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TRANSCRIPT - GR 01 19 24 "***UVA Cdiff Update*** " Stacy Park, MD and Greg Madden, MD from the University of Virginia

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Internal Medicine Grand Rounds

- Hello! Everyone. Welcome to medicine grand rounds.
- Today we have a very exciting discussion by 2 of our fantastic, infectious disease physicians. First, we have Dr. Greg Madden. Dr. Madden obtained his medical degree at Uva. He then left to complete his medical residence residency at Yale, followed by an fellowship and infectious disease, and masters in data science at Uva he is an avid teacher who gives education and medical students, residents and fellows. Dr. Madden has had numerous awards, particularly for his research, and this scholarly work is focused on healthcare associated infections with a special focus on Ceta. If additionally, today, we are very lucky to have Dr. Stacey Park with us. Doctor Park also obtained her medical degree at Uva. This was followed by internal medicine, residency, and infectious Diseases fellowship at Uva. A lot of parallels here today. She has been recognized for her excellence in research and clinical care. She is also an educator across the spectrum of learners, and her scholarly work has an emphasis on antimicrobial stewardship and nosocomial infections. Please join me in welcoming Dr. Greg Madden and Dr. Stacey Park.
- Thank you for that introduction. So this is our plan. We see if this is working
- this. So I'll start today talking about the diagnostic challenge that can be C diff particularly in hospitalized patients. And why that matters potentially in terms of overtreatment how we've partially addressed diagnostic challenges at Uva through diagnostic stewardship.
- And then I wanted to talk a little bit about kind of the recent evolution of recurrent C diff management especially in in the past few years, and then Dr. Park will talk about the most important aspect of C. Diff prevention, and that's an microbial stewardship discussed through a few cases that we've had at Uva clusterioities formerly clustidium, diffuse and antibiotic resistant spore forming gram positive rod makes antiseptic resistant spores that can persist for months in the environment on surfaces and colonize the gut allowing them to spread especially within hospitals and nursing homes, infecting patients with vulnerable gut microbiomes after taking antibiotics, and then it produces a toxin, causing a really significant watery diarrhea, and then it produces it leads to intensive care, and up to a third of patients hospitalized with C diff infection, a few percent will have to have surgery to their colon, and about 5% of Cdf infected patients in the hospital will die with their infection.
- And so the first challenge of C. Diff is diagnosing it. Given. There's no available tests. Unfortunately, that reliably differentiates colonization from an infected state.
- Even pseudo membranes on colonoscopy, which are often thought of as pathenemonic can be caused by things besides, C diff. Pcr is highly sensitive. But it's not specific. The definition of C diff colonization that most folks use is just a positive c pcr which detects the Tcd toxin gene, and just tells you that you have a strain of Cdf capable of producing disease. The current, I call it tarnished gold standard is the cell site. Cytotoxic neutralization assay with something like a 48 h turnaround time. It's not feasible for clinical

use, and still has issues with false positives and patients who are colonized. Patients colonize with Cdf can have toxin in their stool.

- And whatever sensitivity or specificity is quoted with a test, you always have to think what it was compared to as the ground. Truth? Because none of these tests are perfect arbiters. What can be helpful is multi-step testing? I pictured on the right which we switched to as an institution. From Pcr only testing beginning, February 2020.
- The idea is to optimize the predictive value of the toxin enzyme immunoassay, or eia test, which is just a colorometric test shown here similar to a rapid covid.
- By only testing patients for toxin or Pcr. Positive, and then you present clinicians with both results, and then let them decide whether or not to treat which has its own risks and benefits, which I'll discuss. There is a new generation of tests. Coming about, which is just a more accurate and sensitive way, and a quantitative of measure of toxin in the stool. And it uses a technology called single molecule array or Samoa. But I would argue still doesn't like address. The ground truth problem of C diff toxin tests in general, and it's difficult to find a cut off that truly differentiates infection from colonization. So the key here is symptoms with C diff, and of course the primary symptom was C. Diff. Infection is diarrhea and the table on the left is from a clinical, infectious disease. Review article where they rounded up every quality study they could find regarding diarrhea in hospitalized patients, and C. Diff is by far the most common infectious cause of antibiotic associated diarrhea.
- But in the hospital, but non infectious causes far outweigh C diff, and in certain hospitalized groups diarrhea is the rule rather than the exception. For example, up to 80% of stem cell transplant recipients will have diarrhea while they're receiving things like melan during their induction or C diff happens to be proportionally half as likely to be the cause, and in addition to plain, non-infectious antibiotic associated diarrhea, there's a very long list of medications, some of them in the table to the right that can cause both non-inflammatory, but also inflammatory diarrhea, where you'd expect to have a positive fecal lactiferin calprotectin shown here.
- And if you put all this together, consider the following, if you don't have a test that reliably differentiates who's infected, who's not? If you consider roughly, 15% of hospitalized patients coming in the door will have be colonized with Cdf, and therefore have a positive. Pcr, over 80% of hospitals, by the way, including Uva use Pcr based testing cause. It's the most sensitive.
- These colonized patients outnumber infected ones roughly, 5 to one and the presence of diarrhea alone doesn't help us all that much. Because over a quarter of hospitalized patients will have diarrhea of one cause or another during hospitalization. As as a result of all this, historical estimates are up to half, or maybe more, of hospitalized patients who test positive by Pcr might not actually require any treatment. But toxin enzyme immunoassay helps the odds a bit, but isn't perfect. And by the way, this over diagnosis issues not unique to C diff, diagnostic uncertainties. A big problem with other healthcare associated infections. Which is why diagnostic stewardship so important kind of in this context. The same principles apply, for example, when you're deciding to order a ua with reflex culture in a patient with an indwelling Foley Catheter where Pyuria can be caused by the catheter itself, and the rate of asymptomatic bacteria can approach 100, because, you know, the culture is likely going to be positive before you send it. So you know, thoughtful decision making needs to go into whether or not to get the test in the first place and this paper came out in 2,015 and had a lot of people thinking, including myself, that the toxin eia test was perhaps the best arbiter of C. Diff infection versus colonization is pretty cool. Study the author and laboratory, and Chris Pollidge, thinking now is that Duke actually gave a

