a lot of viral infections that one might need to consider like acute Hepatitis B, herpes simplex,

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maybe a primary episode, acute HIV, parvo virus, Zika, chikungunya, all of which can present with kind of flu like nonspecific illness, arthralgias, and rash, and a few others are listed here. Rheumatic fever, something you might want to consider. Reactive arthritis, maybe after an infection with chlamydia, which used to be called writers could have rash And arthralgias or even a frank arthritis. And again, here's again from up to date giving kind of a description of some of the common considerations in the differential and how you might distinguish these. So gonococcal arthritis is typically abrupt, as is reactive arthritis, whereas autoimmune arthritis ease are typically more insidious. And of course, the rash, the characteristics of the rash can be helpful. And obviously, if you see gonorrhea on something that is the most helpful, of course, management has has changed over the years, we now treat for a much shorter period than we did when, when I was seeing all those cases. And the management is to start with IV or parenteral, at least penicillin or Ceftriaxone. Generally, the dose is one gram IV for at least 48 hours or until the patient is clinically improved. And then you could switch to the lower dose of the currently recommended 500 milligrams I am daily of Ceftriaxone. Or if you had an organism that grew on culture, and you knew the susceptibility, you could potentially use fixing, or even ciprofloxacin, doxycycline, doxycycline, or amoxicillin to complete out seven days. For Frank arthritis, the recommendation is generally to treat for a longer period. This is again sort of consensus from up to date seven to 14 days, although you do need to follow clinically. And sometimes these these cases go go on to treat more like a typical septic arthritis from another organism so maybe two or three weeks or even four weeks. And again, you could use an alternate such as ciprofloxacin, but only if you had susceptibility data. endocarditis, of course requires a higher dose and a longer course of therapy, the recommendation is for weeks. And for meningitis, the recommendations that I found were for 10 to 14 days, again at meningeal kinds of doses. So I just want to kind of spend a little bit of time on that that was all kind of textbook, what the textbooks say and what we've known about DGI for years and years. But what's new in disseminated gonococcal infection. And this is a chart that you can pull off of PubMed when you do a search. And it shows you how publications have varied over time. So this is 1952 was never mentioned. And then you start to see spurts of reports and you can see we have a little blip in the last couple of years on reports about disseminated gonococcal infection. So I was interested in, you know, what is that about? And most of it is about really epidemiology. So in general, it's been reported to be .5 to 3% of cases, that's been kind of the party line in the textbooks for more than 20 years. I generally think of it as being less than 1% of cases. Historically, it's been more those who are born female than those who are born male, again with that association with menstruation and more likelihood of having untreated infection for a few weeks because of a lack of symptoms. And historically, it's been a young age. But as the epidemiology of mucosal gonorrhea has changed a bit, there's been somewhat of a change in DGI epidemiology. And in the last few years, we've seen

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a rise in reports of extra genital infection, particularly among men who have sex with men. And these infections are less likely to be symptomatic than standard urethral infection in persons

with male reproductive organisms. So there's a bit more asymptomatic infection across across individuals. And there have been recent reports of local clusters of infections, and I'll go through some of those with you. So one was published in it was reporting on cases in Michigan in 2019, in the MMWR, and this report was generated because they noted three simultaneous hospitalizations for disseminated gonococcal infection in Kalamazoo, Michigan on the same day, so that that was particularly remarkable. And so that generated a big investigation and they actually looked back at 27,000 cases of gonorrhea from the prior 18 months, and they were unable to find any other clusters of infections except what ultimately ends up being associated with this day in, in Kalamazoo, so in their review, they defined a confirmed case of DGI being a sterile site with gonorrhea. So blood is synovial fluid or CSF, or a probable case where they had a positive naat from a mucosal site, plus classic symptoms of DGI, such as tenosynovitis, poly arthralgias, arthritis. And they end up with 13 confirmed cases and three probable cases, from that Aug. 12, which was the day the three cases were admitted through December of that year. So they cluster over that five months. And this is what they found that is sort of a bit unusual, compared to the classic reports. So they ended up having slightly more male cases than female cases, whereas classically, it was the other way around. The age was a fairly wide 16 to 52. But the medium was a bit older than had typically been reported. At 39, there was an association with a lack of housing of 25% of the cases, and associations with drug use, which you can see down here at the very bottom. And the most frequently used drug was methamphetamine. They did try to do some partners, some find maybe links within the drug using contacts. And they found some 27 contacts, but they were unable to find any link cases. And they did do molecular analysis of the gonorrhea that was isolated, and there was a high correlation. So it seemed to be an organism from the same same clade. And that even though they looked for 18 months, other than these cases, they didn't find any other cluster. Then if you look in not actually in the literature, but but sort of through Google search to see about health alerts, there's health alerts that come out, that was in 2019, and 2020. There's a health alert in California, where they are noting increasing reports of disseminated gonorrhea as well. Again, in 2021, you find different locations in California, issuing local health alerts about rises in cases, and most recently, in February of this year, and now in addition to recommending being conscious of screening and not and resuming screening after COVID, they actually say that there has been an association with drug use, especially methamphetamine that they're seeing in California as well. So they are now including individuals who use meth to be individuals who should have GC screening because of these rises in cases.

