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TRANSCRIPT - GR 11 10 23 "Bowman Lectureship: Practicing Medicine in a World with Increasing Antimicrobial Resistance" guest speaker Amy Mathers MD from University of Virginia

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- Good afternoon, everyone officially at 1201 I am Meg Keeley. I am Senior Associate Dean for Education in the School of Medicine. But here I am today with my colleague Mcgarren, from the Department of Surgery. We are here in our capacity as being the University trustees of the Bowman Fund, which we are very proud to have that role.
- We are also very pleased and grateful to be here as part of internal medicine grand rounds for the delivery of what is the 40 sixth Annual Bowman lecture. So I have a list of all of the illustrious Bowman lecturers, and we are adding Dr. Mathers to that list today. So we're really grateful to her and thrilled about that. This is an opportunity for me every year to tell you all a little bit about Dick Bowman, and why we are gathered here to remember him, and also to what I think he would appreciate, really remember him in the embodiment of some of his ideals and spirit. Through our 5 Bowman scholars this year.
- A little bit about Dick bowman. He was originally from Stanton, Virginia, and he lived there with his parents and his younger brother Bill, who joins us for the Bowman event. Every year. He attended Hammond, Sydney, and Farmville, Virginia earned a degree in American history, and then he taught for 5 years before he came to Uva School of Medicine in 1970.
- He worked hard, as his colleague said, to achieve satisfactory grades in the what is now known as phase one or the Pre. Clerkship portion of the curriculum, but he excelled in the clinical pro portion of the curriculum in the in the spring of 1974, during his fourth year of medical school he got married to Elizabeth Williams, who was attending Sweet Briar College, and the 2 of them headed up to New York City. For Dick to train in internal medicine at the New York Cornell Medical Center in New York City. His performance there as a clinician mirrored his performance as a clinician, as a medical student. Where he was, you know, won the respect of his most importantly, his patients, but also his colleagues, fellow physicians, and his attendings and his students. As one of his colleagues there, observed Dick, was one of the nicest persons I've ever met a joy to be or have around. Seldom have I met anyone who got such pleasure from life who enjoyed his work so much, and who balanced the conceptual and the practical so nicely Dick had, developed a special interest in infectious diseases early in his training, even when he was here at Uva and so they were planning to return to Charlottesville to do an id fellowship here in July of 1977. And tragically, he was killed in a boating accident, and was not able to return to Uva.
- I think that almost immediately his colleagues in New York, his colleagues here again immediately establish this scholarship in his honor, this fund in his honor. I don't think any of those original founders or trustees would have thought that we would still be doing this 46 years later. But it is definitely now, really the highest award in the school of medicine for our medical students. To tell you a little bit about the scholars we every year. I ask the clerkship directors to nominate medical students who embody the ideals of Dick Bowman, which is integrity and uncompromising strength of character and personal and professional life, enthusiasm for the acquisition and perfection of those skills which permit the physician to provide the best possible patient care and compassion for the ill, complementing a

scientific approach to their unique problems regarding patients, first and foremost, as persons in need of help and, like Dr. Bowman, the recipients would be open, accessible, and approachable, with a diverse range of private interests and experiences. So every year approximately half the class is nominated which says a lot about our medical students, and then we go through quite a process to narrow that down to a number that we can vote, and we somehow choose 5 Bowman scholars every year, and I would like to introduce you to them. First. I would like to introduce Michaela Mitchell, who's here today? If Michaela could stand and wave Michaela was originally from Rochester, New York, she attended the college of William and Mary, where she majored in biology and kinesiology with a public health concentration, and then did post-back research at the FDA and worked as a medical scribe. Prior to coming to medical school. She is now pursuing an Internal Medicine Residency with a focus on hospitalist medicine. She hopes, and is an ensign in the Us. Navy and is gonna continue her service as part of the Medical Corps after she graduates. I also want to introduce Elizabeth Watt, who couldn't join us today. Originally from Fort Wayne, Indiana, now Northern Virginia, she attended the University of Virginia, where she majored in neuroscience and is currently applying for a residency in child neurology. Simon White also could not join us today. Simon's originally from New York, New York, he attended Duke University, where he majored in biology. He spent a year working as a medical assistant after college as well as pursuing his music career. And he is now applying for residency in urology.

- Abby Williams, who is here today. Abby, please stand and be like remotely Abby, originally from San Francisco, California, and now majored in biology with a minor in bioethics at the University of Virginia, worked as a medical assistant in dermatology. Here in the Charlottesville area.
- And also worked with the as an Emt with the cars. Rescue squad and she is now applying for residency in internal medicine. So keep that in mind. I and then I'm also pleased to recognize. Jack Lawton, with the Bowman Committee. After we honor all of our students at a really wonderful, I think dinner with a lot of attendees from past bowman scholars, faculty deans, etc., and the families of our Bowman scholars, and get to recognize them and hear about what you all said about them as part of their evaluations, which is incredibly impressive. And then a group of us interview all 5 Bowman scholars, and one person is selected to receive a scholarship this year. The person receiving the scholarship is Jack Lawton, originally from St. Louis. He attended the University of North Carolina at Chapel Hill, where he received A. BS. In public health, took 2 years to work as a medical scribe and a Scribe trainer, and is now applying for Residency in urology, and I'd like Jack to come up and accept his scholarship.
- Thank you. Congratulations. And of course you have to get the voting of course and I oh, I didn't change. I'm gonna there's the next slide.
- There we go! I will. Actually now have. There's a picture of the Bowman scholars, so you can have a visual I am now going to let Dr. Harrison introduce our speakers day, Dr. Mathers, I would like to. This is always. We always do this dangerous in advance before they speak, but I would like to thank her for us being the 46 bowman lecturer and acknowledge her with this bottom up to.
- Oh, okay thank you. Thank you.
- Good to see everyone today. Welcome to medicine, grand rounds. I have the pleasure of introducing Dr. Amy Mather's. I'll try to be brief, as you would be much better served by spending time learning from her, but it's hard to be brief about Dr. Mather's accomplishments. She received her medical degree at Loyola School of Medicine in her

Residency at Maine Medical Center, where she served as chief resident. She then came to Uva for fellowship, and has been here ever since.