grand rounds. I think here a little while ago. And he was at an institution at the time that used toxin eia testing, but alone by itself, without pcr, but the lab was in the process of validating Pcr test to replace it.

- And so they started running Pcrs in the background, not yet telling clinicians the results. And so this natural experiment allowed them to compare Pcr positive toxin negative patients or discordant patients who didn't receive any C diff treatment to toxin, positive patients who got treated. And also negative negative patients who we know didn't have C diff. What they showed was that Cdi related complications namely, icu fulminant colitis, mega, colon and death were no different compared to C diff negative negative patients, and that virtually all Cdi related complications. And deaths occurred in patients who were Pcr and toxin pause, pause, and the discordant they also point out that discord and patients all had a kind of similar time to resolution of their diarrhea, similar to C diff negative patients, or more similar to C diff negative patients. But if you look at the data closely, you'll find that Cdi related complications were arbitrated by clinicians that were not blinded to the results of the toxin eia test. And I would argue, we're probably biased by that. And if you look at all cause mortality, the group, with discordant results had almost a 40% higher mortality than Pcr Toxin positive, not to mention 13 of those 162 patients went on to develop a follow up toxin Eia within a month. That was also positive. So perhaps a delay and diagnosis. And there are plenty of case reports out there of patients with fulminance, C. Diff colitis and mega colon that died despite negative negative to repeated negative toxinia tests. This is a small case series and annals of surgery, where they found that 3 out of 15 patients who died of fulminant Cdf colitis confirmed by autopsy, had a false negative toxinia. And so you might be thinking, Why don't we just test everyone with diarrhea, and treat those with a positive Pcr, because it's so sensitive.
- And there are several very good reasons. I will argue why you shouldn't just treat everyone who's colonized with C diff. For one of the most challenging aspects of C diff infection is that it can recur, and with each bout of reinfection the subsequent risk reinfection and treatment for infection, the risk for subsequent recurrence continues to march up, often leading to a vicious cycle of recurrence. And it's important to know that any antibiotic can lead to C diff, and that includes ones we use to treat it because they profoundly altered the microbiome bank. Metro. Even Fedaxam icin can deplete beneficial microbes like firm acute that are related to C diff that naturally compete with it in the gut and even if a patient was simply colonized, treatment could lay the groundwork for a subsequent true infection. This has been born out in mouse models and in one randomized control trial from the early nineties, where they tried to decolonize asymptomatic carriers of C diff and it actually led to higher rates of recolonization. And potentially some infections in those patients.
- The second reason not to treat everyone who's colonized is a misdiagnosis of non c diff diarrhea. As I mentioned earlier hospitalized iatrogenic diarrhea is common, be it laxatives, tube feeds or something else. C. Diff can occasionally be a scapegoat where unnecessarily treating the C diff can cause more problems than it solves. A couple of years ago I partnered with David Smith, Dean of the School of Commerce, and we did a cost analysis, comparing patients with likely true infection versus more likely colonization based on their predicted stool toxin levels measured by their Pcr cycle threshold. We only had the Pcr testing at that time. And to all of our surprise, the patients on the limit of Pcr detection suspected to be colonized with a negative toxin test. On average, their Cdf infections contributed significantly more
- to hospital costs. That patients more likely to have true infection which is not what we expected. Even after propensity, adjusting for all sorts of other pre-existing factors.

