Reflections

The evolution of infectious diseases over a 40-year career

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For 40 years I have kept tabs on the evolution of thinking about urinary tract infections (UTI), and this has been an invigorating element of my professional life. It turns out that following a single disease over a long time can shed light on diseases in general, and it can illuminate our thinking about clinical problems as new tools become available. In the case of infectious diseases, we can be privileged to watch the disease evolve in front of our eyes well within the span of a normal career. We imagine that our medical knowledge is driven by scholarly interest, but it turns out that new tests and interventions can be powerful drivers of interest and research over and above clinical urgency. That makes it instructive to see how each piece of knowledge from microbiology, diagnostic medicine, epidemiology, pathophysiology, and therapeutics has been reflected in our construction of disease scripts and disease relevance.

My first publication was an editorial in the *Journal of the American Medical Association* in April 1982, on the topic of single dose therapy for cystitis.[1] It is hard to remember that this therapeutic strategy was somewhat in vogue four decades ago. In fact, it was literally in *Vogue* as presented in the July, 1982 edition with the catchy title, "Quick remedy for cystitis." While I do not recall being mentioned in *Vogue* in the intervening 40 years, I would not consider my career to have peaked that year.

Since that editorial, I have consistently and regularly been thinking about and trying to understand, urinary tract infections (UTI). Most physicians think of UTIs as a nuisance, unless they are personally experiencing dysuria. From the perspective of students and residents, the diagnosis and treatment of cystitis is self-evident once they learn the algorithm.

One of the earliest breakthroughs regarding UTIs (and well before my amateur editorializing) was the observation that simple quantitative tests can distinguish true infection from colonization or contamination. Every student learns that semi-quantitative urine cultures are significant when >100,000 colony forming units of a uropathogen (the famous 10^5 cfu) are found per milliliter of urine.

The seminal paper describing the rationale for this cut-off dates to 1956 in the *Transactions of the Association of American Physicians,* which may not seem familiar since it ceased publication in 1999, although the association is still going strong.[2]

Dr. Edward Kass (AΩA, University of California San Francisco School of Medicine, 1947) collected urine samples from a variety of clinics and showed that there was a bi-modal distribution of bacterial density in quantitative cultures. The space between very few (0-100) and many (100,000 or greater) was quite empty. He also showed that pyuria was strongly associated by high colony counts. What is less appreciated is that he was not looking at patients with classic clinical features of UTI, but rather people with diabetes, women with cystocele or pregnant at term, etc., who were attending clinics at the Boston City Hospital. The majority of the samples were collected from asymptomatic patients. To this day, clinical microbiology labs present semi-quantitative results which can motivate therapeutic decisions based on 70-year-old observations.

The long life of this observation illustrates how medicine grows around new concepts. If Kass had studied patients with dysuria, he might have found that many of them have pyuria and positive cultures that

do not quite reach the 100,000 cfu/mL level. When this was encountered in the 1980s, it was dubbed the "urethral syndrome" since it was reminiscent of mucosal infections such as chlamydia and gonorrhea as well as cystitis.[3] Over time, the distinction of low colony count cystitis from regular cystitis has faded especially as many symptomatic patients are now treated without collecting cultures. The >100,000 cfu/mL still lives on in the formal definition of a catheter associated urinary tract infection and is still listed as the cutoff for significance in many laboratories. Experts suggest a cutoff of >50,000, but for maximum sensitivity with acceptable specificity, >10,000 may be even more useful. The term "urethral syndrome" has been retired.

