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TREATMENT OF TRICHOMONIASIS – WHEN YOU CAN'T USE METRONIDAZOLE

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[video transcript]

- [Instructor] Okay, the title of my presentation is The Treatment of Trichomoniasis When you can't use Metronidazole I'm going to review the CDC guidelines and the alternative therapies for treatment of Trichomoniasis. Trichomoniasis in the the most common non-viral STI in the United States infecting approximately 3.7 million people. It is currently believed that women are thought to be more infected than men. It's called Trichomonas vaginalis which is a single celled protozoan parasite. It has a flagella, which is a tail-like structure which causes its motility. It's the only protozoan that infects the genital tract. It can cause preterm rupture of membranes and preterm delivery in pregnant women. And it is an increase risk of HIV acquisition in transmission. So, in 70% of the cases, it can be asymptomatic. However, it can also cause vaginitis, as you see on the right, from a patient that we had in clinic. The yellow-green discharge is typical of the vaginitis or frothy grey discharge. It can cause pruritis. On the picture on the left, you can see cervical petechiae, which is a classic presentation for it called Strawberry Cervix, but actually only happens in less that 2% of cases. It can also be found in the bladder, skene's gland, and bartholin glands as well as the urethra. And this is why organisms may not be susceptible to topical therapy. In men, it can affect the urethra, prostate, and epididymis. The rest of my presentation will be dedicated to the treatment of Trichomoniasis. The current CDC recommendations are for 2 grams of either Metronidazole or Tinidazole orally times one dose, or an alternative regimen of Metronidazole, 500 milligrams twice a day for seven days. Metronidazole has actually been used since the 1960s for the treatment of Trichomonas. However, the recommendation for Metronidazole dosing in the CDC guidelines is actually based on these three studies. The first study was done by Spence at Allegheny University Health Sciences in Philadelphia. 167 women enrolled with Trichomonas were treated with either point five grams, one gram, one point five grams, or two grams of Metronidazole and followed up in seven days to find cure rates. Cure rates were determined by wet cref and culture. Overall conclusion from the study was that two grams and one point five grams were equivalent in cure rate. It's also significant to note that three patients vomited after Metronidazole and two out of three of them were the ones who received the high dose of two grams. The last two studies were actually conducted at the same location, at St. Bartholomew's in London. The Thin study enrolled 96 women who were infected with Trichomonas. They received either two grams, orally times one of Metronidazole, or a 500 milligram, twice a day dosing for five days. They were followed up in 14 days with wet prep and culture for cure rates. Overall findings from the study were that the two grams of Metronidazole versus the 400 milligrams twice a day had similar cure rates that were not significantly different. 98.3% in the two gram dosing, and 92.4% in the 400 milligram twice a day for five day dosing. The last study, by Gabriel, was a randomized trial that was done on 95 women who were infected with Trichomonas. The comparative arms were two grams of Tinidazole versus two grams of Metronidazole. And patients were followed up with microscopy and culture. The overall findings were that 95% of the patients were cured with Tinidazole and 97.5 were cured with Metronidazole. So based on these references, the cure rates were approximately ranging from 84% to 98% with Metronidazole. I included the guidelines again, which are Metronidazole, two grams times one dose, or the alternative regimen of Metronidazole, 500 milligrams twice a day for seven days. There are several references for Tinidazole, and I'll review a few of them. Tinidazole, I already discussed in the Gabriel study. The first study showed that two grams of Metronidazole and two grams of Tinidazole were equivalent in cure rate. The next