- The main difference seen was hospital length of stay. Kind of driving those costs. And our hypothesis was that it was related to misdiagnosis of non c diff diarrhea that led to increased costs. So if you're busy treating C. Diff, and the diary is not getting better. And you're not thinking about what else is causing the patient's diarrhea. You're probably gonna stay in the hospital longer. And all the bad things that come with it. And then third peril of over treatment is vre as its name implies, Andra Cox. I live in the gut and I can't imagine a better way to select for vanc resistance than drinking vancomycin and both oral metro and vancomycin are shown to promote vre so you don't want to use them unnecessarily.
- And so part of the and answer to the diagnostic dilemma is diagnostic stewardship, which is just a system that promotes evidence-based utilization of diagnostic tests. And in 2016 the C diff coalition here at Uva deployed this algorithm. When you order a test in epic based on the latest guidance on testing. There are 2 parts, the first just yelled at you. If you had a duplicate order and the second focused on pre-test probability and symptoms. You can't really have C diff infection without some sign or symptom, namely, profuse watery meaning. It takes the shape of its container diarrhea at least 3 per day, usually coupled with one or more of fever, white count abdominal pain, and usually antibiotic exposure, as the risk factor. And this is built into the C diff order set, and which you're probably all familiar with. There was an education camp campaign paired with this, even a a financial incentive to the residents at the time as part of a Qi project. You probably recall seeing a lot of poop emojis around, demonstrating how only watery, unformed stools should be actually sent to the lab. Otherwise they're rejected.
- And the test is refused by the lab, which is now a standard laboratory practice across the country. This was a big success at the time. We reduced the census adjusted C diff testing rate by 41, and reduce the rate of survey lab surveillance defined hospital onset infections. That report to the Cdc. By almost a third first question, was, was this safe to do to reduce testing? We did a deep dive into C diff related outcomes, including potential delays in testing as evident by follow-up testing and the way that tool was set up it was engineered, so that when clinicians backed out of testing because of the decision support, we were able to capture those as potentially prevented tests. And we could compare those patients to patients with a negative. Pcr, so you knew they didn't have C diff and adverse outcomes were essentially unchanged post intervention, if not better. If you had a prevented versus a negative c diff test, and we notice that. Despite despite this big reduction test, we, there's still a lot of patients getting texted with active laxative orders in place at like actively receiving laxatives. And so we added a laxative alert in 2,019, basically displays any active laxative orders and suggest holding them and then reconsidering, testing in 24 h. And this actually dropped testing by another 22 percent. So a a clinical practice guidelines have caught up with this, and now officially endorse diagnostic stewardship, including some language about laxatives for C diff.
- And they say, if you don't have a robust diagnostic stewardship program, then you should at least do multi-step testing. We now we now do both. And so, alas!
- My favorite quotes ordering a lab test is like picking your nose you shouldn't do it unless you have a plan for the results. You should only be testing patients for C diff with symptoms of C diff infection, who you're really prepared to treat.
- So say you've thoughtfully ordered A. C diff test in your patient who has symptoms, and it comes back as discordant. Pcr, positive toxin negative which happens 40 to 50% of the time. And perhaps in the meantime you found an alternative source of the diarrhea or the patient got better without treatment. I think discordant test results can be a real clinical

conundrum whether to treat given the perils of over treatment that I mentioned but also the risks with delayed diagnosis and treatment. And so this is why a Uva, when you get a discordant result it, says, Consider an id consult, and I think this is not a requirement. But I think it's a totally reasonable thing to do if you're unsure whether or not to treat for Cdi and then circling back to recurrent infection.

- It's propensity relapses despite successful treatment is one of the more unique aspects of C diff among infectious diseases, and recurrence is often due to persistence of gut spores, and then relapse of the same strain, but occasionally, reinfection by new strain most often occurs within about a month after finishing treatment for the index infection.
- You're probably familiar with fecal microbiota transplant as a way to interrupt the vicious cycle. But the landscape of anti-recurance treatment has really undergone a significant evolution over the past few years. Use of conventional like single donor stool. Fmt. From has really dipped substantially in recent years, primarily due to covid in addition. There was a 2019 New England Journal report of I think it was espl E. Coli transmission by fmt, that involved at least one death and then, as of this past year, the FDA reinstated an in d requirement for stool material from stool banks. And then finally, there are now, Ni newer anti recurrence therapies that have emerged, including live bio therapeutics, 2 of which were approved in the past year. Thought to be as roughly as effective, and potentially a lower risk for transmitting infectious agents. So this is a list of what I or table, what I call anti recurrent Cdi treatment options, including fmt, which aren't mutually exclusive. There's Fedaxim, which is an alternative to anti-cif treatment that has a narrower spectrum lower recurrence rate compared to the Standard Oral Bank.
- Vesla Toximab, a monoclonal to toxin B. Approved in 2,016, and just in the past year. The 2 fecal microbiota therapeutics. Approved for recurrent C. Diff. One administered rectally the Rbx. 6, 2660, or Rebiota and an oral pill. It's actually shelf stable. It's ethanol-treated stool that has firm, acute spores in it called vows. There's also this is not approved, but the ve 303 is 8 strains of non pathogenic clustridia that are grown in clonal stool banks. This is under investigation, but can be delivered orally the randomized trials suggest these are all fairly effective at reducing your current Cdi but the relative efficacy of these treatments, because the way that trials are set up are are very different. Or optimal combination of these treatments as is really understudied and the rates of recurrent c diff, despite these newer therapies, have not significantly changed, as far as we can tell to date. Recurrent C. Diff may, in fact, be on the rise depending on which data source you look at. And there's a few reasons why I think these are underutilized. One is cost and logistical barriers. Fedax. So Mycen cost on average $5,000 per 20 tablet package, which is multiple times out of bank and insurance often bulks besla tuxmab is over $4,000 a vial and has to be arranged at an outpatient fusion center. And then Rebiota is on the order of $10,000 and ranging a rectal infusion. And then Valls is roughly $20,000. For a course, although there are some patient assistance programs for some of these the second major reason, I think these are underutilizes. Recurrent infection happens weeks into the future and we don't as of yet have a reliable way of predicting who's going to recur and who's not? No accurate way to kind of justify the costs and logistical barriers. These are unpublished data from U. 15 over 1,500 cases at Uva of C. Diff infection and hospitalized patients where we validated the leading risk. Score models from the literature for predicting recurrent C diff within 48 h hours of diagnosis. When a lot of these treatments need to be, you know, started to be arranged. And you can notice that the Roc curves for all these is about point 5, which means they're no better, really than chance predicting who's going to recur and who's not so the most important factor we know, determining recurrence risk is simply the number of