Asymptomatic bacteriuria

Another relic of the 100,000 cfu/mL cutoff is in the definition of asymptomatic bacteriuria. On the surface it might be hard to imagine why urine would be collected for culture in the absence of symptoms, but this is not a rare occurrence. For example, obstetricians look for bacteriuria early in pregnancy, and treat in order to eradicate bacteriuria to prevent subsequent pyelonephritis. The association of bacteriuria with poor fetal outcome is a less clearly established, but this rationale is often deployed to provide a second argument for screening for asymptomatic bacteriuria.[4]

Another clinical setting for urine culture is in the early phase of kidney transplant. Urine cultures are also often checked in elderly patients with unexplained fever, delirium, or failure to thrive. As a result, we have learned that asymptomatic bacteriuria is common in the elderly, especially those who are living in institutions. In particular, it is almost universal in people with long-term bladder catheters. The observation was made that even without symptoms, elderly adults with unexplained bacteriuria had shorter life expectancies. This led to a number of treatment studies that showed little or no benefit in either general or vulnerable populations, including people with diabetes and the elderly with the exception of pregnancy and kidney transplant.[5]

Cultures are often taken from patients with an unexplained problem without specific urinary feature to fulfill the mission of a complete evaluation. When enough random cultures are collected, some may be positive but represent something other than a UTI that needs treatment.

If treatment of this high grade bacteriuria does not improve outcome, what is going on? One school of thought considers this entity a dysbiosis rather than an infection. The normal urinary tract was long thought to be sterile or self-sterilizing. Using sensitive tools such as probes for microbial nucleic acids has shown a variety of organisms in bladder urine in the complete absence of symptoms. With cultures as the previous gold standard, a positive low-level culture was written off as extrinsic contamination.

Many channels of study have converged on a normal bladder flora that somewhat blurs the line of bacteria found on skin and mucous membranes that are also found in urine in healthy people. If that flora is disturbed, the ingrowth of enteric and other bacteria can result. This might account for the paradoxical observation that women with asymptomatic bacteriuria who received antibiotics eventually had a greater number of symptomatic infections than women who did not received antibiotics.

There is evidence that women with unexplained bacteriuria may have a dysregulated innate immune response to bacterial invasion. This is a difficult area to study since relatively few healthy women have >100,000 cfu/mL of bacteria at any given time, and would otherwise not come to medical attention.

When cohorts of women are studied with monthly urine cultures, there seems to be a stochastic distribution of positive cultures.[6] These usually clear by the next specimen collection. Only a small number of women go on to develop a clinical UTI. Guidelines for the management of asymptomatic bacteriuria generally caution against treatment, except in pregnancy and renal transplant.

Upper vs lower tract infections

Investigators noted that the site of infection was important in predicting the likelihood of success in treating symptomatic UTIs. Upper tract (kidney or renal pelvis) infections are more frequently associated with fever and flank pain than bladder or urethral infections. But, as tools were deployed to test the sensitivity of this distinction, it became clear that some patients with apparent cystitis actually could be shown to have upper tract infection.

Collecting urine directly from the ureter (one of the tests to distinguish upper from lower tract infection) was not a practical way to make this distinction, but showed that patients with minimal symptoms often had upper tract infections. The presence of antibody-coated bacteria in the urine suggests an invasive upper tract

origin that often shows up in a surprising number of patients presenting with cystitis who actually have upper tract infections. Since the site of infection influences the duration of therapy, this ambiguity of clinical features predicting site of infection has been challenging clinicians for years. This is especially true when prescribing single-dose therapy, which was documented to be fairly effective for cystitis but disappointing for pyelonephritis. This was state-of-the-art in 1982.

The presumed pathophysiology of cystitis included the possibility that mechanical pressure (perhaps from sexual activity) could push errant bacteria from the external genitalia into the urinary bladder. Once the organisms were suspended in urine they behaved as microbial flotsam on the metaphorical beach of the urinary bladder. In this formulation, the least amount of beach sweeping in combination with natural tides (a single dose of antibiotic accompanied by normal micturition) should be all that it took to return the bladder to its pristine state.

Another implication was that the high urine levels of many anti-bacterial drugs could make quick work of the infection, even for organisms that might be considered resistant if found in different body sites. This observation helped to explain why certain drugs to which bacteria were called resistant could nevertheless sterilize the urine and relieve symptoms, and why single doses could be effective.