- There are some people who the pandemic revealed as true leaders, and of course our palm critic, our id divisions, our journal medicine divisions. They were all called upon them most, but I really think Dr. Mothers was a force of good in a dark time when we didn't have enough Covid tests. She helped create in house tests when we had a nasal swab shortage because of testing, she worked to get the swabs distributed across the state. Meanwhile her practical work did not mean that her research suffered. Her scholarly work is vast. When Covid started having v variants, she began applying whole genome sequencing to better understand the disease. She applied wastewater surveillance to covid monitoring and transmission and of course, as you will hear today she has devoted her career to understanding and slowing the development of multidrug-resistant bacteria. She is the medical director of antimicrobial stewardship and the associate director of clinical microbiology but near and dear to my heart. Dr. Mathers is known among the residents as a fantastic teacher, with a positive attitude, and for working around the clock. She gives you the same time vigor and dedication. If you are calling at 2 A. M. Or 2 PM.
- And we talk about the triple threat of a great researcher, a teacher, and a clinician. But Dr. Mathers manages all of these while also being a very fun enjoyable human. Please join me in welcoming Dr. Amy Mathers.
- Oh, it's also generous. Hold on! Let me turn my mic on.
- Well, there it is. Okay. Everybody can hear me.
- Thank you very much. I feel really honored to be here. And speaking bowman I mean, it's very humbling having read about Dick bowman and congratulations to the students. I did try to take and integrate sort of the spirit of Dick Bowman, and it's that concept of trying to balance the conceptual with the practical so nicely that I'm hoping to bring to you all today. And there's been a lot of emergence around data around antibiotics, and how they work. And the fact that we're don't have many more. So I do have some conflicts of interest. Am I gonna talk about any of that today.
- So today I want you to just take a step back and think a little bit differently about antimicrobials. If you'll take this journey sort of with me to think about them as a therapeutic class, because they are very, very different than all other medications that we use. I'm gonna talk and about sort of why antibiotic resistance is important where we're at globally and in the Us.
- and then why some of the market forces are really important to think about, and what's coming down the pike in terms of the next antimicrobial also, how are we going to preserve these antimicrobials and talk a little bit about stewardship and limiting the collateral damage from antimicrobial use, and then just use some cases to describe. How are we managing really highly resistant antibiotic infections at this point.
- So just definition, get it out of the way. What is antimicrobial resistance? This gets tossed around a lot. And now there's a bunch of people that are working in the environment and in veterinary medicine and whatnot. But I think, as a homo sapien, I want to claim antibiotic resistance as the definition that it's when antibiotics don't work in a human to cure that infection, that a bacteria that was once susceptible has acquired resistance and is no longer killed in human infection and so bacteria only have a few ways of doing this. They can make some workarounds and develop cell processes, so they don't need the mechanisms in which the antibiotic was blocking. They can destroy antibiotics like beta lactomases and hydrolyze the effective antimicrobial. They can change their binding site or they can keep antibiotics from getting in, or they can kick them out as soon as they come across.

- So that's it in antimicrobial resistance. If you just learn those things you're kind of done.
- Except so again, thinking about antibiotics as a concept, you know, when we developed antimicrobials, we really target mechanisms that are specific to bacteria and then aren't present in humans. That's how the drugs work. That's how they were all developed. Right? So I don't have a cell wall or penicillin binding protein in any of my cells. That's why penicillin doesn't destroy my cells, and it destroys bacterial cells.
- And the problem is that in the world of you know, the world that we live in is the vast majority of microbes are actually friends. So if you've had a piece of bread or had a yogurt. Today, you had an antimicrobial help feed you today or a microbe help feed you today. And they're wonderful. And 99.9% of bacteria are here to help us, or are just trying to mind their own business.
- There are some bacteria in the world that are always pathogenic. So I've never heard of a mild Anthrax infection or colonization. And so, you know, there's some that are sort of out to kill humans.
- But the vast majority of bacteria are sometimes a pathogen, and sometimes not a pathogen, something like E. Coli or staph aureus, and so in modern medicine those are the bugs that we're really talking about, and that's the focus of this talk again, though. Unfortunately, because antibiotics were designed to kill bacteria, they don't really care if they're killing the friendly Smiley ones or the the ones that are out to get us. And so there's a lot of collateral damage that can happen. And again, there's been some emerging data about how this works. So how does antimicrobial use actually promote resistance. And we're gaining a lot of understanding. And I thought these were really nice, helpful schematics out of nature, showing that a recent review showing sort of intrinsic resistance. So in that first panel you've got. You know your gut microbiome. You've got a few C. Albicans. You got a few C diff, but you expose antimicrobial, you know, to your gut microbiome, and you kill off all the things that you kill off, and C. Diff, and C. Albicans, which aren't necessarily affected by, say, Cephaslin, are able to proliferate another way that antibiotic resistance can be promoted is that you've got one resistant E. Coli to Cephasoline, say, and again you expose your patient to Cephasolan, and you select against all the E coli that were resistant, that we're susceptible to Caslin leaving behind the resistant bugs or what we're having more understanding about is when we really knock out certain microbial populations that allows other populations to proliferate because there's more nutrients available, such as anaerobic therapy leaving behind anerobacterialis and anerococus to proliferate whether they're susceptible or resistant antimicrobial exposure leading to resistance. I think we're just at the cusp of understanding some of this nuance. It probably makes a difference which antibiotic you use.
- How long you use it for? Do you take it orally? Do you take it? Iv. And then there's a lot of patient factors. What's the immune status, nutritional status? And I think a lot of other unknowns that are going on. But if you deselect so how does antibiotic resistance really spread, and sort of shown here. Right? If you deselect for certain bacteria like C. Diff shown here you kill off all the other microbes, and then that there's a lot of C diff going around, and then you can spread it to the patient next door, right? So that's just by enriching for pathogens. You can then spread them, or resistant organisms, or most commonly in urinary track infections, we select it against that e coli. So now we have is resistant e coli in the gut floor, and that's what then seeds the Gu track and causes an antibiotic resistant infection.
- What, I think again, is an exciting time is this impact that antimicrobials are having, and our ability to understand how antimicrobials might affect other disease states besides resistance. And so you get an antimicrobial. You wipe out a bunch of flora. And what we're

now understanding is is that your gut microbiome doesn't really go back to what it once was for a very, very long time, and I'm not sure we really understand how long that is.