prior episodes. And this underlines the importance of taking a really good history when you have a patient with C diff. You know what antibiotics they've been on, how they've been treated within past, and how many prior episodes.

- And so here I'd like to put in a big plug for the complex C diff clinic here at Uva, which is a multidisciplinary group, Dr. Warren, Doctors Warren and Shen, from Id and Dr. Ben from Gi. If you have an inpatient with recurrent C diff or outpatient or just a complicated or severe infection. Even a first occurrence think it's reasonable to refer your patient. This is the best way to gain access to those anti-recurance therapies that I mentioned. They can arrange rebiota infusions. For example, this is also helpful in patients with the history of C diff, who may have other causes for diarrhea and helping to distinguish colonization.
- From infection, to minimize over treatment. And this is the number to schedules, the same as the general id clinic number. Just tell them it's for the the complex C diff clinic and for patients who that live in the Roanoke area. Or you know Lynchburg. Dr. Warren actually sees patients in in fishers built to be more convenient. And on to Dr. Park. Thank you.
- Alright. So Dr. Madden just finished telling you how common diarrhea is in hospitalized patients. Diarrhea is also very common among patients taking antibiotics in general. It depends on the particular antibiotic and what data you're looking at. But up to a third of patients receiving antibiotics will have diarrhea, and among those with diarrhea about 20 to 25 is due to C diff infection.
- So systemic antibiotics predispose patients to C diff infection by depleting commensal bacteria. Patients become exposed to C diff from spores from the environment that can then germinate in the intestinal tract and under con ideal conditions, meaning a normal microbiota. The other commensal bacterial populations enable production of secondary bio acids that actually directly inhibit C diff, grow both, and they also compete with C def for other energy resources. In that state it doesn't necessarily go on to cause infection. However, if you disrupt this population with systemic antibiotics, you decrease that competition for other energy resources, decrease the production of the secondary bio acids, and then you can get continued growth of C def, and eventually toxin production and severe colitis. So how do we protect our patients from C def. So I think the first thing as physicians is we can wash our hands with soap and water after we've seen patients who are infected with C def prevents spread to other patients. C. Diff is resistant to killing by alcohol disinfectant. So that's why it's important. You'll see these signs reminding you to use soap and water when you've care for those patients. Or really, if you've, you know, come into contact with stool, or, have visibly soiled hands. After caring for a patient.
- But I want I'm primarily going to talk about today is how we protect our patients by being thoughtful about the antibiotics we give them, avoiding giving them unnecessary antibiotics and using them wisely when they are necessary, which is frequent.
- So when it comes to C diff, risk, duration does make a difference this study on the left is not exclusive to C diff, but I really like it. It was done by Valerie von and some others at a group of Michigan hospitals a couple of years ago they looked at hospitalized patients with pneumonia and basically reviewed to see how many got excess duration for pneumonia after hospitalization, and they found that nearly 70% of patients got excess antibiotic duration for pneumonia with the Median excess of 2 days of therapy. But what I really like about this is that instead of relying on provider or emr documentation of adverse events, they actually called patients by telephone and surveyed for any potential side effects. And so they found that for each excess day of antibiotics there was a 5% increase in some sort of patient reported adverse event, primarily gi distress, diarrhea, or candidate, mucoputaneous candidiosis.

