**ANTHONY ATALA:** Thank you. It's really great to be with you this morning. What a pleasure to see all of you. And you know what I thought I would do today is just really give you an overview of UTIs. So much has changed, actually, in just the last five years, so I think it's a very timely topic. Basically, we're going to talk about these areas today. I want to talk all the way from prevalence to prevention and we're going to go through each one of these, and all the slides are in your handout as well.

So basically the prevalence of UTIs, as you know, it's most common in males in the early period, about zero to one years. And this is due to the fact that you're not circumcised. The effect really ends about six months of age. That's really when the effect ends, but it kind of trails down very, very slightly to one year of age when it's most common in males. After that, it's really most common in females and basically overall, about 3% to 5% of girls and 1% to 2% of boys will present with a UTI sometime during their growth.

Their recurrence is fairly high. It's about 40% within one year and about 50% within five years from the national statistics. Basically, we're going to go ahead and look at how do we know it's a UTI and, as you know, there are various ways of obtaining a urine, a clean void, a catheterized specimen, a suprapubic specimen. Basically, the fact is that a suprapubic specimen has really lost favor over the last several decades. It really has. When I was in training, this was really a common way to do this. Nowadays, you know, it causes a lot of anxiety for parents, so it's really not a great way to do it.

The one message, though, is no bagged specimens, right, unless you really, really are just doing a screening. But if you really suspect a UTI, of course, you don't want to get a bagged specimen because a positive culture is not going to tell you anything. It's not going to really tell you anything with a patient, really, it's just a contaminant or just a regular pathogen. So what you really want to do is, if you really suspect a UTI, it's best to stay away from a bagged specimen.

In terms of the diagnosis, basically you know about pyuria. It's not specific for a UTI. And the positive nitrite test is only accurate in 50% of the cases. So it gives you an indication of what you have, but not necessarily a definite diagnosis. So the definite diagnosis, of course, is the culture and it varies. Now this has also changed, by the way, so this is a new standard. It used to be that greater than 10 to the fifth colonies, so basically you had greater than 100,000 colonies in terms of a clean voided specimen. That remains. And that's now changed in terms of a catheterized specimen. We used to define that a catheterized specimen used to be 10,000. And now, it's basically 50,000. So that's really changed. And suprapubic expressmen used to be 1,000 and now it's 10,000.

So these parameters have changed. The clean voided specimen remains the same, but the catheterized specimen and suprapubic specimen standards have changed. Basically, as you know, the most causative pathogens are E. coli, the most common, Klebsiella and Enterobacter. And in terms of predisposing factors, basically anything that causes retention of urine is going to lead to added chances of UTIs. At room temperature, and this is what I tell parents, the doubling time is about 20 minutes. So if you start out with just one bacteria in one at 0.0, within eight hours you have enough bacteria to become a UTI if the patient doesn't empty.

And so it's really interesting, because patients, especially girls, are actually having bacteria going to the bladder all the time. The distance between the urethra, the outer portion of the urethra, and the inner portion of the urethra for a female, is less than the clicking point of your pen. That's how small the distance is. So actually, bacteria can get in there all the time. But what actually prevents the UTI is that they're really flushing the bladder all the time allowing for no retention. So it's really a number one thing that we look for in terms of how often are they voiding. In terms of bacterial properties, let's go back to a little bit of our medical school days, just to remember some of our concepts. But basically, it's bacterial adherence to the uroepithelial cells that involve specific adhesins, what we call adhesins, and basically they're associated with pili or fimbriae.

And this is actually a typical picture of what it looks like. You can see the P fimbriae there and how that bacteria uses that to attach to the uroepithelial wall. This is actually a true picture of a bacterium. You can see here all the fimbriae sticking out of the bacteria. So you can see how these things can latch onto the uroepithelial walls. In terms of treatment, as you know, we can use Bactrim or Septra, which are sulfa drugs, cephalexin, amoxicillin, nitrofurantoin. These are usually the most common treatments that are used and IV treatment is now another change. That's really rare. You know, if the patient is dehydrated and you really can't keep anything down, that's really when you go for an IV. You can also use IM dosing at the office and that also works.