- We know that that is contributing potentially or microbiome shifts are contributing to graph versus host disease, colorectal and obesity. And so these disease states that could occur because of antimicrobial exposure. I think we need to be really thoughtful about this class of antimicrobials.
- Here's just some data out of Israel showing a lot of patients that were exposed to gent, septasm or cipro, and then looking a year out at how likely they were to have resistance to gent, septasm or cipro. And you can see with septas exposure, there's not that much resistance that emerges. But with fluorquinones there is a really long tail that doesn't really go away even at a year, and you're likely to have a fluorquinone resistant isolate after exposure to Cipro.
- This is another sort of controversial paper. And I don't. It's not practice changing for me, but I think it's at the edge of some of the stuff that we are starting to understand about how the microbiome might promote disease state, and so why we don't want to overuse antimicrobials, and this is a paper out of Michigan that they looked at all the people that got treated with vap across all the units so ventilator associated pneumonia. And so the patients that were enrolled in this were 3,000 patients over, like a 3 or 4 year period that had to be on the ventilator for at least 72 h, and were treated with Iv antibiotics, and they looked at people that got early anaerobic therapy, and the people that did not. Most of that early anaerobic therapy was piptase or metronitis. They did include September's anaerobic therapy. But there weren't that many patients included in that just kind of weird. But anyway, what they found was that exposure to early anti anaerobic therapy had an effect on mortality. and I don't know they can't explain the mortality with ventilator associated pneumonia that they subsequently got. But what they did show is they were like more likely to get a subsequent andero bacterialis ventilator associated pneumonia, which had a bad outcome and a higher mortality. So I think I'm not sure what to do with that, because I don't know that I can tell you. Well, just go ahead and use Cephen and sleep easy, cause I'm not sure that's the right answer, but you know, I think it's like it's food for thought.
- All right, shifting gears a little bit. Where are we at with antibiotic resistance? So it's not going well. There's an estimated almost 5 million deaths associated with antimicrobial resistance in 2,019 globally.
- It's estimated to be the third leading cause of global death, and it's the twelfth leading cause of death. If you just take the people that have resistant isolates and died directly from that resistance because they didn't have access to treatment or didn't get treated with an effective antimicrobial.
- And so you can see here the Us. Isn't the worst, but we're not the best. And we're definitely not, you know, in the running for sort of some of the stuff that's in the green. But here in North America, high income, North America is where we sit. And so there's our attributable in the dark bar and associated antibiotic resistance. Of course this is not. You know. This looked at 23 different pathogens. But about 40% of this mortality is accounted for by 2 pathogens, e coli and staph aureus, and I think those are 2 that we want to keep an eye on and are going to be really problematic as we think about antibiotic resistance it also doesn't impact everybody equally. And so for the pediatrician audience. You can see there that it impacts sort of different ages of life differently depending on where you're at. And so the neonatal countries, with a lot of antibiotic resistance and very little access to new agents. Have some of the highest mortality in neonatal but you know, Staff aureus isn't completely forgiving, or E coli for patients in the Us. Either. Tiny patients.

- In the Us. Alone. You know, antibiotic resistance. Death attributed to that resistance is approaching the top 10. So it's not too far off. It's not listed or ranked, but it's 42,000 deaths are attributable to antibiotic resistance alone. And so this is sort of how we stack up compared to some other countries.
- Well we just had a viral pandemic. So maybe things got better. Things did not get better with antibioticrobial resistance during the pandemic. They got worse. A lot of the data I'm showing you is from 2019. That's in part to the fact that people couldn't report because they were so busy. The same people that report antibiotic resistance that do stewardship that do infectious disease and do infection control. We're really busy with this pandemic.
- And so there was decreased amounts of reporting infection control resources went largely to Covid. A lot of stewardship resources here and elsewhere went to Covid and to managing patients with Covid. And I think it's an important stat to remember for a viral pandemic. 80% of patients hospitalized through October 2020 got an antimicrobial antibacterial. It's partly because we didn't know what to do. We didn't know at all what we were doing, and with influenza there is a, you know an association with a post influenza, pneumonia, bacterial pneumonia, with group, a strap staph aureus and we didn't have anything to offer people. So why not give them stuff tracks on an ease of throw? but it didn't work, and it did select for resistance, and probably Cdf cases, etc., etc. And I think we're still paying the price for that, because there are increases in antibiotic resistance that we're seeing now.
- Okay, so that's where we're at with resistance. Well, science will come along and save us. So II kind of got this thing going where I think about, you know global warming. And you sort of like, well, yeah, things are getting hotter. But like, what am I gonna do? So some scientists will come along and they'll fix it, and they'll figure out how to get carbon out of the atmosphere, so I'll have my plastic diet Coke, anyway. I just, I think it's really important to recognize that I think science could really help us. But we would have to really invest, and antimicrobials have a different market stressors than almost all other therapeutics. And so I think it's important to understand why that is. And it then informs what antibiotics are coming to treat these drug resistant pathogens. And so antibiotics don't recoup their cost. They're like a horrible investment for a Pharma Company. It's because they're expensive and hard to discover. We already took the best targets from bacteria that don't exist in humans. I don't think those new. The other targets are going to be found.
- They're modestly priced, you know, for in the early 2 thousands, late ninetys, antibiotics were free at most pharmacies because they're thought to be a public good and should be available to everybody, and everybody should have access. But then it's hard to recoup costs. If you're going to give them away for free, and people just don't have the stomach for paying a lot for antibiotics.
- Doctors only prescribe them when they there's nothing else to do. So if you bring a new antimicrobial to the market, I will tell you that I will restrict to that antimicrobial as the chair of stewardship, because I don't want to lose that antibiotic by over using it and then they lose their potency over time. Which is why I'm giving this talk, and you usually give them for a short of time period as you possibly can. And so, unlike anti hypertensive, you only take them for 5 days, maybe, rather than the rest of your life.
- And hydrochlorthioside is just as effective in eightys as it is today. Compared to Campicillin.
- So this is kind of just to show you some of the investment and the profit there on top and cancer treatments. And then antibiotics is in the negative there for profits, and compared to all the other subspecialties. And this is kind of what, over the last couple of years, what this