- I think the compelling thing is that among Lewis who said yes, I had a side effect. Almost 40% actually went to a doctor. So another healthcare visit related to the side effects from those excess antibiotics. So we also have data from surgical prophylaxis literature that demonstrates there is a duration, dependent increase and risk of C diff on a day by day basis so compared to giving less than 24 h of surgical antibiotic prophylaxis, which is the referent for the study on the right, giving 48 to 72, or greater than 72 h of antibiotics had numbers needed to harm of 90 and 50 respectively. For C diff risk, so every day does count.
- We also know that not all antibiotics are created equally when it comes to C diff risk. This is by no means an exact area, and you can find a lot of variability in the literature. But this is some summarized data from a systematic review that looked at various antibiotics or antibiotic classes, and the risk of C diff infection.
- So you can see that carpipenam, Clintamycin, Quinolones, and later generation Cephalos, foreign have been found to be particularly high risk. And then among the Cephalos Warren's first generation. Cephalus foreign, do seem to carry less risk than some of the later generations.
- Kind of in pairing with this the National Healthcare safety network or Nhs. N, which is a entity that coordinates reporting of certain things like hospital acquired infections like cloud C or hospital and set C diff. Now does enable in a microbial use data reporting for the past few years. And now, actually, as of this year, is now mandated, that hospitals report this data.
- So to that end they actually have different categories of antibiotics, including one that they call antibiotics, associated with increased C diff risk, and that includes some of these third and fourth generation, Cephalos, borin, squintalones, clindamycin etc. So it is important to remember that patients absolutely can and do develop C diff after receiving antibiotics outside of this group. But that's also why it's important to be as selective as you can.
- So here at Uva all hospital onset. C. Diff infections populate the Uva health data dashboard daily. When a new case comes up, the C diff coalition reviews all cases. Sometimes you'll hear from us as we're gathering information about it to see the antibiotics and testing rationale. We really appreciate all the engagement and discussion. When those cases do come up. I'd like to share some basic data specifically about our hospital on set C diff cases for 2023 and internal medicine patients to Orient. To you. This includes any positive C diff test, meaning pcr, whether toxin, negative or positive, that was collected on hospital day for or later cases are attributed to service based on the primary team. At the time of testing.
- For the purposes of this talk I've pulled out cases that occurred on general medicine. Make use Ccu. Acute cardiology and ontology, and all of our cases are reviewed for opportunities for improvement or ofis and quality improvement. Speak both in terms of testing and antecedent antibiotic use, and we use a 90 day period as our look back for the antimicrobial exposure.
- And this is just a visual summary by location of all C. Diff cases in the hospital for 2023 there were a total of 76, 33 were toxin positive. I've highlighted the medicine cases in Orange, and the Medicine Department has a big footprint on inpatient care, and also a big footprint on C diff cases at UV. As well.
- So for calendar year 2023, and medicine there were 46 total cases, 20 toxin positive and 26 toxin negative. We did have an increased trend. The last 2 months of 2023, with 4 toxin positive cases each. And I'm hoping that being here in front of you today will help us keep that trend. Not continuing into 2024, we did have 9 c. Diff related mortalities, including 5

that were directly attributable or primarily attributable to C. Diff. and then 4 that were likely or partly attributable.

- And then, during that time period, we also started tracking as of august treatment and toxin negative cases. So we had 10 out of 13 toxin negative cases or 77 that received treatment. Based on what Dr. Madden told you. It's a little bit statistically improbable that all of those patients had true C diff infection, and having reviewed them, there were some that certainly seem not to be true infection, but definitely keep in mind some of what you've heard today about the downsides of over treating and when you've got that discordant result, don't be afraid to to call for help if needed looking at our of eyes. A little more than half of patients had at least one antibiotic prescribing ofi identified within the last 90 days. At least 30% recei received at least one antibiotic course that wasn't indicated.
- Looking at that, those of eyes by type and indication, pneumonia was by far the most common reason for antibiotics that weren't indicated on review with hap, Bap, and capped together, making up about 18 out of 26 of those instances uti was the next most common reason given where antibiotics were indicated, and then we had a few cases involving prophylaxis or dental complaints, rounding out that category ofi's in terms of spectrum or duration, were less frequent with skin and soft tissue, infection and cap being the most common indications where therapy was deemed to be broader than necessary on review.
- Testing of fis were less common than antibiotic biotic of occurring in about 35% of cases. The most common were a lack of consistent clinical features, in other words, abdominal pain, fever, voicemail concern for sepsis. An alternative explanation of diarrhea, I'll say frequently those went together with both of them I identified. For many cases. There is also a small collection of instances where testing was obtained, based on smell of stool, which we know isn't predictive or in patients who didn't have the frequency or consistency of stools that would make us concerned for CJ.
- The most common other that's listed on here was actually patients who were already being followed by Id consulting teams, and no one thought to ask them their opinion on the testing before sending it so II won't belabor testing, since we've already discussed it so much. But please do keep a broad differential and your hospitalized patients with diarrhea assessed for those signs and symptoms. And if Id's already following at least talk with them, if you're thinking about sending the test so I did wanna go through a couple of our cases. So start off with, one is a 74 year old male who has a prior history of cardiac transplant. Almost 2 decades ago diabetes and C. Kd. Came in with acute hypoxic respiratory failure due to Covid, had a very prolonged admission that was complicated by ventilator dependence. Among other things, he did have some diarrhea throughout his course, but had some escalation and abdominal pain on Uva Hospital day, 149, which prompted seed of testing that was discordant.
- On 90 day review he had received 23 days of antibiotics, 16 for the indication of pneumonia, and throughout his admission to that point he'd received 44 days of concern, antibiotics directed at bacterial and pneumonia, including 22 out of the 32 first days that he was here for his his covid. I mapped out some of his hospital course leading up to Cdf. Each box is a day. It's colored in antibiotics were given on those days, so you can see he started off. continuing a Cephopian course that was started when he presented with Covid at the outside hospital for total 7 days. Then, a week later, after being activated, he has increased work of breathing, gets reintebated. Fetum gets sent. Bruce normal aurophyll Flora eventually, but he gets 7 days of cephapen.
- Then he ends up developing hypothermia, and since he was on Zephyr Pm, he gets on Meripen for 3 days eventually gets off of that. Once workup is negative.