Finding the source

In the 1970s it was known that the source of uropathogens in cystitis was the gastrointestinal tract. Bacteria that cause UTIs also adhere to colon and genital mucosa. The ultimate source of these bacteria, which enter the alimentary system, was a bit unclear in the 1970s since they are ubiquitous in the environment (including animals and food). In several studies, the same uropathogens causing UTIs in patients seeking treatment were also found in the GI tract of their partners. This includes men with pyelonephritis who shared these bacteria with their asymptomatic female partners. It was unclear in which direction the bacteria were traveling and whether they were conveyed via genital or alimentary tract contact.

More recent studies indicate that households often share strains of bacteria even if only one, or even no, member has clinical illness. The modern technology that confirms this has shown that households also share strains of bacteria that are similar to, but distinct from, the strains of the same species being shared in other households. This raises the question of whether the intra-household clonal dissemination arises from intimate or sexual encounters conveying flora from one partner to the other, or from general sharing of commensals associated with environmental objects, food, or pets. Over time, the households usually clear their colonization for reasons that are poorly understood.

The high level of precision in these household studies owes its success to a more low tech approach that was designed to answer a clinical puzzle at the end of the 20th century. In 2001, multiple college health services personnel noted an increase in the recovery from urine of *E. coli* resistant to trimethoprim-sulfamethoxazole—a previous reliable treatment for cystitis.[7] Once the health services showed these strains of *E. coli* to be similar within their own campus, and not so different from other TMP-SMX resistant strains from other campuses, there was a mystery afoot.

The natural next question was whether these same strains were being carried by other students or community residents. It was impossible to distinguish intimate partner contact from sharing food and toilet facilities as a common source of these strains. This trigger of finding a modestly resistant organism seems old-fashioned in the current era of multi-drug resistance, but illustrates the opportunity to explore deeper trends via careful observation and follow up. This unexpected resistance was the marker that led to the more detailed analysis showing community-wide dissemination.

Before WGS

In an era before whole genome sequencing (WGS), more basic tools provided a window into the epidemiology of gut carriage of uropathogens in patients with, and without, symptomatic urinary infection.

The ability to perform increasingly granular analyses of strains within a species has been essential to understand the epidemiology of UTIs. Early studies discerned variations by looking at surface markers such as somatic, flagellar, and capsular antigens, by identifying virulence factors and other phylogenetic commonalities. Pulsed field testing was able to distinguish strains of bacteria by looking at DNA segments as they migrate under varying electrical pulses. Although it is relatively easily done, it may miss subtle differences that are important, or it may be fooled by genetic deletions or additions that have little bearing on the base chromosome.

WGS is a more fine-tuned technique that can find every base substitution or deletion. It is most often used to characterize clones within an evolutionary radiation. Sequence typing (ST) finds a stable subset of strains distinguished from other sequence types by virtue of highly preserved genes, called housekeeping genes. While these genes are important to the function of the organism, tiny genetic variations that are physiologically unimportant serve as subtle markers of evolution.

A popular way to utilize WGS is to start by determining sequence type and applying WGS within each ST. For example, *E. coli* sequence type 131 is a strain that has circulated world-wide since the early 2000s, and is associated with broad antibacterial resistance including to most beta-lactams and fluoroquinolones. This strain is well suited to intestinal carriage and does not cause disease inside the gut as do some other *E. coli*. But it is a notorious cause of extra-intestinal infections including UTIs.

In 1982, the most commonly used drugs to treat cystitis were sulfisoxazole, trimethoprim-sulfamethoxazole, ampicillin, and nitrofurantoin. There was well recognized resistance to ampicillin, and amoxicillin-clavulanate, which was first FDA approved in 1984, and was later added to the list. Resistance to these first-line drugs was low, but there was fear that occasional resistance could disseminate as it had for beta-lactamase producing *Staphylococcus aureus* from earlier decades.

