Fall 2022

CathetersPLUS™ Your one-stop shop for urological supplies

CathetersPLUS™ Education Series

The Urinary Microbiome with Dr. Curtis Nickel

Below are key highlights from Dr. Nickel's recent presentation on the Urinary Microbiome for our CathetersPLUS™ Education Series – an exclusive series of talks on the most important topics in Urology, chosen by you! Please contact your Red Leaf Medical representative for information on how to participate in upcoming sessions.

Discussion

- Learning objective: The bacteria in our body, including our bladder, kidney, and prostate, are our friends, not our foes

What has led to this awareness is modern non-culture technology such as next generation sequencing, by which we can identify the bacteria in our body by their genetic fingerprint. The old way of doing it, which has been going on for 100 years, is traditional plate culture. However, we can only culture less than 2% of the bacteria in nature, and probably less than 2% of the bacteria in our body.

When I went to medical school, the traditional dogma was that the urinary tract is normally sterile, and when you grow bugs on the petri dish from urine specimens, it means that you have a urinary tract infection (UTI). Well, the reality is, the urine is not sterile. The three photos below are next generation sequencing and PCR where we look at genetics of the urinary microbiome in the bladder.

Figure 1.1

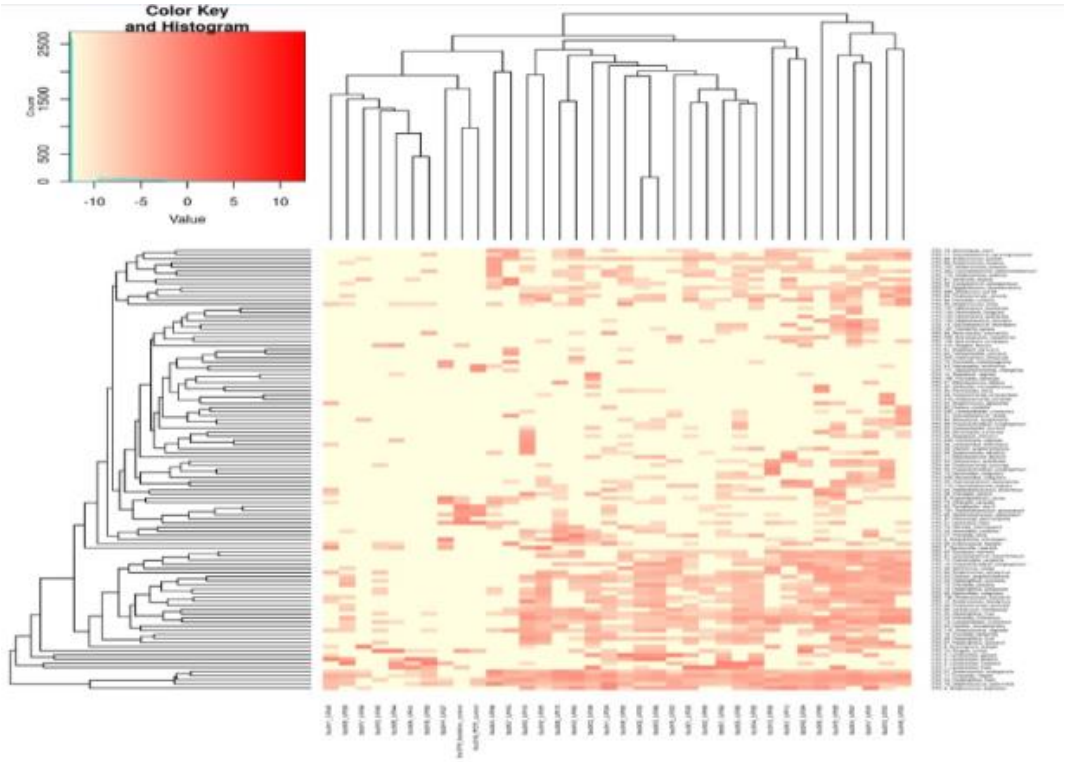


Figure 1.2

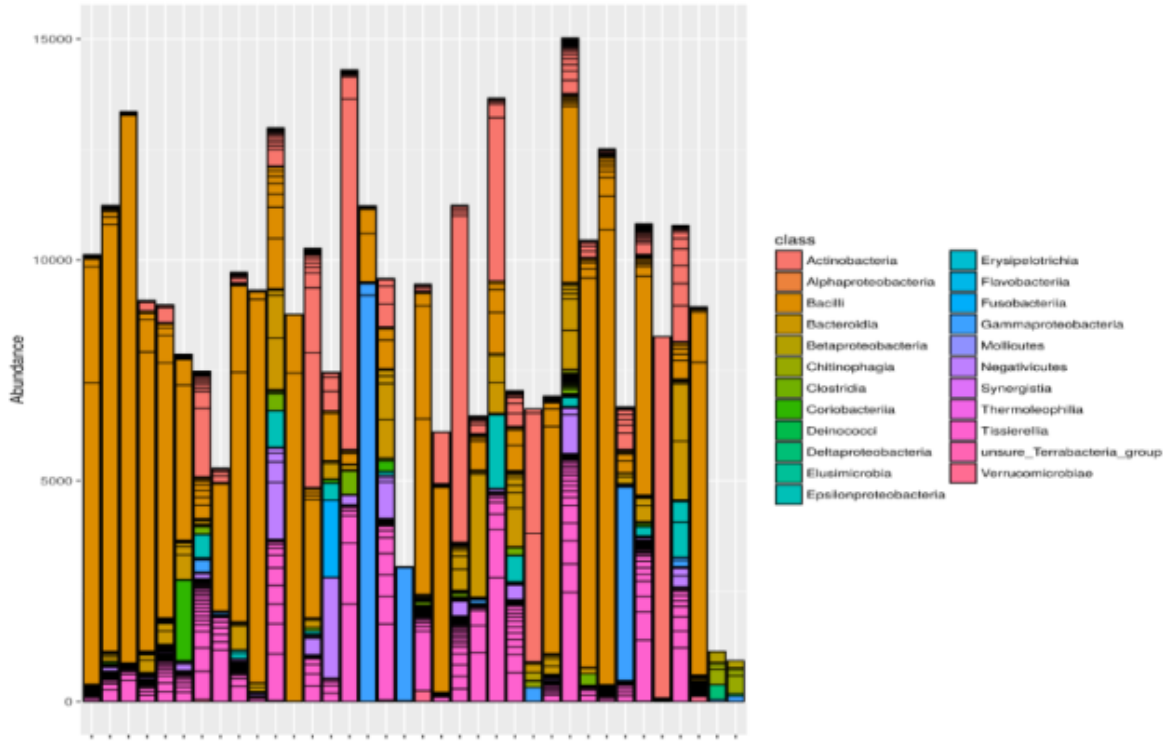
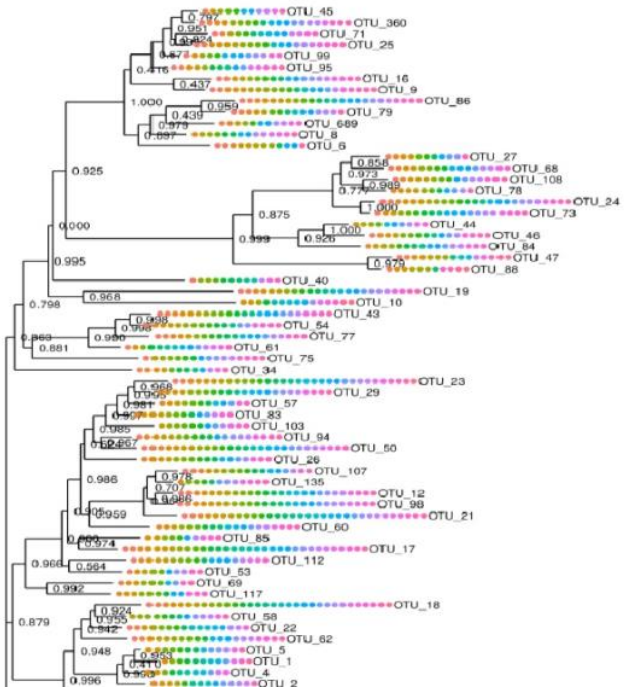


Figure 1.3



They are pretty pictures, sort of like Microbiome art, and somewhat difficult for the uninitiated observer to understand. Suffice it to say, the bladder is a microbial jungle, not a sterile organ.