- But then, somewhere along the way a Ct. Chess was obtained and he had bilateral opacities. So he got another course of Sapipene 7 days. Speedum culture also grew normal oropharyal. Flora at that time.
- And then, similarly, he about 2 weeks later has this episode where he's a little bit altered. You remake not clear exactly what's going on. He gets started on setup team pending freedom cultures which subsequently returned with normal or referring to Flora, but nonetheless he gets 70 as a staff ofine and then, just as that's finishing, he has a worsening white count some concern for a calculus cool assistitis, and ends up getting escalated to mirror. Pennam given all his Sapphem exposure previously, so I didn't keep in annotating because I figure you guys are picking up what I'm putting down here at that point. So I'll move on. So I'm gonna do a little bait and switch. We're talking about C. Def. But since we had so many opportunities and pneumonia, I wanted to go through some common places where I think people get a lot of astray. So what's the diagnosis here?
- Anyone? No one was tricked. You're supposed to say pneumonia. And then I was, gonna say, I haven't given you enough information to tell this pneumonia. It's a long infiltrate pneumonia is a clinical diagnosis. So in order for this to be consistent with pneumonia. You need to know that this is a new lung infiltrate, and that there was clinical evidence that that infiltrate is infectious in terms of some combination of fever, leukocytosis, period cough hypoxia.
- And I think one thing that frequently trips people up is not, you know, keeping in mind that abnormal imaging findings on chest X-ray or Ct. Lag behind clinical resolution of pneumonia by quite a bit. So I'm showing some data here from a study in 2,004, where they perform serial chest X-rays every 3 weeks on adults mature adults, 70 and older, who came in with a cap, and they repeated this until 12 weeks, or until a radiographic resolution. They also stratified by comorbidity index, which is indicated by the dotted, dashed, or solid lines, and then they separated it out by, you know, low bar or multi-lar low bar pneumonia.
- So, as you can see for multi-lobar pneumonia, even in patients without comorbidities, more than half still had persistent abnormalities. 3 weeks in overall resolution by 3 weeks occurred in 35% of patients. Resolution by 6 weeks occurred in 60, and resolution by 12 weeks occurred in 85, so that conveniently works out to kind of a rule of thirds in terms of resolution by 3, 6, and 12 weeks respectively. And if you look specifically at hospitalized patients with pneumonia due to Covid. Similarly, only about a third have resolution of imaging findings by around the 3 week mark.
- You may have noticed a conspicuous absence of respiratory cultures as an element of diagnosis. And that's partly because positive bacterial cultures aren't necessarily diagnostic by themselves, particularly in ventilated patients where this can be problematic. So it's studies of intubated patients who undergo tracheal, aspirate sampling, such as the one shown on the bottom left, right? Depending on what? You'll have bacterial colonization in in over half of patients after 2 days of intubation. So if you send those respiratory cultures in patients with non-specific signs or symptoms. There's a good chance. They'll be positive, regardless of whether the patient has pneumonia or not. And in a study published last year they looked at patients who had new fever or leukocytosis without any other clinical signs or symptoms of pneumonia, and they looked at ones that had respiratory cultures sent versus those who didn't. Not surprisingly. The people who had respiratory cultures sent got more days of antibiotics. But what they also did is they had a Committee of Id Physicians review, and only about 5% of those patients actually would meet criteria for that based on the possible that for the Idsa ats criteria.

- They also had them review and determine what they thought the most likely ideology of that fever. Leucocytosis was, which was mostly non infectious for the the bulk of them. But they also did identify about 20% of patients that had an extra pulmonary source of infection. So that really sort of highlights, this risk that you could be anchoring on a positive respiratory culture and missing something else which could be significant if a different anti-privial regimen would be better for that extra pulmonary resource or a source control procedure of some sort is needed and delayed because we're treating that.
- So here's another case of a 73 year old female recent left Mca infarct CAD. Ckd. She comes in. She had a post post cardiac arrest at her rehab. She's got bilateral basal opacities on chast X-ray get started on piptaso for concern for pneumonia. Cultures grow normal, Flora, and eventually that stopped on hospital day 4.
- Then she's transferred to the floor on Hospital Day 7 has a witness aspiration event, and then a met call overnight for tikipnia leukocytosis get started on self-track accident due to concern for aspiration. Pneumonia, and then, 3 days later, has watery diarrhea and leucocytosis, and is diagnosed with C diff.
- So this patient essentially receive 7 days of antibiotics for aspiros aspiration, but in neither instance likely had an aspiration. Pneumonia. At the time those antibiotics were given. The aspiration is really common. Even normal, healthy people sleeping at night will aspirate small amounts of orophyndal bacteria, but because it's a low amount and we have normal mucosiliary clearance and normal immune systems. We don't just get pneumonia. Every time hospitalized patients might be at risk of having larger macro aspiration events. They also might have other factors that make them more at risk, so in that setting they can get an initial numinitis and be at higher risk for subsequently developing aspiration pneumonia, because it's maybe a larger burden of bacteria aspirated, and they might have impaired nicotine variants, immune disruption. Things like that. But this doesn't occur immediately, and it takes at least 48 to 72 h from the event for pneumonia to develop.
- So, of course, some people have naturally wondered. Well, if we give in a box upfront. Does that at least prevent pneumonia from setting in and there was a retrospective study published in CID in 2,018 that tried to look at this they looked at patients with acute aspiration clinically, and they separated out from those who received initial sort of prophylactic and microbial versus those who just re received supportive care and after adjusting for patient level predictors and antimicrobial prophylaxis, was not associated with any improvement on mortality or likelihood of transfer to critical care. It was, however, associated with an increased chance of subsequent escalation of antimicrobials. And fewer antibiotic free days. So basically trying to prevent the development pneumonia didn't seem to work and it put patients at risk for needing even broader therapy when they did eventually develop pneumonia, anyway.
- And then finally, just another sort of common theme. I think that comes into play in instances of antimicrobial overuse. Is this sort of fear of missing something, fear of sepsis yet to come, whether it's positive urine culture that comes back. That was said for unclear reasons. In the first place, or maybe it's a faint opacity and a patient who really seems to have volume overload clinically. But there's something kind of this pool to treat rooted in, some, that some idea that maybe we're missing something, or there's something we can nip in the bud. Make sure that our patient doesn't get septic later. However, I present to you a counter argument of some admittedly circumstantial evidence that unnecessary antibiotics might actually put patients at increased risk for worse outcomes and increased risk of sepsis in the future. So the figures on the left here are from a pretty cool mouse model study, where they basically obtained genetically identical mice from 2 different