So basically we talked about retention. So what are some of the defense mechanisms? Obviously, regular bladder emptying. So when we look at children who have a lot to UTIs, we usually counsel the family put them on avoiding schedule. You know, have them go to the bathroom every two hours while awake and that usually works well. There is also killing of the bacteria by the bladder wall that has its defense mechanisms, and, of course, the anti-bacterial properties of the urine itself. So all those things help the patient to not get the growth, continued growth, of the bacteria.

All right. So now we know that we have a UTI, right, and we obtained a urine specimen. We know that there was a UTI. What do we do then? How do we work it up? So basically, you're going to do an ultrasound of the kidneys usually and that's the recommended path now. You're going to do an ultrasound. In the old days, it used to be an ultrasound and a VCUG with your first documented UTI. You would get an ultrasound and a VCUG. That's now changed. Now you just get an ultrasound.

Now, and we're going to talk about the VCUG. There are circumstances where you really do want to get one, but we'll talk a little bit about that. Then the other thing that's changed over the last decade is really understanding the relationship between constipation and UTIs, right? This didn't even touch upon this area just until the last decade or two. And then you're going to look to see whether you want to do additional workup like a MAG-3 or a DMSA renal scan. And that's usually, we don't do it unless we see that there's a lot of scarring in the ultrasound.

So let's talk about the practice guidelines. And in 2011, we published clinical practice guidelines through the AAP, and the American Academy of Pediatrics, of course, and the pediatric urology section of the American Academy of Pediatrics. I was involved. We had membership in this committee, but there was a lot of controversy, really, on what to do with UTIs based on what was recommended by the practice guidelines. Well, let's talk a little bit about this. One thing to really understand is the practice guidelines were really focused on babies that were two to 24 months. So basically, it just covered the age from 2 to 24 months and we're going to go a little bit into that as well.

So basically, this is straight out of the Clinical Practice Guideline. If a clinician decides that a febrile infant with no apparent source for the fever requires therapy because of ill appearance or another reason, that your specimen should be obtained by catheterization, or a suprapubic aspiration for both culture and urinalysis before an antimicrobial is given. So basically, that's the first part of it, and here we talked a little bit about this already, what we're going to define as a positive culture. And the drug treatment you're going to do it orally, or parenterally is equally efficacious, so choices based on practical considerations. And the choice of drug is based on the local sensitivity, so that has not changed, and the duration of treatment seven to 14 days. So this is all standard at this point.

Now this is where the major change occurs. And this is basically only when you obtain a renal ultrasound and when do you get a VCUG? So basically, once you get the ultrasound, you get the VCUG if you see abnormalities in the ultrasound. This is with your first documented UTI. So you want to see whether there is any hydro present, and kind of nephrosis. You want to see whether there's any dilatation present. You also want to see whether there's abnormal renal size discrepancy.

Let me talk a little bit about abnormal renal size discrepancy. The fact is that when you read the ultrasound and you're looking at the size of the kidneys, you have to keep in mind that the left kidney is 10% larger than the right. Very important point. Because you look at the ultrasound and the ultrasound will say both kidneys are 7.2 centimeters. Oh great, is this normal. Actually, it's not normal. Because at that point, that left kidney is actually 10% smaller than the right. So you have to keep that in mind. The left kidney's 10% larger than the right so you have to compensate for that difference when you're looking at your study.

Also if you see any bladder wall thickening. So basically, any abnormality on the ultrasound will then guide you to a VCUG. So that's the change. Before it used to be you get an automatic VCUG. Now you want to get a VCUG and, again, this is between 2 to 24 months of age, you're going to get a VCUG if there are these abnormalities present. OK.

So once you've confirmed the UTI, then you're going to basically look at other things. If there's a recurrence of febrile UTI, then you want to get a VCUG, if the study has not been obtained with the first UTI. That's the main message. So the main thing is you're really placing a lot of emphasis on follow-up and making sure that these families are going to be consistently following up with a pediatrician.

So you're going to change, of course, things depending on how you feel about the family's reliability, right? If this is a family that you may not see, that may not have good follow-up, you may want to get the VCUG from the get-go. If it's an infant, if it's in the first two months of life, you will get a VCUG. OK. Because that's a high risk period for the baby. So before two months of age, you will get a VCUG and then you're going to also think about social considerations about getting a VCUG. And then if the patient presents with a repeat UTI, and you did not get a VCUG with the first UTI, then you're going to get a VCUG. So it's really changed.