is looks like. Here's the number of oncologic therapeutics that have been investigated made it to preclinical clinical trials and then approvals. This was in a 2 year period.

- Again, basically venture capital funding compared to oncology and antibacterials is pretty weak, I would argue, though, that like it's gonna be really hard to practice oncology without antibiotics.
- So what? What we? This is just one last kind of slide on this. When penicillin first came into market. You can see there. And it's attributed, it's thought, to be attributed to a vast improvement in human survival in the number of years that humans survive, especially as it's related to death from infectious diseases and back to that sort of well, what does antibiotic pipeline look like? Unfortunately, of the new antibiotics which I'll talk about at the end that have come to market for a lot of these antibacterials that I'm focused on. There aren't any new targets. There haven't been a new target since the eighties. And so we're going on 40 years without a new target for antimicrobials. And that's not changing even with the antibiotics that are coming to market right now that I'll talk about. They're not new targets. They're modified targets, which means the bacteria already loaded with resistance mechanisms and get around them very quickly.
- I did say, this is, this was from the welcome, and I actually do think that we need to call out that Badacqueland, which is a Tb drug, is a new target. And so that came out in 2,012. So I put a little asterisk there for completeness. Of the drugs that are in the pipeline. 64 new targets are in the pipeline for antibiotic resistance for bacteria. 38 are targeting Tb. And C diff, which I don't hate Tb, and C diff. I just am telling you that's not what's killing everybody. And C. Diff is actually collateral damage often because you used antibiotics.
- And then uti and skin and soft tissue, which doesn't leave a lot for sort of new, aggressive emerging pathogens. Beige targets are new targets potentially, or new approaches and the red targets are modified.
- I just want to put this in contrast to another infectious disease to say that I don't just. I'm not just bagging on oncology, you know there were 1,030 drug targets for Covid alone between 20 to 21. So we can do this if we want. And then that's a picture of what's actively in the pipeline for on the FDA site.
- Okay so let's think about how important these are. If you want to imagine a world without antimicrobials at work, you can just look back 80 years. And this is data that I've shown before in grand rounds. Actually, because I love this paper because it shows how many people died from Terp from just getting a very routine procedure. When we don't have antibiotics, and so they dive e coli bacteria sepsis strep staff. And then they did die also of a granularcytosis, because all we had was sulphur. That wasn't really a sulfa drug like it was not trimethoprome sulphur, mind you, and so it's really important for modern medicine to have effective antimicrobials, surgery, dialysis, chemo, inflammatory conditions, all of those new drugs that we want to use on patients to make their lives better and longer. They need antibiotics because it often modulates the immune system, such as you can't fight infection as well.
- Also organ transplant. We know antibiotic resistance, antibiotic resistant infections, cause increased risk of hospitalization length of stay cost likely of going to the Icu and death. We also know that C. Diff is a collateral infection causes a lot of morbidity and mortality. We here at Eva still review every C diff case. That comes through that snows a comial in the hospital. Because we wanna make sure that we're optimizing antibiotics around this and that. We're not misusing antibiotics and leading to C diff in the hospital so the Cdc has gotten on board and really pushed that. And again, historically, public health and hospitals were somewhat divorced, but because of antibiotic resistance and some other stuff Cdc. Has recognized. They really need to get in the antibiotic resistance game and so improving

antibiotic use has become a public health imperative. And several of the things that I'm gonna say are about how the government is here to help with antibiotic use. But it's important to remember that that this is a really important priority for the Government and for us, and having gone you know, and lobbied politically around antibiotic resistance and funding and whatnot. It is a bipartisan issue, which is heart warming, cause there's not much that is and so what can we do? So fine?

