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WHAT'S NEW? HIGHLIGHTS FROM THE CDC 2021 STI TREATMENT GUIDELINES

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[video transcript]

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So hi everyone. Again, my name is Ashita Debnath PGY2 infectious diseases pharmacy resident at the University Medical Center. For this presentation we'll be discussing the class of drugs for the Nitroimidazoles . And looking beyond just metronidazole. I have no disclosures for myself. The learning objectives are listed on this slide. By the end of the presentation, you should be able to compare and contrast Metronidazole, tinidazole and secnidazole and summarize the 2021 CDC updates in regards metronidazole use in treating trichomoniasis and lastly, evaluate allergies and identified drug interactions and adverse effects related to metronidazole. Let's first begin by reviewing the Nitroimidazoles drug class. These agents can diffuse into the organism inhibit protein synthesis by interacting with its DNA and causing a loss of helical DNA structure. This results in cell deaths therefore these agents are typically classified as bactericidal nitrile imidazoles are active against gram positive and gram negative anaerobic bacteria and they are also active against protozoa. This chart summarizes the main differences between three agents we will be discussing today, as depicted on the left. These agents are considered Nitroimidazoles because they have a nitrogen group and an imidazole group in their structure. These agents are similar in your safety profile, they are generally well tolerated. They do have some central nervous system adverse effects associated with them that are mainly with prolonged therapy, but they're generally reversible. And we'll discuss a little bit more in terms of the safety profile of this drug class later in this presentation. In terms of the indications since metronidazole has been approved for much longer, there are more FDA approved indications and more places where it has been studied. So this includes triggering the nicest bacterial vaginosis, H. Pylori, pelvic inflammatory disorder, along with a variety of other infection caused by anaerobes or protozoa such as intra abdominal infections and skin and soft tissue and actions. To knit is all and seconded is all do share the indications of triggerman, diocese and bacterial vaginosis with metronidazole. However, metronidazole is really regarded as the drug of choice due to the fact that there's really only limited data evaluating the safety and efficacy of tinidazole. And second, it is all when compared to the years of data that we have with much dissolve. In addition, these agents are typically more expensive, so metronidazole, its average wholesale price is about 60 or 280 cents per tablet, whereas tinidazole is about five to $10 per tablet. And for a two gram dose, it's potentially about $20, where a second it is all just typically dose at two grams in a single dose. That's about $340 tinidazole has a couple of other indications where it has been studied as well such as h pylori infection and non gonococcal urethritis. A potential advantage of tinidazole and SEC that is all over metronidazole is that they have longer half lives compared to metronome is also tinidazole is 10 to 15 hours. Second is all is about 18 to 29 hours compared to eight hours with metronidazole. This allows for the potential to be dosed less frequently. And these have been evaluated as single dose options as well in cases such as bacterial vaginosis. What's also worth noting is that metronidazole comes in multiple formulations, it can be given IV it comes as a tablet capsule oral solution, and it can

also be given topically as a cream or lotion or even a gel, whereas tinidazole and Signet is all are only available as tablets.

04:22

So where does all this information come into play in regards to the recent CDC updates and treating tricking the nine assists. The previous recommendation was the single veterinarian is all two grams given by mouth. However, based on literature, as you can see from the chart on the right, actually a higher risk of treatment failure associated with a single dose specifically in HIV uninfected non pregnant women. This says a specific systematic review found an overall 87% higher risk of treatment failure with a single dose therefore the guidelines updated the recommendation to a multi dose regimen of metronidazole 500 milligrams by mouth twice daily for seven days, there may be a concern that a multi dose regimen in comparison to a single dose can actually allow for non adherence inundation. But the data that looked up this really suggests otherwise. The alternative regimen listed includes tinidazole, a two gram dose of just one time dose, and then for men, it's still recommended a to use metronidazole two grams po once. There's also recommendations in cases of patients presenting with a hypersensitivity reaction to metronidazole. So if a patient has a history of urticaria, angioedema, or anaphylactic shock, it's first necessary to evaluate for each true allergy. So when did this patient have allergy? Was it to the metronidazole? Or were they on another medication? How long after the dose? Did they have a reaction? Have they tolerated the medication since so if the if the patient didn't have like an immediate reaction or if a patient reports the symptom to be stomachache, it's really important to evaluate if it's a true allergy and whether or not patients can receive the metronidazole. If it is a true immediate IGE mediated response, the two options that you have is to use another agent which may be using second line therapy, or the other option is to desensitize the patient. In cases like Trichomoniasis, or the alternative is tinidazole, which, as mentioned, is in the same class and has similar structure to veterinarians all we have to look into cross reactivity. So there's limited data in terms of cross reactivity with tinidazole arcsecond. Second, it is all specifically with tinidazole. There has been some cross reactivity reported by oral tests and at least three cases, there was one case or sport case report that looked at metronidazole cross reactivity with techni dizzle. And they found no activity noted. However, again, we really have less experience with these more recent agents. And since they are more expensive, we potentially have to rely on the other option of desensitization. So desensitization is a process that allows for gradual introduction of the offending agent in this case, metronome is all to allow the patient to temporarily tolerate the medication. It allows for more controlled degranulation of the mast cells and basophils. But it's important to remember that in these cases, the patient still remains allergic to the medication. This essentially allows for the medication as mentioned before, to be used well, alternative agents that may be associated with greater treatment failures or agents that are unavailable, such as a pair of Meissen or betta Dean. In cases of Trichomoniasis, desensitization may be an option for those patients. However, there's really limited data on in terms of establishing protocols that have been used for desensitization to metronidazole. So these are two examples of protocols that have been published. These protocols increase in a logarithmic fashion about every 20 ish minutes to allow the patient to achieve the concentration at the full dose at the end. These protocols are from the