So OK, so enough about the VCUG. Let's talk about now that know that you've done the work-up, you've done the ultrasound, you've done what you needed to do, what is actually causing the UTI? 40% of the time it's going to be reflux, OK, for a well-documented UTI. These are the statistics, if it's a well-documented UTI. Bladder dysfunction is going to be the other 40% and obstructive prostheses like posterior urethra valves and things which are less common, are going to be about 10% of the time. And then about 10% of time it's just going to be just predisposed. Some of these babies who are predisposed to UTIs due to genetic variability and genetic properties of that specific patient, genetic predisposition.

So this is actually another change because this bladder dysfunction that we are talking about has really been a major emphasis now over the last couple of decades in terms of really trying to get down to treatments that will allow us to manage UTIs in a good manner. And complications of a UTI, of course, are renal scarring and that can be for many reasons. So when you get a UTI, the challenge is that, if you do have a febrile UTI, and the UTI which means that indicates that it probably got to the kidney. By the way, a febrile UTI doesn't necessarily mean that it got up to the kidney and a UTI without a fever doesn't mean it did not get to the kidney, right?

You know that you can have these patients that came with three UTIs, no fevers, you do an ultrasound, you see all these renal scarring, and they never had a febrile UTI. So you can't go by that, but we're using standards to actually guide our practice. So basically as you know, things that can really lead to renal scarring are the reflux, the susceptibility of the host, obstruction like valves or UPJ obstruction, ureteopelvic junction obstruction, the host inflammatory response, or delaying therapy. Any of these things can lead to renal scarring so you really want to make sure that you address these possible complications.

All right. So basically here one of the major things that you need to know is that they have to be treated promptly, right? If you don't treat them promptly, there's more of a chance of the bacteria to start doing their damage up in the kidneys. So basically, prompt management, of course, is important. And the other thing is that you want to prevent hypertension and renal failure. This is an interesting fact that you may not recall. But what was the most common cause of kidney failure in the 1960s? Reflux. Reflux was the most common cause of pediatric renal failure. So we've come a long way to where we are today. So you know it's really easy for us nowadays to say, oh, well, you know reflux it's not important thing, you can manage it, et. Cetera.

But the fact is that we do have the history behind us to show us what can happen if you don't treat it. So that's the main point. I mean we've done really, really well with reflux because we've put so much emphasis on the right way to treat our pediatric population, but the fact is that if untreated, the consequences can be actually quite severe. So we do have to always be thinking of reflex in the back of our minds.

So let's talk a little bit about reflux. So as you know, the way that reflux occurs has to do with how the ureter enters the bladder. So here's the ureter, OK, and basically what happens is that the ureter courses through the bladder wall. And it's coursing through the bladder wall and it's giving you all that extra muscle. And if you don't have this muscle over it, then it causes reflux. So if you have it all the way down in the normal position, you have this long course along the bladder, which acts like a valve and prevents the urine from backing up as the bladder fills. But the further back you are, in terms of that muscle wall, the more chances that you have reflux and the more severe the reflux is. So that's really what causes the reflux is the position of the ureter in the bladder wall.

And we then grade reflux from grades one through five. And basically, with great five being the most severe, and great one not getting up to the kidney. And so we're going to manage these patients, of course, based on the degree of reflux that they have. The chances of resolution, let me go back here a second, the chances of resolution for grades of reflux from zero to three are quite high. Basically up to 80% of patients with reflux from grades one to three will resolve by age five. 80%. So my standard, my personal standard, is that I will not intervene in a baby with reflux grades one to three before age five.

I just actually keep monitoring these children because the treatment is you're doing open surgery, or deflux, and we'll talk a little bit about that as well, and they have their pluses and minuses. But basically, zero to three, I basically just watch them unless other factors come into play, right, and that's why we do the serial ultrasound. So we do the serial ultrasound so we can look at the growth of the kidneys. So we have to monitor and we have these curves, right, the renal growth curves that we all follow that show us that the kidneys are actually growing at the right pace.

So that's one of the things that we look at. We look at UTIs, recurrent UTIs despite antibiotic prophylaxis, if you're having breakthrough UTIs that is something that leads us into intervening earlier. If the regrade of reflux start getting worse, that is something that will lead us into doing the surgery earlier. But usually I'm a firm believer in letting nature take care of the problem before we have to intervene.