vendors, but differed only in the microbial diversity of their gut microbiome. And then they did a sepsis challenge model where they did a sequel, ligation and puncture, and they basically resuscitated them with antibiotics and fluids to mimic sepsis care. And basically they found that the mice with the lower gut microbial diversity survived at much lower rates than the ones who had the higher diversity microbiome, and then they co-house those mice so that they developed the same microbiome which it turned out mimics the higher diversity microbiome. They did the sepsis challenge again, and then they found that outcomes are the same. They survived at the same rates. Once their microbiome had the higher diversity and then, as far as humans, there have been a couple of large epidemiologic studies that have sort of tried to look at surrogate markers of microbiome disruption and future risk of sepsis. So on this one study that I'm showing they basically looked at patients who had an admission for

- Sepsis initially or or sorry infection, or C diff infection as sort of surrogate markers of microbiome disruption. And then they looked at their risk of 90 day readmission for sepsis, and they found that those who had initially been hospitalized for infection or C diff, after adjusting for confounders, had increased risk of 90 day readmission per sepsis.
- They did not have any increased risk of non sepsis readmission, so sort of to try and control, for you know other patient comorbidities, or risk for re admission in general so might be thinking, Dr. Parks are hates, antibiotics. Not true definitely. The second best thing in modern medicine after vaccines. But I think this wonder drug status leads us astray frequently.
- We all know. Use of antibiotics, like most medical treatments, is a risk benefit calculation. But I think we default to the calculation that you see here, with the concerns on the left swaying us to use antibiotics and those on the right against. But I think in reality it's much more different in nuance for particular patients.
- This balance can look really different. For example, your average patient with just leukocytosis or just fever, might look something more like this patient you're considering antibiotic peripheral axis for current utis who's already had C diff 3 times. They might look like that.
- Someone coming in with I saw a patient recently Rsv multiple Apache infiltrates on imaging got bank and and outside hospital. Despite the fact that she had multiple documented severe cutaneous reactions, including dress Sjs to both Bank and Southern's, got started on. Moxie here had a rash, apparently also had a rush out patient with Moxie unclear. Exactly what was going on. But she was on room air feeling better, and had Rsv. So we felt like antibiotics, did not the risk to not outweigh the benefits.
- Admittedly, there are lots of patience, but it looks like this. But still feel obligated to remind you that reality is probably more like this, and you can shift the balance by being thoughtful about your calculation by minimizing the collateral damage when you are prescribing antibiotics. So would just remind you that this framework. The 4 moments of antibiotic decision making are kind of a helpful way to try and make sure that you are reducing risks for your patients.
- This starts by, I would argue most importantly, making the right diagnosis, starting empiric therapy and obtaining cultures that are appropriate, based on what you expect reassessing at 48 to 72 h to see if you can stop narrow change to oral, and then picking the right direction or duration based on that right diagnosis that you've made and then, when in doubt, you can always phone a friend. This is our friendly Ast team, always happy to help out with questions, and then just wanted to make a plug for our institutional guidelines which we have for uta uti have that C diff cap and surgical prophylaxis. Not that

you guys necessarily would look at that one. But please do check them out so hopefully. I've persuaded or reminded you that the decision to use antibiotics doesn't usually look like this more like this, and we'll take any questions.