- I can talk to Congressional people. But I'm talking to you guys at grand rounds.
- What can you do? Well, make sure that you're not spreading antibiotic resistance in the hospital. You're washing your hands. You're adhering to infection control. Do be aware of the types of resistance that you have in your hospital, and that your patients might have, and how you need to choose antibiotics based on how much resistance you have.
- But I think what I want to finish with is, make sure that you know we improve our antibiotic prescribing, because all those things that I showed the beginning where we're seeing antibiotics selecting for resistant infections. Let's do what we can to not have collateral damage.
- So at the heart of that is antimicrobial stewardship. So what is it? This is a slide bar from heather cause. I think it's nice looking. But it's the right antibiotic at the right dose, right duration to decrease the collateral damage on antibiotic resistance. C diff cost and improve patient outcomes. So sometimes we get called the antibiotic police, and I'll take that. We are a little bit policy. But we also are just trying to make sure that you get mit Ctl and the best antibiotic for your patients. Sometimes it means I'm calling you and saying, Please start myopenum and stop Septaraxone, or whatever it is, because I want your patient to get the right drug. Not the most narrow spectrum necessarily just want the least collateral damage for the infection. They have 3.
- So how can you decrease collateral damage? There's been a lot of papers coming out about shortening antibiotic courses. We have surgeon here in the room. Basically, what we know now is that it's really the dose in the or not. Days afterwards that prevent surgical site infection is just that dose that's needed. So shortening courses, shortening courses for treatment of urinary tract, cap, collapsy, bacteria, stop empiric antimicrobials when cultures are negative make sure that you're reading and understand how to interpret microbiology and I think it's here that, knowing your infectious disease syndrome, and what that looks like is really important.
- And I say this in the, you know shadow of Dick Bowman, who, you know it's essentially the best way that you can prevent and manage antibiotic resistance is to be a really good clinician and just pay a lot of attention. To what infectious disease syndromes look like. What don't they look like having kind of guts to stop antibiotics. It's harder to stop antibiotics than it is to keep them going and just know that. But you're protecting your patients, and you're protecting the subsequent patients. And so it's really, really important that we pay a lot of attention to this. It is really hard. And there's a lot of anxiety around P patients when they look sick target and narrow therapy whenever possible. Pay attention. If you're you've got an ampicillin susceptible. E. Coli, please use ampicillin. Know your guidelines and know who's at risk for Mdro.
- All right. So all you need to know to treat an infection is the source of infection. Is it pneumonia. What is it the type of antibiotics will work to kill the types of bacteria that cause infection at that site, you know, knowing that if you're in a biliary tree, or you've got biliary sepsis probably don't need vancomycin, because that doesn't work against E. Coli. And so, knowing what type and knowing something about your antibiotics or reaching out to pharmacists that can help you with that. Please don't ever give nitrogen for a systemic infection, because it only works in the urine and then understanding resistance. And who's

going to be acquiring resistance is going to be critical? I do think I'm gonna kind of finish out here with this is just going to get increasingly difficult, and we've already been facing some of this difficulty in the Us. For a while, and I'm going to try to walk through. What does that look like? And so what does the future look like?

- So I put this slide up. This is one of my original mentors from Maine. Actually, Rob Owens. He's a farm D, and he sort of put up this work chart that I love because it shows you how hard picking an antimicrobial is. You have to know a lot of stuff, and we just do this at like 2 am. I don't know is what the last guy did. So. That's what I'll do. But really, you do need to know. Infectious disease, your patients, your antibiotics does this patient even need antibiotics, and which ones are you gonna use? And all the things that have influenced your decision to start an antibiotic? It's quite hard we talk a lot in sepsis about. Did the patient get antibiotics in time? And I'm always like, you know what? When you open up epic and you type in antibiotics, there isn't an order that comes up right. You have to pick one of those antibiotics. And so and that's really critical to making sure that gets in in time.
- So because this is so hard and it's getting harder. I think this is an important concept, and it's trying to distill it down into a little bit of an easier how to cookbook. Choose an antibiotic. So it's the ideas is it's the 4 moments of decision making. This came from a Hopkins group. Trying to simplify this out of age. RQ. Work. So moment one, make the diagnosis. Moment 2. Do you have the right cultures and which antibiotic? Are you going to pick?
- Moment 3? Can you stop narrow or change often? This is a few days later, and then, once you've decided what infection they have. How long are you going to treat it?
- That's all you gotta do. So I figured I would take a case from actually this last week. I just went fishing in epic to find a good case that would reflect this. I'm going to go ahead and just preface that this is not an easy case. It is a hard case, and I'm not trying to make anybody look bad. But I just want people to. It's very illustrative of how hard this can be so. 69 year old, with myelogenous plastic, was hospital day 15, still in the hospital because of recurrent gi bleeding that nobody could stop and kind of figure out ended up kind of not doing well on the floor, and needed to be transferred to the make you for respiratory, hypoxic respiratory failure.
- Moment one does the patient have an infection that requires antimicrobials?
- Well, Amy, I have no idea you have not given me enough information about this but maybe and I think you might be thinking, is there respiratory failure being driven by an infection? And so that would be pneumonia right? Bacteria multiplying in the lung parenchema, causing hypoxemia.
- Well, thankfully, at Uva we've got some guidelines around hospital and ventilator acquired pneumonia. I don't think these are widely used. But that's okay. You kind of have this in the back of your head, anyway. But do you suspect pneumonia? Does patient have leucusytosis, fever, hypoxemia, and or perulin sputum. And what does the chest X-ray look like? You cannot diagnose pneumonia in the hospital without a chest. X-ray.
- If they've been in the hospital for more than 48 h which our patient has. We're on the right guidelines. If they've been in less, you should be using a different set of guidelines.
- And so we kind of ask all these questions do they have signs and symptoms, hypoxemia secretions?
- Is there another cause of the respiratory failure? So this is just this patient.
- They were a fever at the time. They had a white count of 10.5, which is nice and like
- on the cusp of anything. They ultimately continued to decline in the Mcu, and right before that they had this chest. X-ray. So not easy to read. I mean, there's a lot going on in this patient's long in the in a lot of different spots. And so this was read as bilateral airspace

opacities, and a similar distribution to one that had been seen previously before. The respiratory decline. A density from previous which may be evolving airspace disease. So moment one we're back to that. Do I need to start?