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There have also in the past three years with that bump in the literature, numerous reports of endocarditis, osteomyelitis, septic arthritis, including prosthetic joint arthritis, some associations of with eculizumab and abscesses, various abscesses reported. And that one case I just want to run through is the 16 year old with five days of left wrist pain and redness couldn't make a fist also had bilateral ankle soreness and a lesion on the left foot seen here circled was febrile and had point of point tenderness at the base of his thumb, he had no urethral discharge and that lesion that I mentioned. So here you can see at an elevated white count, slightly elevated CRP and 16. So he was treated with IV clindamycin. With concerns I think for a septic arthritis, perhaps due to staph or strep, and had no improvement over four days, further history was taken and they realized that this patient had had multiple partners. So on day four of

hospitalization, has STI testing, and ultimately has a positive urine with a clear video positive naat GC as negative as a positive pharyngeal GC test. And ultimately goes to the OR for exploration of the thumb has joint fluid with a negative culture and is treated for both DGI and that urethral chlamydia. And this group reported on this case, and a similar case with the rash and in panel a over there, where they use meta genomic sequencing to identify the organism so they they basically did whole genome sequencing off of joint fluid and we're able to find gonorrhea. So, so this was using a more sensitive test although that in both of these situations, they were fairly certain because they had a mucosal gonorrhea test. And then in Canada, in Manitoba, they've had a remarkable rise in both gonorrhea cases, as was described by CDC. And in DGI cases where they went from five positive cases 2013 To 2015 to 95, positive cases 2017 to 2020. And they just have reported in a webinar last week but but not yet published, their molecular analysis that showed a new clade a new distinct clade in their area that was associated with this bump in cases. And that same group has also did use molecular testing, although they just used a naat testing. And they were able to use their, as a study, they use their Optima TMA test on joint fluid, they had 177 cases of joint fluid. And what I've highlighted are those that were GC positive on the abdomen test, so it's not FDA approved to use for synovial fluid. And it was positive for four where they knew that the culture was also positive. And they found an additional eight that were culture negative for GC, but naat positive. On the other hand, they had another large more than 100 cases of septic arthritis that were due to other organism, other organisms that other than GC, where they had positive cultures where the GC naat was negative, and the culture was positive for either staph strep ecoli, or they had synovial fluid that was negative altogether, and was also negative on that. So they were quite concerned that even though they had had, as I said, they had gone from five to 95. Culture positive DGI cases, if the NAAT is really picking up almost twice as many, there might be additional cases that they're missing.

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So in conclusion, DGI remains, I think, somewhat difficult to diagnose, you have to have a high index of suspicion and be familiar with the syndromes that it causes. You want to think about dermatitis synovitis, arthralgias, and septic arthritis. And even considering it with endocarditis, meningitis, and abscesses are less common. Both host and organisms seem to be important. There are these increasing reports of cases from some locations such as California, Michigan, and now, Manitoba. And there seems to be at least in in these two, two areas in the US in association with methamphetamine use, it is recommended that blood culture and that testing at all sites be done. And I think in looking at the literature, the mucosal tests were positive more often than in the distant past when when we only had access to culture. The US, the CDC, because of the rise in cases in California and Michigan, has put out a new case report form for surveillance that is fairly detailed, and they are asking that any individuals who have isolates that are associated with a DGI case that you send those isolates on to your health department, and who will send it on to CDC for analysis. So in New York, that would be sending it to Wadsworth, we in New York, as far as we are aware, have not seen sort of clusters like this, although locally, we've seen in the last two years, at least a few cases of arthritis and one case of endocarditis that I'm aware of. And then one last thing, this is a you can find. I've got the link up here. And if you Googled disseminated gonorrhea frequently asked questions. It's a very helpful handout that was put out by the California Prevention Training Center in response to the

the clusters of cases they're seeing. So I'll end there and see if there are any questions. These are the same. Links to the cards that were mentioned.
[End Transcript]