- Hey, guys? Great talk. The question for Dr. Matt and I was intrigued by the cycle threshold. Proceeded for currents as a predictor. Do you think that's dead in the water cause? I was wondering a little bit better than coin flip, but every cycle threshold as a dependent, variable as a positive test. What was the ground? Truth through the outcomes? Pcr cycle threshold more as a proxy for toxin eia positivity. A low cycle threshold correlates with a high organism burden. It's usually information that, like just the lab knows and isn't released with the test and in some institutions. In fact, the correlation so good don't actually do a physical toxin eia test, and actually run a report of virtual toxin Ea based on the Pcr cycle threshold. So you can actually use the Pcr cycle threshold to predict toxin positivity. And we we did that as part of that study I mentioned, because we didn't have we hadn't deployed multi step testing but I think of kind of the Pcr cycle threshold as a another imperfect kind of test. That we shouldn't hang our hat on and we should rather focus on the patient their symptoms guys, but when you talked about the cases that we had at Uva, I had written down that 33 of the 76 cases were toxin positive.
- That's overall, not just medicine. And so how did those patients end up getting diagnosed? And what's the natural history for for that tox, or sorry toxic negative population that felt like a high toxin negative population to me. And I think that's really tricky for our residents who we try to reassure about these discordant patients.
- I will, I would say. The reason so many are toxin negative is probably cause it's enriched for people who don't actually have C def I know we only had 35% testing ill-fies in medicine.
- I couldn't give it off the top of my head, but I can say confidently, would be higher if you looked at some of the other departments that were more enriched. For like this patient was getting laxatives and someone just to test. Oh, okay, okay, so what? What conditions would you say to our residents? If you have a discord and seat it? Should you call your id position?
- If you're still not sure that they have, if they have infection or not. With that test, I will say historically, at a I looked at this. A little while ago, 75 80% of discord in patients at Uva historically, have got treated at least initially with it. An initial 48 h of treatment is what I looked at. So most patient, discordant patients end up getting treated. Which kind of lines like we're probably over treating. But it's the difficult part is, who right?
- And who do? We have time to, you know, figure out other sources. If the patient's critically ill. you know. it's pro, you know, we're probably gonna be a little bit more likely to to treat empirically while we look for other sources. But just because patients with C diff can get really sick, really fast? that makes sense.
- We're hammering on this question of discordance, Greg. But another question related to that. Do you see prospects for better
- clinical prediction algorithms? Or, you know, fecal based tests to help sort out discordance. Yeah. Other strategies for further risk. Stratification of that group. Yep, people have been looking at biomarkers. Immune biomarkers seem promising.
- And and it's the topic of my project that I'm working on now, looking at immune side of kinds, because it's really your immune response. That kind of dictates.
- How you're gonna do with C diff infection down the road. And you know, figuring out better models now that we have, like AI and and Emr, with lots of clinical predictors. I'm you

know, trying to focus now on predicting recurrence for because I think that's a big gap and kind of our clinical management right now.

- I think, for me just to put a fine point on having done a lot of these reviews for a lot of years, reviewing sort of every case when we were reviewing it, when we weren't testing the toxin right behind the scene, just to be clear, you can have a Pcr positive. And if you're doing really good pre-test probability, meaning you're only sending it on. People that have a high white count have crampy abdominal pain and bad watery diarrhea.
- It's they could have C diff as the driver without a talks and positivity. So I just wanna make sure that that. And that's why we report both here, Eva, because it's it's it's safe. It's really hard, some of the data to look back on and be like, well.
- it looks. It's just hard cause in your clinical case, like Greg Nice or Doctor Madden nicely pointed out. Some of those people go on to see if and was that a under diagnosis or a, you know. And so it's a very hard, that's what the tensions all about. And so I think about the 12.5 false negative autopsy proven C diff rate that I mentioned earlier. For Antigen. So you always have to think about that when considering these discordant patients. And I think the cringe part for us, looking at every case in the hospital is some people get sent.
- C. Diff for it. Smell bad, you know, and you're like, well, that wasn't a, you know. And then it's discordant. You're like, well, as I mean, you know. So it's it's taking all of that. Why did it get sent? Did it get sent overnight by somebody who didn't know the patient very well, and all those things so great, grand rounds in your last slide or one of your last slides. You suggested that changing to oral antibiotics was a good thing to do to prevent C. Diff.
- If you're using the wrong antibiotic for the wrong duration. Do you know of any data that that's gonna make any difference?
- Oh, of course, moments of microbial decision making in terms of, you know, good practice. If you have a good oral option at 72 h, go ahead. I didn't really need to imply specifically that foresee did. That's preferred. Yeah. but thank you for making sure. I clarify that. Because, yeah, that was not the intent of that statement.
- Great Todd, thank you anecdotally. Here we use a lot of bank tapers for recurrence. C. Diff and not Fedaxa, my son, just wonder if you could comment on in an ideal world. We'd probably be using more Fedax Mycen. But I've been on the end of trying to get insurance to approve, and and that's just for a 10 day. Course, I think there's like $5,000 that I quoted. So getting a taper of Fedax and Mycen is really difficult to, because most of that is going to be given as an outpatient, and you don't.
- I don't love the idea of giving someone bank and then switching them, you know, switching therapies personally, and so yeah, there's a real cost barrier and and the tapers are part of manage, you know management of of cases where you have repeated
- episodes.
- I don't have a question. I just wanna say, I think this is some of the best done. Qi that I've ever seen. You know. I've been involved in a lot of qi, or seen a lot of qi, and a lot of it's really poorly done. And I think the work by this whole team the way that the clinical decision support the way that things are monitored and the ongoing efforts to improve diagnostic stewardship, antibiotics, stewardship. So anyway, just a comment, it's very excellently done and hopefully a model for many of the other efforts in the organization to improve quality.
- Thank you. Thanks.