As mentioned, this is very complicated. In the charts below, I am trying to find out if there are certain types of differences between males and females, and there are. Additionally, I have found that there are different types of female groupings as well. In figure 2.2, we have picked up at least 3 different types of female microbiomes in healthy individuals. Thus, even the healthy microbiome is influenced by gender. Whether you are on hormones as a female, what your diet looks like, your genetics, your geography, whether you have been on antibiotics in the past, other medications, other comorbidities, all of which impacting the bugs in our bladder.

Figure 2.0

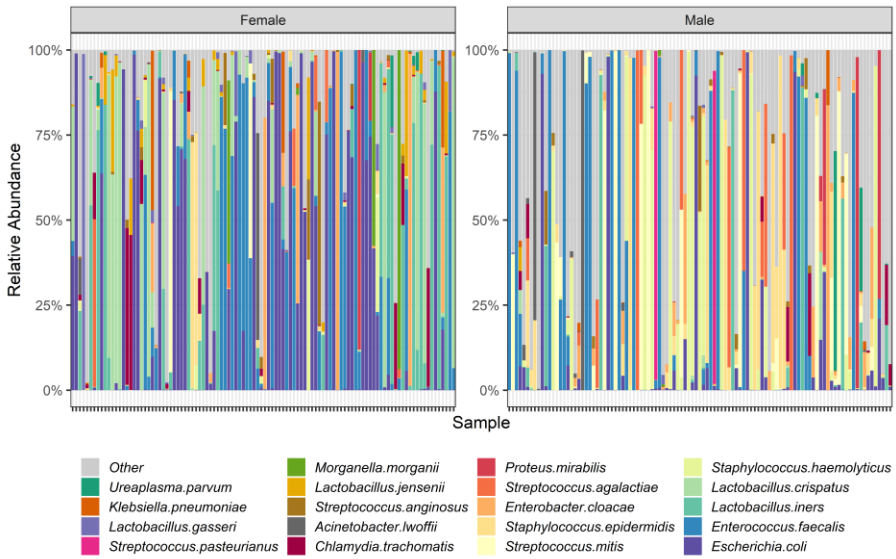


Figure 2.1

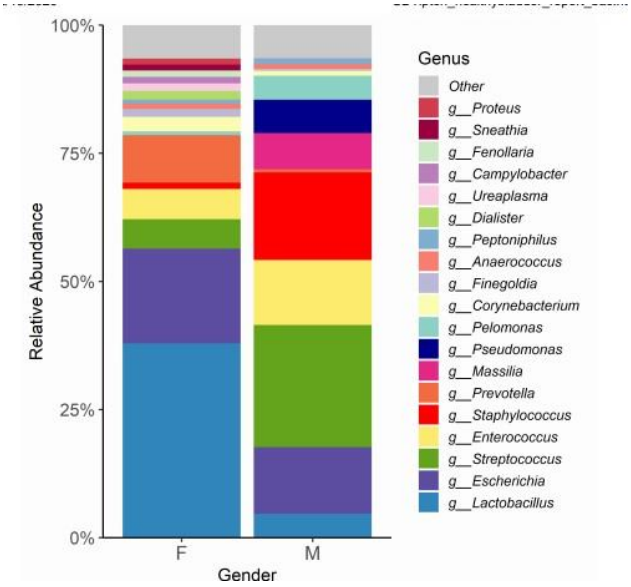
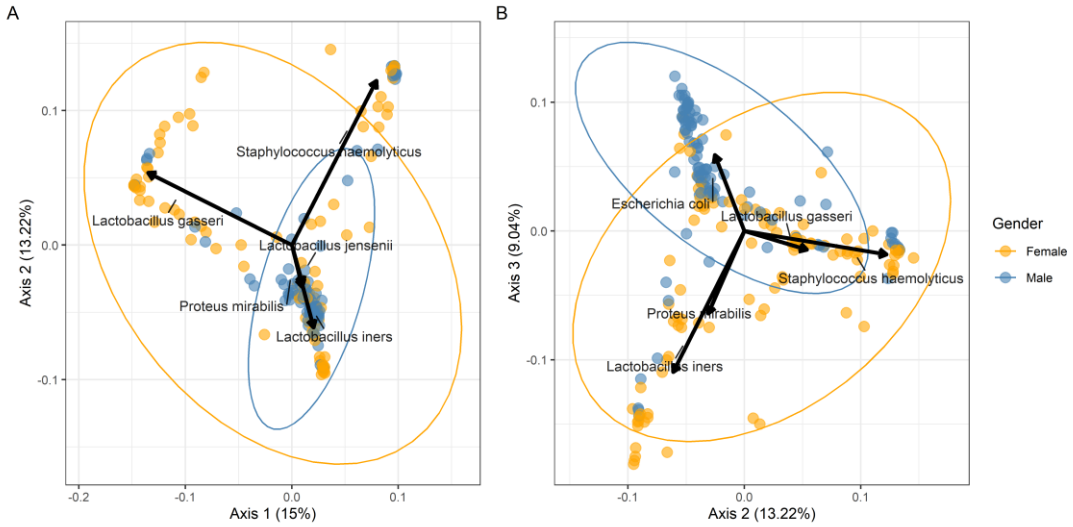