study was actually a double-blind randomized trial in Bangkok, where they split the dose of Metronidazole and gave 800 milligrams twice a day for two doses and compared it to two grams of Tinidazole. The cure rates for both were similar. Tinidazole actually had a 100% cure rate versus Metronidazole, oops, sorry guys. Yeah, Tinidazole had 100% cure rate and Metronidazole had a 98.5% cure rate. The next study, done by Apte, was a multicenter survey study where they surveyed several countries in Asia, including India, the Philippines, Indonesia, New Zealand, and they studied patients who received Tinidazole for various infections. In the Trichomonas part of the study, 859 women were infected with Trichomonas received two grams of Tinidazole, and the cure rates were documented at 95.2% The last study is a meta-analysis that was in the Cochrane database, and it included 54 studies. It looked at the therapies for Trichomonas and found that a single dose of Metronidazole or Tinidazole had approximately 90% cure rate, and that intravaginal therapy was suboptimal to all therapy. In the CDC guidelines, cure rates for Tinidazole, based on the literature, were 92-100%, and the CDC guidelines recommend Tinidazole, 2 grams orally in a single dose. Next, I'm going to talk about allergies. What do you do if your patient has an allergy to Metronidazole or Tinidazole? Metronidazole or Tinidazole are nitroimidazoles. You can see here highlighted, they have very similar structures. And there are actually a few case reports which suggest cross-reactivity. This is an article, the summary of providers who called the CDC hotline from 2003 to 2006 for patients who were allergic to Metronidazole. You can see that there were several significant reactions. 6.9% of patients had anaphylaxis, 11.3% had facial edema, and a significant number, 46.5% of patients had hives. There were some that did not have significant reactions, like gastro-intestinal intolerance, which would not be included as IgE mediated reaction. For those patients with IgE mediated responses, which would be, for example, facial swelling, angioedema, which is swelling of the tongue, hives, shortness of breath, stridor, anaphylaxis, desensitization can be undertaken. It is the recommendation by the CDC. And here's a protocol that was recommended from the study. I will revisit this study later in my presentation. So, now that we've covered guidelines in allergy, I'm going to delve into the more nebulous area of recurrent and persistent Trichomoniasis. I'm sure this is what you've all been waiting for. The most important thing is before you call something recurrent or persistent Trichomoniasis, you really need to rule out the reinfection. 'Cause if the partner isn't treated, the patient could just be continuing to get reinfection with Trichomoniasis. After following the standard treatment guidelines, what's next? The CDC recommends an algorithm for following standard therapy, which I'll review now. I'll go through the algorithm following standard therapy. Once you've given your patient two grams of Metronidazole or Tinidazole, and maybe repeated that treatment and they still have Trichomonas, you can give them 500 milligrams of Metronidazole twice a day for seven days. If the patient continues to have a Trichomonas infection, you can then give them the two grams that are recommended, Metronidazole or Tinidazole, for an extended course of seven days. Following that, if they continue to still be positive for Trichomonas and are symptomatic, you can test for susceptiblity. This is a picture of the InPouch culture which you inoculate with the Trichomonas and can be sent to the CDC. The CDC does include their telephone number and their website for attaining these cultures and for mailing them to them, so they can do the susceptibility testing for Metronidazole and Tinidazole. Lastly, they recommend the high dose of Tinidazole, two to three grams times 14 days, in an attempt to overcome resistance and this is often given with intravaginal Tinidazole. Great, so when that doesn't work, what's next? But these are some of the alternatives and definitely not the exhaustive list of medications that have been used in the history of Trichomonas treatment. Now, as promised, here's the Helms article revisited. This is the article where the providers called in with patients who had