- Does the does the patient have an infection?
- Well, it was decided by the team that because of worsening respiratory status and the complicated chest. X-ray. Maybe they have pneumonia.
- Moment 2. Have you ordered the appropriate cultures? So I will say that blood cultures were sent at the time when this patient first transferred over to the Mccu, and immersive surveillance was done speed of culture was not obtained, but once the patient was intubated they were bronked so Because they got intubated they did. They did have a fever, I guess. I thought they didn't have a fever right at that time, but they ended up on Levifed initiated, got a blur, Sona's and blood cultures.
- The Gram stayed, for the BA. Was negative. The mercenaries were negative.
- I think everybody in this room is like, Well, boy pressers and a fever, and this patient with that chest X-ray.
- I'm starting antibiotics. So which anim microbial, do we start? So we're still in moment 2, which is a little confusing, because there's 2 things you have to do in moment 2. But which one do you? Do you order so for a hospitalized patient like this we recommend cephapen.
- It's got good pseudomonal coverage. It will cover extended antibacterials. And so that's actually what was done. Okay. this is where I think we're. I don't know. We'll just, I want to say, room for improvement. But anyway, we'll just say, this is where it gets a little dicey moment. 3. Can you stop the antimicrobials? Can I narrow therapy? Can I change from Iv to oral? I don't think anybody would change this patient to oral therapy on day 3 but a lot of times. You basically start antimicrobials, and you wait a couple of days for the cultures to mature and the other things to happen. Also, because the patient had a negative mercenaries, they were able to not start bank in the first place.
- So we're day. 3 cultures from the BI. And blood are all no growth. Ycount is 12. They're off pressers. They still have some secretions, and they have had 2 favors to 101 chest X-rays unchanged. And there's the differential, and that was the exact read.
- And so at 72 h we're asking, you know, what do you do next? The Cpis score can be helpful. And again, that's about fever, white count secretions, all the things we just talked about. But we've got a negative culture. So what do we want to do?
- We didn't do anything. We just kept the cephalopene going. So that wasn't really one of the options. If the culture is negative. you should consider stopping antibiotics, or you should think about a subsequent diagnosis. Maybe this patient's doing a little bit less the worse. They're still having a fever. I'm not sure what that's from.
- Maybe the pneumonia and the fever are the respiratory issues and the fever aren't related.
- But I think this is where we're tripping up a little bit. We've got a sick patient, and it's easy to just keep the cephapen going because stopping it. You're not sure if the patient had pneumonia or not. But we're not paying attention to our cultures, and I think this is why I'm bringing this up here. Because if this was just a one off case I wouldn't be bringing it up. I think we're doing this a lot. And this is where we're getting a little hung up.
- Day 6. We're still on cephalopene. And the note says, consider broadening the patient's antibiotics. I think if we were going to do that, we would need more culture data. But we didn't get more cultures.
- They did have a PE an episode of hypothermia. This is like straight from the note. So I apologize to whoever's note. It was unclear source of infection, ct. Sinus pending possible pneumonia, and so we don't ever make it to moment 4. And we just kind of keep the

cephapen going, because what's the duration of antimicrobials. And I need for this infection. We haven't really made a diagnosis of an infection.

- And so I think that's where we're really struggling. Well are we struggling at every other hospital has this right?
- I don't know but what's coming is that we are going to be reporting our data for how we're using antibiotics to the Federal government, and be compared to every hospital in the country. So that is coming, and all reporting for antibiotic usage and antibiotic resistance will be mandated. January 2020. Fourth. This is a lot like our caudi and collapsey that people are more familiar with, but it's called a sar, a standardized antimicrobial administration ratio. I think the problem is, you don't want to be a hospital that gets to 0 right? That would be the hospital that doesn't use antibiotics, which is not what we want. We want people to use antibiotics. We just want them to use them wisely, and so they try to account for. Are you a university hospital, do you do transplant a whole bunch of other things?
- But you know there's our saar. And again generally, this is a picture of the Uva star currently, and we said a little bit like we use a little bit less than hospitals that are sort of like. I don't know what that means. Maybe we're not treating infections enough. I don't know but what I wanted to talk about is this, sar, from our icu's from our mic, you and cicu
- This is a C diff, related. Sr, so you can see here that the government has decided what antibiotics are associated with. C diff most. And it's these guys.
- And then you look at our rate in our Icus, which is our cue and ricu. And what does our antibiotic usage look like in terms of those antibiotics. And what you see up there at the top is, we're quite a bit above one. We're like 1.5, and better for the last almost 2 years, and when you break it down it looks like it's more mic you than it is Cq. For these particular antibiotics, accounting for, which makes sense. You do use more antibiotics in the mic you than you do the sick use. So that's correct. But I think that most of this has been driven by our use of Cepheim, actually. And so here's a graph of our rates of antibiotic use of Cepheim in our micu alone, and then there is a schematic of what do we use in the Mcu? And it's Cepapeman Bank is the most frequently used per 1,000 days present. So I think what I really want to leave you with is like avoiding spiraling empiricism right like where you don't. And this wasn't my term. This is coined by somebody else, and it's inappropriate treatment or unjustifiable escalation. Escalation of treatment of a suspected but undocumented infectious disease. My patients really sick.
- The cephalopene didn't make them better, so I'll switch them to Miro, and then I'll switch them to Little Ad Bank, or and then I'll add mica. And actually what we need to go back and do is make the diagnosis and change in in sort of spectrum should be done, you know, sparingly and usually with data. And just remember your 4 moments of antimicrobial prescribing to find your way.
- So in the last, like 5 min. So I leave time for questions. I just wanna talk a little bit about where we're at with antibiotic resistance, I think for some, my Id colleagues. They have to know this sort of cold. What I want you guys to know about this is antibiotic resistance is here, and it's probably going to get harder and harder to use some of the new drugs, because the drugs that have made it to market are all very niche and target very specific resistance mechanisms. So in septic shock, we know that early antimicrobials are critical. This is across all species of bacteria. When bacteremic you need active therapy. So this is a study showing improved outcomes when you have active antimicrobials against Staph Aureus strepnuma, all of those organisms you have better outcomes, and this is defined in this study as within 6 h.