Figure 2.2



It is complicated to the fact that we know now that the bugs in voided urine, catheterized urine, within the urethra or in the vagina are all slightly different. They are interrelated communities within those areas that promote the health of the vagina, the urethra, the bladder, and even higher up the urinary tract.

We (and others) have undertaken several studies trying to figure out the microbiome of urologic chronic pelvic pain.

Figure 3.0

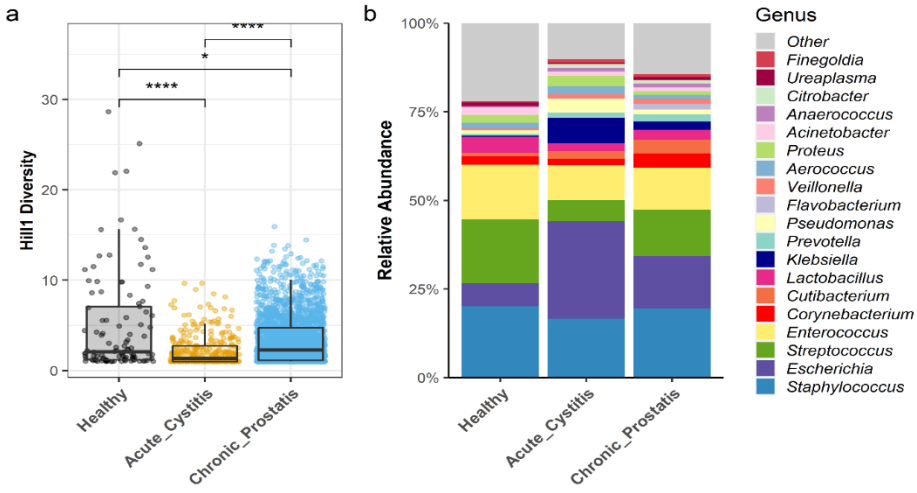


Figure 3.1

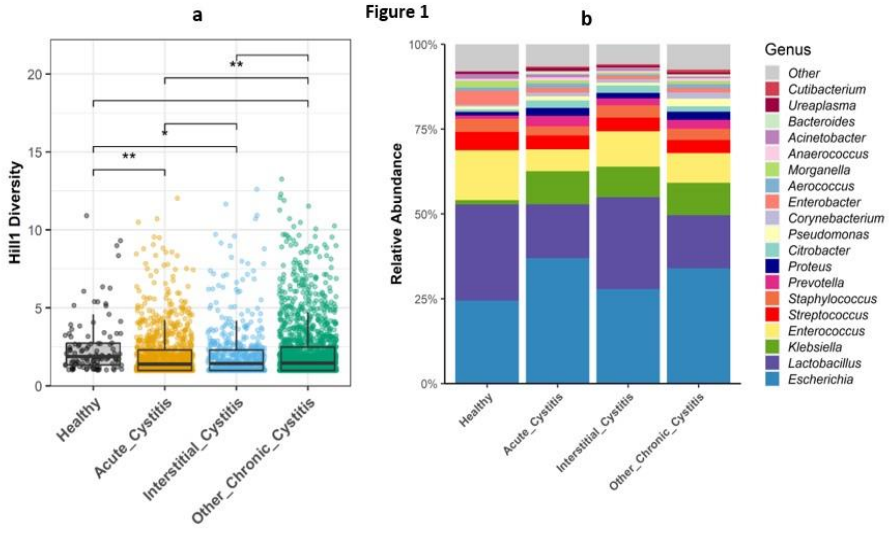


Figure 3.2

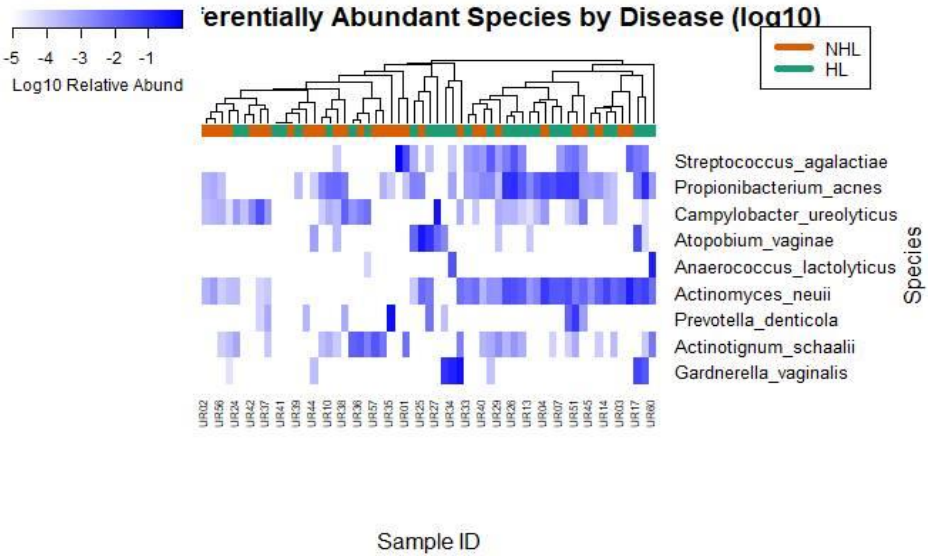
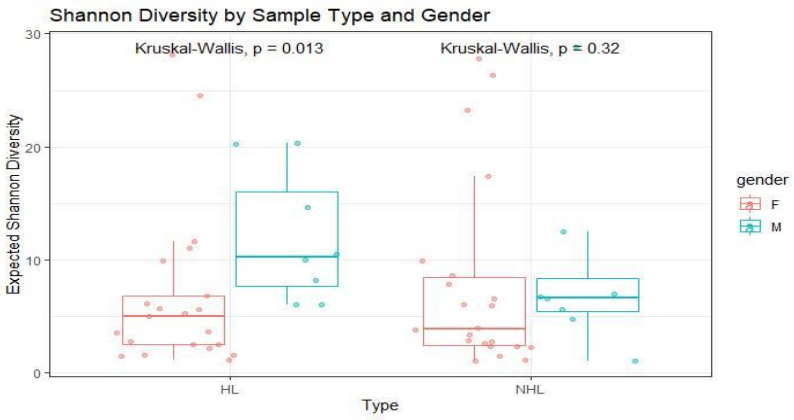