Metronidazole allergies for advice on how to treat them. On the right, you can see alternative intravaginal therapies were given. I will give the caveat that this was provider decided. This was not the CDC recommendation. On the bottom you see cure rates. So these are the patients they were able to follow up with, and you can see that the cure rates are actually pretty poor. For Betadine douches, it was 75%; Paromomycin, 25%; Clotrimazole, 50%; and Furazolidone, zero. The numbers are small though. But if you look at the left side, where patients actually underwent Metronidazole desensitization, they had a 100% cure rate. And this is why desensitization is really the recommendation for patients who have a Metronidazole allergy. The data for some of the alternative therapies is really limited in case reports, but I will review some of the literature. The one published case report using the Betadine intravaginal therapy for a resistant Trichomonas. This was a 36 year old female with a three month history of vaginitis, yellow discharge, and results were positive for Trichomonas. She was given an exhaustive amount of therapy. She got Tinidazole which was repeated twice. She got Flagyl, 300 milligrams tid for seven days. Her husband actually received treatment as well for 14 days and did have a negative urethral swab. Susceptibility testing was done and it did show resistance. The patient ulitmately got Metronidazole, 1 gram tid, plus intravaginal nightly Betadine douches for 14 days. There are several case reports which did show the benefit of the Betadine or the Povidone-iodine douches. However, case reports are biased in that they do select for positive outcome. Trichomonas can be a self-limiting disease and many of the case reports do include a large combination of therapies. This is a study by duBouchet that looked at Clotrimazole. Patients were randomized to Metronidazole, two grams orally, Clotrimazole, which is an anti-fungal medication, 200 milligrams intravaginally for seven days, and various suppositories, as you can see. The results of the Clotrimazole were not encouraging, with 11% patients, that's five out of 45 patients were cured for Trichomonas. The next study looked at Nonoxynol-9, which is a contraceptive. It was studied in a randomized trial where patients with Trichomonas were given two grams of Metronidazole, or 150 milligrams Nonoxynol intravaginally for three nights. The study, unfortunately, was ended early due to the poor results in the Nonoxynol arm. Only three out of 17 patients were cured. So, in terms of alternative therapies, CDC guidelines for the above therapies, states that they really did show minimal success and they are not recommended. But there is hope. The alternatives that the CDC does show are anecdotal benefit for boric acid and Paromomycin. This was a case report of two cases of patients who had resistant Trichomonas, received a battery of treatments which included Metronidazole, acetic acid, Paromomycin, Clotrimazole and failed. The first case, the patient received a combination of Clotrimazole intravaginally, alternating with intravaginal boric acid, 600 milligram capsules for six weeks and was able to obtain a cure. In case two, the patient received, at the end of their treatment, boric acid, 600 milligrams twice a day, plus gentian violet intravaginally for a month, and was able to eventually obtain a cure. Lastly, I'm going to discuss Paromomycin. Paromomycin also does have case reports, and we have used it recently in our clinic and have recommended it periodically on our CEI hotline. This case series was published in CID in 2011 with two patients who had symptoms for years with resistant Trichomoniasis. You can see the burden of the disease on these patients. The first patient was a 54 year old woman who had seven years of Trichomoniasis. It was treated with Metronidazole, Tinidazole, she was given it intravaginally. She actually received Paromomycin earlier in her course. They set up susceptibility testing and was found to be resistant to Metronidazole and Tinidazole. This woman received Furazolidone, Nonoxynol-9, Tinidazole, Betadine douches and potassium permanganate. So basically, all those alternative medications that I had discussed previously. Her last regiment was that she received Paromomycin

intravaginally, 250 milligrams in a five gram cream, which is a 5% dose. And she received it nightly. Plus Tinidazole, one gram, three times a day orally for 14 days. This combination resulted in a cure at six weeks by wet prep and culture. The second patient was a 29 year old who had Trichomonas for two years and was symptomatic. She had six treatments of Metronidazole and three treatments of Tinidazole, was found to have a resistant Trichomoniasis infection. Eventually she underwent the same therapy of the 5% intravaginal Paromomycin cream nightly, plus the Tinidazole, one gram, three times a day orally for 14 days. And she was cured at six weeks, and again, when they check her at three months, she was still cured. Lastly, I included a third case report of a woman with discharge for 10 months. She again underwent multiple therapies. The reason I included this case report was to highlight that she received Paromomycin intravaginally, 250 milligrams for seven days. However, she developed ulcerations. This is a caution with these patients as Paromomycin can cause severe ulcerations and sloughing of the vaginal mucosa, which ultimately will be the reasons that it does cure the Trichomona infection. However, patients should be advised that, if they start this therapy this could happen. If they start to develop ulcerations and sloughing of the vaginal mucosa, they should stop therapy. And these symptoms will resolve with stopping the therapy. The patient was ultimately cured when checked for wet prep and culture at the six week period. Now, in conclusion, Metronidazole or Tinidazole orally are recommended treatments for Trichomoniasis. If a patient does have an allergy to these drugs, desensitization is recommended by the CDC. In cases of resistant Trichomonas, first, the attempt is to overcome the resistance with a higher dose of Metronidazole and Tinidazole. However, if this fails, alternative therapies, anecdotally, Paromomycin and boric acid have shown some benefit. But this is an area that does require further research. These are my references. Thank you. And I'd be remiss if I didn't make a plug for our hotline. The CEI phone line is 866 627 2342, extension four, and you will either get to talk to Dr. Irvine or myself. Oh, sorry. Actually it's 866 637 2342 I apologize.

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