Now the recurrence rate of a febrile UTI depends on the reflux grade, and this is actually showing you the recurrence rate and what happens with prophylaxis or no prophylaxis in terms of recurrence. So the initial recommendations were that you would start to give prophylaxis for reflux or grades three or above only. Those were the initial recommendations that were made from the AP study, pending the RIVUR study, that large study, as you know, we were involved in that study here. We appreciate you helping us out with your patients because these patients were entered here and in our institution here at Wake Forest for this study. There were a total of 692 patients nationwide.

The very first nationally, randomized, controlled study looking at prophylaxis against no prophylaxis and these are the outcomes. The bottom line is that the study was just published in November of last year in the New England Journal of Medicine just about five months ago, and this study showed there is definitely a difference. If you get placebo against prophylaxis, you have a 50% higher chance of getting recurring UTIs than if you don't. And so basically, the recommendations based on the RIVUR study were to do place these children on prophylaxis. So that's back to that recommendation again. And there's been some controversy about that.

You know, and basically, it's very hard though, it's very, very hard. You know, sometimes we're all busy and we get these phone calls into the office, and our nurses start calling us, and you know, they're making decisions and it's very hard to manage this if you don't have a standard. You can get in trouble if you don't, you know, because now, if you don't have the prophylaxis. So it's really better to put them on prophylaxis. That's the bottom line. Of course, use your discretion. You know, if it's a patient who's older, over age five, who really has not had any challenges, has a low grade reflux, then you can be a little more flexible. But the younger, especially when their younger, when those kidneys are more susceptible to damage, you really do want to place them on prophylaxis. So that's really just hot off the press from this study that was published in the New England Journal just a few months ago.

OK, so what are the treatments? So the treatments for reflux are either open surgery or deflux. So let me talk about open surgery first actually. So open surgery has really been the gold standard. It really has been the gold standard for the field, mainly because it's 99% success rate. And once a child comes into the hospital, what we do is we do a small incision underneath the belly button, a Smiley incision and the Pfannenstiel type of approach just like a c-section, very low, small incision, four centimeters. You go in and you repair the reflux. And the way you repair the reflux is by creating that tunnel that the patient should have had to start with. So remember that picture we showed of what causes reflex, all we're really doing is lengthening the sub mucosal tunnel of the ureter. It's a 99 percent effect in this. However, the patients do need to stay in the hospital for two days and you know the recovery is a little bit tougher than the other condition.

The next treatment is endoscopic treatment and it's a very nice procedure because instead of having a one hour procedure in the operating room, you're doing a 10 minute endoscopic treatment and, basically, the patients go home the same day right after the procedure, and recovery is not nearly as complicated as doing open surgery. But the challenge with this procedure is that the failure rate is 50%. The overall failure rate per patient, per ureter, the success rate per ureter is about 66%, but you're not treating ureters, you're treating patients. So the patient has bilateral reflux, then you have a 66% chance that per ureter, you will treat that patient effectively. So in fact, the overall success of this procedure, per patient, is 50%.

So you have to really counsel families and that's where that balance comes in because you know you're placing that patient under an anesthetic, right? You're going through the whole process, the pre-op process doesn't change. You're going to take that patient through that whole process of going to the operating room, you're going to put patient to sleep, There on another anesthetic you're going to treat the patient and 50% of the time, there's not going to be the outcome you desire. So we do use deflux. Personally I use the deflux, but for very, very, specific patients.

So those patients have low grade reflux. The higher the greater reflux, by the way, the higher the failure rate, so that's overall 50%. So if they have low grade reflux and they are older, where they have not had a chance of resolution, then I'll go ahead and do it. Also those patients who just don't want that, you know, yearly VCUG, I try to really then lengthen the time of the VCUG, rather than go in earlier for the deflux. So I'd rather go a year and a half to get the next VCUG than doing this procedure, unless a patient and the families are really, really resistant. So my personal standard is still open surgery and I'll do the deflux for very, very select patients. And practice patterns change, but the statistics are real. So you need to let the statistics drive sometimes what you do.

OK. Dysfunctional voiding. We've talked about bacterial challenges we've talked about reflux challenges, so remember, 40% of patients are going to have a UTI because of reflux, 40% are going to have a UTI because of dysfunctional voiding. And so this is really the group of patients you really have to tackle in a very different way. So these are usually patients who are already toilet trained, right? You're not going to have dysfunctional avoiding on a patient, of course, who is not toilet trained. So after the patient's toilet trained, you start focusing on this. And usually there is what we talked about earlier, they're not emptying their bladder adequately.