Figure 3.3



I have been very interested in interstitial cystitis and prostatitis. Figure 3.0 and 3.1 showcases thousands of patients in which we studied the microbiome. In figure 3.0 we compared those who are healthy to those with acute cystitis and chronic prostatitis. In figure 3.1 we compared those who are healthy to those with acute cystitis, interstitial cystitis, and other chronic cystitis. Whether we look at diversity or abundance, you can see there are some slight differences. However, the differences are not that significant, so, we were never able to find a smoking gun or pattern that differentiated interstitial cystitis or chronic prostatitis from healthy individuals by looking at bladder urine. Now, when we did look at a subgroup of interstitial cystitis (Figure 3.2 and 3.3), patients with hunner lesions, we can see a difference. When you look at figure 3.3 with Shannon diversity, there is a difference in diversity between those with hunner lesions and those with non-hunner lesions. We also have filtered by males and females. Slight differences were found but not enough to tell a complete etiological story.

So, now, for interstitial cystitis, prostatitis, and even hunner lesions, we are not able to implicate bacteria as the cause, but it does appear to have an impact on the symptoms.

The urinary microbiome is associated with other urologic disease, of course, UTI, which is when the microbiome has gone bad. Additionally, it is associated with prostate and bladder cancer, infection stones and other types of urinary stones, for example. The microbiome is associated in all these conditions; however, the question is, can we manipulate our microbiome for urologic health? Even at this stage we can, because through diet, exercise, avoiding stress, good sleep hygiene, avoiding environmental pollution, and above all, avoiding antibiotics, we can strengthen our urinary microbiome and help discourage disease processes. We also know how all 6 of these things improve our general health at the same time as improving our microbiome.

When it comes to urinary stone disease, we have been able to look at recolonization of the gut with a bacteria that appears to disappear with calcium oxalate stones. We are looking at how to disrupt aggregates of bacteria and are learning how to manipulate the mechanistic effects with bacteria and stone formation. This is all now in the research realm and not yet ready for clinical practice. Every year we see papers at the AUA and sometimes the CUA meetings, where it is made known that this could be the future to help us prevent and treat stones.

What about for cancer management? Well, we know that there is a tumorigenic microbiome, in other words, a microbiome that is associated with cancer. What we want to do is promote a healthy antitumorigenic microbiome, but it's becoming a little difficult to figure out what that is. We are looking at microbiota-based markers for cancer risk or detection. In doing so, we can see those bad actors in the microbiome, which means that you have a higher cancer risk, or may even allow us to detect cancer early on. We are also determining how the microbiota enhances treatment success because we know, particularly in bladder cancer, that certain microbiomes a patient has dictates greater success of not getting advanced disease. We may also soon target bacteria in the microbiome to bypass treatment resistance mechanisms of tumor cells and use the bacteria to deliver the anticancer agent to the cancer cells themselves.

The best model for the manipulation of the urinary microbiome for cancer is one invented by my mentor Dr. Al Morales in Kingston. He presented his novel ground-breaking work on BCG first in the 1970s. BCG is alive attenuated bacteria that are instilled in the bladder and through immunologic mechanisms, prevent or treat bladder cancer. These immunologic mechanisms treat carcinomas in situ and prevents early-stage superficial bladder cancer. This was in the 1970s, using attenuated live bacteria, introduced in the bladder, but BCG is still the best treatment for carcinoma in situ and early bladder cancer.

UTI is the one condition that the urinary microbiome is most involved with because that's when one bacterial species, usually one that's uropathogenic or virulent, takes over.

We do have supplements to manipulate our urobiome, that being: cranberry, intravaginal estrogen, D-mannose, and probiotics. We now know its very important that if patients are going to receive a cranberry extract, that it has at least over 30 milligrams of proanthocyanidins (PACs). In the case that PACs are not there and not verified, that cranberry extract is probably not doing anything for the patient.

As far as probiotics are concerned, they appear to help in some patients, but the evidence has not really confirmed the benefits. Even though the trials were not all together successful, I have many patients who swear by it. Others find D-mannose useful for E coli UTI prevention. Additionally, intravaginal estrogen treatment for postmenopausal women has proven efficacy in reducing recurrent UTIs.