- So how has it been practicing in a place where you have crazy high rates of resistance? I do want you to know that in the world the Us. Has some of the highest Mersa rates in the entire globe. So I talked about, you know, we looked at all those other rates and other countries and whatnot, but our Mersa rates are much, much higher than most most of the world definitely higher than Europe, Australia, other countries.
- So what's the impact of that? Well, this is our glycopeptide use. It's 2,015. I couldn't find any more updated data, but this is how much vancomycin we use compared to the rest of the world. I think some of those countries may not have access. So that's a different problem. But yes. Oh, well, I'll keep going yeah, I can use that. So what one you know good news piece is that the university? Because of probably diagnostics and thoughtfulness, and figuring out how to live in a world with a lot of Mersa. We actually have been doing better with our vancomycin. So this is data that was compiled by heather, Cox and shows sort of across the hospital how much bank we've been using. And I think it's because of of diagnostics that we are able to get rid of bank sooner.
- We're paying attention to that. Mersa Narys is negative or mecha positive on a blood culture. And so what I want to finish with, too, because I do micro and I do. Id is where the diagnostics and how fit and how can they help us, you know, with emerging resistance. Empiric therapy is going to be harder. I hope we don't end up in this situation where all patients admitted to the Icu have to start with a carpop, but we may end up there we need mechanisms to guide specific therapy, and I'll show you a case here in a second where? You know, you couldn't have guessed at using one of the novel and microbial for everybody, because the resistance is just too niche and varied and then susceptibility testing used for refinement. And so resistance markers can allow for refinement in the space of bacteria kind of when you use antibiotic susceptibility or resistance data in your decision making to manage a sick patient.
- So we've had this for a long time. Our blood cultures get gram stain. We call that to you. But then we put it on a rapid molecular diagnostic, and since 2,014 we've been calling that goes directly to the fellows in this workflow that used to be really convoluted in the way that we did it. But when we went with the rapid diagnostic we wanted to make sure we got our money's worth, and we went ahead and streamlined it, and it goes straight to an Id consult. And by doing that we had improved mortality at Uva. In our 30 day, mortality in the management of staff aureus. And so that's impressive. So the pairing of diagnostics, these are not all mercy patients either was better with Msa. Management as well.
- And so pairing of diagnostics with good clinical medicine improve mortality, and the last thing I leave you with is, what about gram-negative, resistant organisms? And so this is a recent case. Some of you may know it. 59 year old. Liver. Transplant note. History of travel outside the Us. Had been in the hospital much like our other friend, with gi bleeding for a while and he became Lukeupenic and Septic. He gets started on Cephopian bank transfer to the Icu. And this is what comes out is a blood culture that grows e coli. And it states that there's Ndm. And I would be surprised if a lot of our house staff know what that means or what they should start. If you get this tag, and that's why all of these come to the stewardship team and we will call you it doesn't go to the fellows because we manage to Graham negatives on the stewardship team, and we take these 24, 7. But this is what the susceptibility profile looks like of an E coli that carries Ndm. It's pretty awful.
- And when we know in gram negatives, just like in all the other species that time to active antimicrobial therapy saves lives especially in very, very sick patients. I will say that patient did not survive that infection.
- Another role, that emerging. So when we think about carbapenum resistance, and I didn't point out but that E. Coli was carbapenum resistant carpentum resistance is emerging and

has been emerging 35% since 2,019 through the pandemic but it's changing. So carpopenum resistance is really complicated, and I won't get into it. But it's not as straightforward as Mersa. And so what happens is a gene of drug resistance can end up spreading in between a bunch of different bacteria and so that gene of drug resistance that hydrolyzes all carbapens as tree, and Ms. Cephalosporins can be shared across a bunch of different species. So species don't show up and say, Hey, I'm C. Re, you have to kind of know what you're doing and where to look and what species they might be most common in.

- It's gonna be increasingly important, because what's happening is the genes of drug resistance which in the Us were pretty much all Kpc have now since 2018, really started changing. And we're seeing more metallocarbases, which is what ndm is a metallo carbapenamase. This is data that will be released yesterday next week for antibiotic awareness week. But the Virginia Department of Health was kind enough to share it with me for this talk.
- Showing that now in e coli, it is just as likely that in the State of Virginia you will have an Ndm. As you will a Kpc. And for those that care or know what that exactly means is, there's not a lot of therapeutics. Well, Amy, who cares about this alphabet soup? It's a lot of letters and numbers, and I don't know. I'll just call an id consult you should call an Id consult, because these are the new drugs that have made it to market, and they all have super niche ways that they work. So basically, the new drugs were designed such that they worked against very specific enzymes of resistance.
- And so Sephazine AV backdam will work against Oxa, 48, but not Ndm. And, as you see across here, there's not much that works against Ndm. And suffitter a call, and that, made up convoluted isn't on the market. You just have to cobble that together. Therapy is something you probably shouldn't do without help.
- We do know, though, that if you use rapid diagnostics like the one that I just showed you where Ndm. This is a study out of Cornell. A colleague of mine, Mike Satlin, showing that Kpc. Pcr. Positive in the blood culture actually did get patients to therapy quicker and change mortality at 30 days. So in these drug resistant pathogens, even though this letters. All this alphabet soup is really complicated. It's gonna be really important for the management, because those patients need drugs that are active. And
- Maripentum isn't active against them. So
- I think I'm gonna so there, I finish with sort of, you know, practicing medicine in an environment with increasing antimicrobials. Resistance is going to be a balancing act. We're going to have to protect and preserve the antimicrobials and the microbes that we have.
- Well, we're simultaneously making sure we know how to manage and identify patients with antimicrobial resistant infections, and we'll put a plugin next week is antimicrobial awareness week.
- You're supposed to wear purple, which seems really weird to me. But November eighteenth, through the 20 fourth I am protest for turquoise and then call and antimicrobial stewardship whenever you, you know, need help prescribing. Call us call us call us. We'd love to talk to you so. Thank you very much, and I'll
- thank you that was so interesting.
- I think we all really wanna be good stewards and like, and really like, wanna make that effort. I think some of the things that I've noticed both inpatients, but maybe more on the outpatient side is trying to get patients on board. And so I was wondering if you had a spiel that you could share with us about how you go about counseling patients that might kind of push back on us, trying to be good stewards of antibiotics, and if you focus on, like the

individual risk that it poses to them, or more of the epidemiologic risk that it poses to them when you do the counseling.