90s, so their target dosing is a bit different from the recent CDC recommendations. The protocol on the left is an oral desensitization protocol. That is administered over a 24 hour period. For the smaller doses as you can see about step one to step five. These are in volumes. So we don't have tablet strengths that allow for this small concentration. So these doses have to be compounded patient specific. On the right is an intravenous metronidazole desensitization protocol that transitions into tablets later.

09:14

There was one study that reviewed about 59 women who were treated for tricking the nicest where there was this potential for these patients to have reactions such as urticaria, and facial edema and their history. Out of the 5941 women were treated for tricking the diocese 37% were treated with a metronidazole desensitization protocol, and all of them were successful. Eight of them received the oral protocol and seven receive the IV protocol, which were listed on the previous slide. 42% of patients were treated with an alternative interventional agents such as Paramon Meissen or betta gene, and in these patients there was only about a 30% success rate 22% of the patients He had no clear history of hypersensitivity and were actually treated with a standard metronidazole or tinnitus all regimen. And again, this last bullet really highlights the importance of inquiring more about the allergy and assessing whether or not that specific medication can be used. There has been one protocol that was published recently that looked at tinidazole desensitization on one patient. This patient was any unable to tolerate oral or IV metronidazole. And they actually ended up getting short of breath which this specific study characterized as non life threatening. They tried conducting tinnitus all desensitization, which the patient was not able to tolerate. So they decided to create a desensitization protocol for tinnitus all. In this case, it was successful. However, one limitation of this protocol is that they, they ended up turning, determining that their shortness of breath was more non life threatening, which in my opinion, probably a little bit life threatening. So in whether or not this can be applied to a patient that presents with a true severe allergy is kind of questionable. And lastly, the investigators also pre medicated the patient prior to the final dose of tinidazole with diphenhydramine. So if this were to ever be treated another patient this should be taken into account. to loop back about some of the other adverse effects that are associated with this class of medications. The most common reactions that are ordered include nausea, diarrhea, dry mouth, and patients can also complain of this metallic taste while taking the medication. These reactions are dose dependent, they're relatively mild and they are reversible. The more serious central nervous system effects such as attack, encephalopathy, seizure, and peripheral neuropathy are reported with more prolonged therapy. And they are mainly found to be reversible as well. Some rare but serious effects. Out foreign patients include some allergic responses such as Steven Johnson Syndrome, and other effects like myopia and word vision and ototoxicity. metronidazole induced peripheral neuropathy is probably one of the more serious effects that may deter clinicians from using metronidazole. The mechanism by which this happens is not really understood to this day. A systematic review from 2018 found peripheral neuropathy to be extremely uncommon in patients who receive short courses of therapy, which was defined as four weeks or less. Where we really see this peripheral neuropathy in patients is in patients who receive more than 42 grams total, essentially more

than greater more than four weeks of therapy. In this case, the incidence was 18% and those receiving prolonged givers are sent in patients receiving less than four weeks. If a patient develops peripheral neuropathy, it's important to consider stopping the agent if possible, and then treating the peripheral neuropathy with physical rehabilitation as well as treatment of the neuropathic pain. Whether or not tinidazole insect is also shared this potential adverse effect due to the similarity in their structure and just similar safety profile they potential however, in these cases are in the indications were attended as on segment as all may be used, they are again given as a short course or even a single dose, so they may present as an option in those cases. This table includes examples of drug interactions to be aware of when initiating a patient on a Nitroimidazoles . Some to highlight on this chart include in the order on where the levels of immune are on may be increased. So it's important to monitor for four sides or ventricular tachycardia