Many believe in the benefits of probiotics (yogurt, sour cream, probiotic milk) that add lactobacillus and other good bacteria to our microbiome. Now, the big news microbiome marketing is prebiotics. In other words, foods that promote the good bacteria, so rather than probiotics with the good bacteria that you're introducing into the vagina or the gut, you are feeding the good bacteria and trying to starve the bad bacteria. Examples of prebiotics include asparagus, garlic, wheat bread, bananas, and many more.

An important study published in 2015 showed that asymptotic bacteriuria seemed to prevent symptomatic bacteriuria. They divided patients with a urinary tract and asymptomatic bacteriuria infection into two groups, one left alone and the other treated with antibiotics. The ones treated with antibiotics had many more recurrent UTIs than the group who had no treatment for their asymptomatic bacteriuria. The conclusion is then, if you treat asymptomatic bacteriuria, particularly in the aged population, you are more likely to have a symptomatic, real episode of cystitis.

The other concept that is very exciting is urine transplants in the patients with chronic cystitis. Introduction of a live attenuated nonvirulent E coli injected into the bladder after antibiotics eradicated the virulent bacteria. The group that had the urine transplants had smaller percentage of symptomatic UTIs over the years compared to the group that received a placebo transplant. This is going to be very important in the future for those with neurogenic bladders or those that require chronic foley catheterization.

We've been very involved in the work of MV140 which is a whole cell inactivated bacterial vaccine, developed in Europe for recurrent UTIs. There were 5 or 6 studies in over 1700 women that showed its benefits and safety. Recently we have published in the New England Journal of Medicine Evidence, a randomized placebo control trial that shows significant benefit in reducing UTI in women, making at least 55% of the patients infection free. We've just completed the first North American early experience study in Kingston. We have 64 women with recurrent UTIs, an average of 6 per year, vaccinated. In the year following, UTI rate dropped by 79% with over 40% being UTI free. So, my belief is that this vaccination strategy to impact the urinary microbiome in women with recurrent UTI is the future for Canadian women. I think this approach represents the future for the prevention of UTI.

Now, going back to our microbiome, are the bacteria our friends or our foes? Well, its not black and white, we can't go in and use antibiotics to kill everything in the bladder. What we want to do is through the various mechanisms that we talked about to try to help our microbiome become healthier. Either through foods or additives, or the future which I believe is vaccines, we will get a better and healthier urinary microbiome. That way, we are not only going to suppress UTIs, but also all the other urological diseases that we discussed.

Q&A

1. **If a patient is not symptomatic, but in the labs, we see that it's an infection, the doctor should avoid giving antibiotics as you said that it can develop cystitis?**

Correct, any time the patient is asymptomatic, unless they are having some sort of endoscopy, cystoscopy, or operation, its best not to do a urine culture. This is because if you get a urine culture and the lab says there is E coli infection for example, well in fact the patient doesn't have infection; they have asymptomatic bacteriuria. That is a condition in which bacteria are living in symbiosis with the other bacteria in the bladder. Which, we know its irrefutable now that if you treat that asymptomatic bacteriuria, you disrupt that nice balance of all the bacteria and you are more likely to get an infection. Now, what is worse is you are more likely to get an infection that might be resistant to that antibiotic eventually, so you hurt yourself in 3 ways:

1) The side effects of the antibiotics
2) You aren't helping the patient at all, and you are setting them up to get real symptomatic cystitis
3) You are increasing the possibility that you are going to get antibiotic resistance at some point in the future

It is very difficult to avoid treatment when you see a lab reporting that the E coli is a certain level of infection, but it is better not to.

2. You spoke about the urine transplant, are there clinics where we can do this?

No, not yet, they are experimenting in Scandinavia primarily, it hasn't got a lot of funding because it doesn't look like there's a lot of money to be made. So, the industry hasn't gotten involved really. But, if you look in the GI system where people get an overgrowth of infection, what they do is they use potent antibiotics to kill all the bacteria in the gut, including all the bad and the good guys. Then, they perform a stool transplant through a pill to repopulate with good bacteria. Now, they did it with a single E coli in the bladder and obtained good results, just think if we could take a healthy patients microbiome, concentrate it with all the good bugs, and put that in the bladder, I think we would get an even better result.

All information reviewed and approved by Dr. Curtis Nickel.