- I don't think the epidemiologic risk plays with anybody. It doesn't play with you guys again. I mean, I well, I don't wanna give you mirror, but because, like, what about next year, you know, like you got a sick patient er you want the patient in front of you. Right? So that doesn't play. And that's not how we practice medicine. We practice medicine, taking care of the person in front of us. So I also, I partly give you some of that microbiome data that we do not really understand the collateral damage from antimicrobials fully. And I think we're coming to that now. And so I think that trying to incorporate some of that thinking and some of that downside and it's part of why I present it to you here today is like we don't really know all the impacts of you know, knocking out all your antaropes, long term or short term. You know the colorectal cancer risk. I think there's really good data that that is real and graph versus host. And some of the other things. There's just more and more increasing robust data.
- Having said that we have created a flyer for the Urology clinic because they because when they do pre-off urine cultures, their patients call. Say, I need antibiotics. It was positive. And they're like, no, that's just for staging. So we've created a handout of why you might not need anime microbial. And so we could share that also with a, and try to get some education in just handouts to patients about why you might not want to.
- Yeah. I'm the surgeon in the room I was intrigued by your comment about you know, draining fluid collections when possible, because you know you, you can treat lots and lots of fluid connection collections and surgical problems, perhaps with antibiotics, if you give it long enough but it also then turns into, are we using them? Right? Are we using the right stewardship? And one example of that? I'll just ask. Your opinion is that there has been a move towards trying to treat non-complicated appendicitis with antibiotics.
- And the data seems to show that you can do it under certain circumstances and meeting certain criteria. But you have to treat them for a week, and then the recurrence rate is anywhere I've seen anywhere from like 10 to 40 within a year. So II still share with patients that the standard therapy or standard of care would still be operation. But people kind of get scared by operation. So but they only get one dose of antibiotics right? If it's uncomplicated. And so to me, there's actually a a consideration to be weighed there, both for that patient, but also for the overall use of antibiotics for that kind of conditions. So I was interested in your comments on that.
- Yeah, I mean, I think there's 2 things. So I'll make a first comment that that whole idea of draining the focus a lot of times. What we see in infectious disease practice is, you know, a pocket of infection, and I just know it's medical therapy is not going to carry the day but it will make the patient look a little bit better until they have a chance to relapse, and they come off the antibiotics. And so it's very hard, because nobody wants to take, especially a really complicated patient with a hostile abdomen which I understand back to the or and sometimes it's not possible. And so how that interplay between that. But if you have a focus of infection that you know needs drainage, giving antibiotics potentially selects, for, you know harder to treat infections down the line, especially if you have a source that's gonna keep seeding. When I've got patients that have like Crohn's and keep getting intra abdominal abscesses. The last thing, the thing. It's so critical to keep those patients on short course antibiotics because you're selecting their gut flora, so that the next time they get an intra abdominal abscess, it's going to be more and more resistant. Chronic pancreatitis is another one where we see these almost untreatable.
- You know, pseudo Cis, that get infected. Having said that, I mean, II do think that it's powerful data that antibiotic appendicitis data is powerful data that you can treat sort of the

surgical infection with antibiotics, but the relapse rate. And so I think it would just be an individual decision for me, you know, like. I think, making sure that we've got full understanding of the collateral damage that antibiotics might cause, and then the counsel, the rates of relapse. I think it's an interesting concept. And again, we need to keep preserving the antibiotics. So that that is an option for patients, because if we had resistance, or if you were in Southeast Asia, that wouldn't be possible. There's no antibiotic that would work for Community Flora to actually get away with doing that. Just to throw one element of nuance into the examples you gave. Like, credit Chronos or a pancreas. Yeah, yeah, yeah, yeah. Yeah. The difference between those kinds of scenarios when you're trying to train fluid and treat versus appendicitis, and said with appendicitis, you've got a one and done surgical cure boom right? With the other examples, you're thinking, yeah, you're dealing with surgery absolutely.

- Again, if you have sort of a one-off surgical infection, you're seated with the floor that you walked in the door with. Right and not, you know. That's what you're infected with.
- If you keep having infections, you end up seated with more and more resistant infections. And so that is very different. And that's part of why that works. So you know, or could potentially work.
- Thank you so much.
- Maybe every id doctor here will know why. This is a dumb question. But II feel like, maybe you'll tell me my understanding is that patients like our cancer patients who are getting neutropenic. What they're colonized with my understanding is that they start being colonized with more of these gnrs, and that's actually what is living in them. And it's more dangerous. The bacteria they're living in them.
- So you said we don't use bank quite as much because of the mercenaries. So if you don't want Sephine to use, be used as much, where's our pseudomonasnares like? Why, why can't we get some more information like that, because it is really helpful. Yes yeah. So well, it's really hard. Because and ultimately, for the neutropinic patient you have to have pseudomontal coverage, because pseudomotis is such a problem. And there's just like, you know. 5 meaningful antibiotics that cover pseudomonas. And so it's a little bit trickier. But I think there are hospitals that are looking at like fluorquin alone. Prophylaxis. Should we be giving Fluorquin alone? Prophylaxis? So again, my colleague at Cornell is doing a study right now, looking at patients, Aml. Patients that go on and off. And they're cipro prophylaxis, not giving cipro prophylaxis based on a peri rectal swab showing. They have cipro resistant e coli, you know, or cipro resistant organisms? Should we be giving that to that patient? And is it preventing the next infection, which is what we're hoping to do with ciprophalaxis decrease the number of infections. But as we see, increasing resistance is that gonna work forever, I don't know, we don't know. But so thanks, thanks everybody.