And you know they're not emptying their bladder adequately and I usually ask the families, do they delay the time that they go to the bathroom, do you see them do the little dance? You know, or do you see them squatting? You know, like they will go and squat real quick and then come back up because when they are squatting, they're actually compressing their musculature and that's a sign that they're actually suppressing their voiding urge.

So I ask the parents about this. I say, well, do you ever see, you know? Because if they say no, no, they really did go to the bathroom, well how often do they really go to the bathroom? They'll say, well, you know, four times per day. Well, they're a child, you know, they're three years old, they should be going not four times a day, they should be going 8 to 10 times a day, Right? So the frequency of voiding at least every two hours, average about every two hours, while awake. And make sure that you ask about the dance and the posturing.

The challenge with patients who don't go to the bathroom to empty their bladders is that most, more often than not, those are the same patients that we have that also don't go to empty their bowels. OK? Pretty much, so that's why you're seeing this connection. They don't like going to the bathroom to empty their bladders, they're not going to want to go to the bathroom to empty their stools. And so that's a problem. Why is that a problem? Basically, constipation becomes a problem really because of the way that we are thinking about potty training.

The fact is how can you ask a baby, that is, you're changing the diaper in this baby, and they have a diaper that has stool in it five times a day or four times a day. OK and now you're going to switch them to toilet training and now they're only going to go and empty your stools once a day. What's wrong with that picture? So here's a baby who was stooling three to four times a day and now he's only stooling once a day. So that's the problem. That's why we're seeing such a large number of patients with this challenge. We're not training them correctly to start with. So we have to start focusing on that as well.

And we look at high residual urine. So once they do that, once they don't go to the bathroom frequently, what happens to the bladder is that if they don't go to the bathroom frequently and they are basically allowing the bladder to expand and they're inhibiting the contraction of the bladder, then that bladder muscle becomes tough. It's like working out. You're going to the gym and working out that muscle. Well, that child, that our patients are actually working out their muscles their bladder muscles major problem it's OK to have a muscle on your biceps it's not OK to have a strong muscle in your bladder the bladder muscles very fine and it's basically one of the only muscles in the body that keeps the pressure low while it's filling up.

So as your bladder fills, you're not feeling an increased pressure in your bladder. Your bladder pressure remains entirely the same. That's why you all just had coffee this morning, you're not sitting there, OK, now my bladder but 25% full, now my bladder is 50% full. You don't get the urge till your bladder is full. And that is because that muscle is very nice and soft and you're allowing that muscle to expand without any rise in pressure. Compare that to the child that's doing this contraction all the time and they're working out their muscle. Now their muscle's very hard and tough and the moment it starts rising in pressure, they start feeling it and leaking. So retraining that bladder is extremely important. So those are the facts, really, to keep in mind when you're treating these patients.

Here is a chart of what happens, as well, in terms of the voiding dysfunction. You basically, under normal conditions, you have this low bladder pressure on the left, OK, and the sphincter that is active, so basically you're going to empty your bladder, and when your bladder empties, your sphincter is going to basically be active and it's going to relax. OK. So you have this motion where the bladder empties and the sphincter opens. The child, who has dysfunctional voiding, they have been contracting their bladder all the time, often when they get the sensation to go, into their bladder, they're contracting their sphincter. They're contracting their sphincter, that pressure is being transmitted to the bladder, they're exercising their bladder, that muscle is getting tougher.

So a child with dysfunctional voiding does the following. They empty their bladder, but their sphincter's doing this. And when sphincter does this while they're emptying their bladder, you have a milking effect. The urine goes down the urethra, picks up the bacteria from the periurethral area and the perianal area, and brings it right back up. And that's how the bacteria gets up to the bladder. The urine goes down and up, and basically brings your bacteria right up with it. And so then you're damaging the bladder further by exercising that muscle and you end up with a very tough bladder. And so that is why we basically look at these children. When they get to that point, that's really when we obtain a urodynamic study. Yes, OK, five minutes? Perfect. Almost there. So when you get these bladders, that's when we go to a urodynamic study to see what the actual functionality of bladder is. When it gets to that point, and we do the urodynamic study, that's why we see the high pressure contracted bladder and that allows us then to guide the treatment.