14:11

immunoassay immunosuppressants as well are drug interactions like tacrolimus and cyclosporine, where those levels of tacrolimus and cyclosporine maybe these as well. So, those doses, the level should be monitored and the dosage should be adjusted accordingly. Warfarin is a another drug interaction to be aware of. So concomitant use can increase Warfarin levels, so it's important to monitor the INR and watch out for any bleeding and the patient and to adjust the warfarin doses accordingly. Sip three four inducers, which are commonly like feel barbital, rifampin and phenytoin may increase the elimination of metronidazole. While SIP green for inhibitors such as some adenine, a decrease the level of MetroNet is also this should be taken into account In terms of looking at the safety effect of the safety profile of metronidazole, as well as the efficacy. There also have been some case reports about metronidazole and its potential to prolonged, etc. This is specifically in cases where patients are also on medications that prolonged QT C as well. So, in those cases, it's important to monitor by using EKG and potentially adjust therapy if needed. Another topic where we have a bit more information about is the use of metronidazole in pregnancy, so the package insert recommends avoiding metronidazole use during the first trimester due to cases of fetal malformation. However, published data suggests that metronidazole therapy really poses a low risk in pregnancy. There's been multiple cross sectional and cohort studies among pregnant women evaluating both the single dose as well as the multi dose regimen, and they found no evidence of tratto genericity or mutagenic effects in the infants. Therefore, the CDC recommends to weigh up the risk versus benefit in patients who are pregnant regardless of their pregnancy stage. If they're symptomatic of Trichomoniasis, they should be tested and they should be treated as the benefit is that there is symptomatic relief, it can reduce sexual transmission. And although perinatal transmission of Trichomoniasis is uncommon, treating the trick in the diocese can prevent any respiratory or genital infection in the newborn. metronidazole is also secreted in the breast milk. Studies have looked at, you know, oral therapy and a women and looking at the plasma levels of the drug metabolites in the infant. And they have found that there are measurable levels in the infant, but they're a lot less than the maternal plasma levels. There also have been, there also has been no evidence of any adverse effects that infants but clinicians may still advise mothers to defer breastfeeding for about 12 to 24 hours after maternal treating with

metronidazole. In terms of tinidazole and segni, dizzle. There's only limited data involving human subjects in general. So in terms of the animal data that is out there, it indicates a moderate risk associated with these agents. Therefore tinidazole On second is all should be avoided in pregnant women. And breastfeeding should be deferred for about 72 hours after the single oral dose. Resistant patterns in Nitroimidazoles may not be well identified, because we typically don't perform sensitivity testing. There are reports suggesting about four to 10% of resistance to metronidazole in cases of tricking the diocese and there was one study that looked at tinidazole resistance and reported less than 1%. There's also a few case reports out there suggesting that tinidazole is effective in treating patients with refractory Tricom nicest foreign patients have failed metronidazole treatment. In this specific retrospective review of 24 patients, they actually found a 92% cure rate in using higher doses of oral or vaginal tinidazole. In terms of cross reactivity with resistance in the metro middle class, this is not very well documented in literature. So we're really unaware if whether or not there is resistance to metronidazole if the other agents can potentially be used other than the case reports that I've suggested.

18:38

Lastly, I want to discuss the old ethanol warning. It was believed that metronidazole can cause this die self brand like reaction on ethanol metabolism, which leads to symptoms such as severe nausea and vomiting, and therefore it's recommended it was once recommended to counsel patients on metronidazole to avoid alcohol use during therapy. However, mechanistically when you look at it thyself gram inhibits hepatic aldehyde dehydrogenase, which results in an accumulation of blood acetyl hot acetaldehyde concentrations after ethanol consumption. And when looking at the metronidazole mechanism, it doesn't have the same mechanism. So there's really this controversy about whether or not this is an actual risk and whether or not this nature of the interaction is real. A review regarding alcohol consumption during metronidazole treatment reported that there was really no evidence of a dice off gram like reaction. And what really has been determined is that this old warning was based off of lab data and individual case histories. And it's likely that the ethanol alone or certain ethanol independent side effects such as nausea and vomiting associated with metronidazole might be explaining the suspicion of the deisel for him like effects. Therefore, the need to counsel patients on refraining from alcohol use while taking metronidazole at this point is really unnecessary and this is one of the recommendations included in the CDC updates. To summarize all that we discussed today in the class of nature imidazoles Jeanette is on second it is all are pretty similar to Metro tonight is all except that except that they have longer hoplites. And since they're relatively newer they have been studied and a few indications. The class of nitro metals overall are generally well tolerated, but adverse effects and drug interactions should be evaluated for patient. There are still limited published literature on desensitization protocols for metronidazole. And as we mentioned, there was that one report on tinidazole. And in cases where you know, alternatives may not be the most beneficial for patients such as with the indication of trek from analysis, it may be necessary to follow a desensitization protocol to allow the patient to temporarily tolerate the regimen. Due to the lack of reported evidence, the ethanol and metronidazole warning should no longer be a consideration during counseling. And lastly, it's important to remember the update in recommendation and trick of an ISIS treatment specifically in HIV uninfected non

pregnant women that ace multidose regimen of metronidazole. So seven days and metronidazole is recommended over two grams as a single dose due to better curates. That's all I had for today. I can take any questions.

[End Transcript]