So the treatment, voiding schedules that your child passes urine every two to three hours, you want to do double or triple voiding, you want to avoid the child holding the urine so that pattern where you can go to the bathroom every two to three hours while awake, or every two hours, well, you always say every two hours, because you know if you say every two to three, it's going to be four. So if you say every two hours, is going to be two to three, so it's what you tell the patient. Positive reinforcement techniques, right? Have the family give positive reinforcement. If they do this throughout the day, they get a prize at the end of the day, right? You don't want to punish a child, you want to reward the child for this behavior.

And if we really think that they have a dysfunctional bladder, before starting anticholinergics, you really do need a urodynamic study, otherwise, you don't know what you're treating, right, so you're treating blindly. And what I tell the families, once they present at this point, I let them know upfront, you know, this is going to take several years. This can take several years to manage this because they can start on the anticholingergics and they think that they're going to be OK within a few months and that's not going to be the case.

And then the dysfunctional elimination syndrome. Let's talk a little bit about constipation. But basically here you have the typical KUB. Look at this KUB. It's totally full of stool and I actually show the KUBs to the family to really drive the point. I show him the KUB and I tell them, this is six feet, they have six feet of intestine, and all six feet are full of stool. And then I ask them what the size of their stools are. And everybody uses the Bristol Stool Chart, right? Everybody uses it, many of us we use the Bristol Stool Chart, but the one thing that I asked the most actually is not about the Bristol Stool Chart. The thing that I ask the most actually is, what is the size of their stool? And not the length, but the width, and I have the mom or the child show me how big it is and you will be amazed.

You know, how wide, I mean, it will go like this. That's how wide the stool is. And guess what? The size of the stool for a child should be no bigger than my pen, the width, the width should be no bigger than my pen. So it's a dead giveaway that these children have elimination challenges with their constipation. So what we do is we give daily Miralax. There are many regiments, this is the regiment that I use are. There are many, many regiments, but this is one that is very nice it's mild. You don't have to change the child's habit much. We do Daily Miralax, just a dose every three days based on the stool chart. So basically, when we look at the stool chart, if they have two types one, two or three, I gave them a larger, the maximum dose.

Type four is normal. But remember, not normal while you're clean them out. So type four and five, I use a medium dose. Type six and seven, I use a low dose of the Miralax and they adjust the dose every three days. And then we do bowel clean outs at regular intervals. Regular interval could be weekly, bi-weekly, or monthly, depending on how bad they are. And it's usually a several year process because they have five months of stool in there. And you have to clean it out and I explain to them, not only do you have to clean out all that stool, but they're still eating every day, right? So you have to stay ahead of it and, basically, three things need to happen. They have to get all that stool out of the six feet of intestine, then they have to wait for the intestine to shrink back down, so you can start peristalsing again so they have a mental picture of what to expect for the future.

So prevention. Complete and regular bladder and bowel empty. Hygiene. So this is bathing, and frequent diaper changes for the baby, right? You want to make sure that if they have a diaper, that you're changing it frequently and that you're wiping from front to back. Even you have to teach parents too I'm sure I'm sure you all do to wipe from front to back even with a diaper, right so they don't have the stool come up to the genital area. Avoid bubble baths, of course, and avoid vaginal avoiding which is, I make sure that if they're female. I always ask about how do they sit on the toilet or sitting with their knees together or their knees apart?

And, of course, I ask them without giving them the answer. I'm like, how do you And they usually point have their legs together and I say you want to have the legs wide apart so your end goes into a toilet not up your vaginal cavity, That's what I explained to moms. So what I tell them is, have your child sit face in the toilet for the next day just so you see how wide your legs really have to be when you empty your bladder and that will avoid urine going back into the vaginal vault.

So basically to summarize then, I hope I've given you a good overview of UTIs and what to expect. We've talked about prevalence, diagnosis, predisposing factors, all the way to prevention, And I hope this was useful for you and basically in terms of recurrent UTIs twice, you want to make sure that you have the adequate diagnosis, that you identify all the risk factors including dysfunction avoiding and constipation, that you do a thorough work-up, that you treat the cost of course and then when we talk to families. that we focus on prevention. Thank you for your attention.