That prediction was prescient as resistance to all of these agents (with the partial exception of nitrofurantoin) began to pop up worldwide. New drugs, including beta-lactamase stable cephalosporins, fosfomycin and eventually fluoroquinolones, were developed and marketed. There was hope that new drugs could help keep up with progressive development of resistance. Fluoroquinolones provided broad anti-bacterial activity with little fear of resistance. Their mechanism of action appeared to preclude plasmid-based resistance since they interfered with plasmid replication.

This optimism was poorly placed because several kinds of new resistance began to emerge including resistance to antibiotics given only parenterally. Although beta-lactams were not preferred drugs for UTIs (except in pregnancy), they still had an important role in hospital-acquired UTIs. However, a burgeoning beta-lactam resistance problem was driven by an explosion of genes encoding easily transferred enzymes called extended spectrum beta-lactamases. They conferred resistance to drugs such as ceftriaxone and ceftazidime, and the plasmids with their genes could easily cross species lines.

Fluoroquinolone resistance began to emerge, and to no one's surprise it was also plasmid-associated and easily transferred. The *E. coli* ST131 bacteria referenced were disseminated worldwide and usually contained multiple resistance genes including several beta-lactamases.

The story of the evolution and conquest of beta-lactamases is fascinating in its own right, but a specific extended spectrum beta-lactamase in *E. coli* ST131 (called CTX-M-15) has its own interesting biography.

The CTX-M family

The CTX-M family of beta-lactamases originated in another member of the Enterobacterales (the same Order as *E. coli*) called Kluyvera. Within Kluyvera, an environmental gram-negative rod that rarely causes human infection, does not confer resistance to beta-lactams. But, once the CTX-M gene moved into *E. coli*, it provided high level resistance to critical antibiotics such as third generation cephalosporins.

However, CTX-M did not stop there. Countless point mutations and deletions within the genes for CTX-M resulted in a broad range of resistance phenotypes in *E. coli* and other enteric bacteria. The chance transfer of CTX-M into *E. coli* might seem like a stroke of exceptionally bad luck for humankind. However, it is known that CTX-M has entered *E. coli* on at least nine separate occasions, and each was from a different strain of Kluyvera.[8] This suggests a low barrier to entry of this genetic element from Kluyvera into *E. coli*. Awareness of this gene movement was only provoked when we tried to use advanced cephalosporins and encountered treatment failure. In a world where these cephalosporins are not regularly deployed, there is no evolutionary advantage to retaining these genes.

Unlocking the cause

Unlocking the cause of sporadic and recurrent UTI was a challenge in the 1980s, and continues to be one today. A mix of host and microbial properties was always suspected. Familial predisposition to UTIs was associated with certain blood types. While changing one's blood type is not practical, it might be useful to predict risk of infection or recurrence based on blood type. Papers from the 1980s and up to the present call attention to associations between blood groups and infection, and the most consistent association relates

to the Lewis types, and to secretor status.[9] While this makes physiologic sense, because blood types are essentially surface elements that are also present on mucosal cell, that could be anchors for specific bacterial virulence adhesins. Part of the enthusiasm for this research was an as yet unrealized optimism that immunity to UTIs could be induced by a vaccine against the bacterial adhesins that attach to these molecules.

It is hard to imagine a robust market for a vaccine to prevent UTIs against only one of many kinds of potential uropathogens when life-saving vaccines for other diseases go unused. Maybe that represents the comparative optimism of the 1980s when solving big problems seemed to be a matter of trying hard enough.

Three days are better than one

Whatever happened to the single dose strategy for treating cystitis? The simple answer is that subsequent studies found a sweet spot of three days to be better than single dose therapy. Even with relatively short follow up times, three days of antibiotics yielded better outcomes with minimal added toxicity. Increased treatment duration to a week and beyond offered no benefit and was understandably associated with more cost and side effects.

Nitrofurantoin seems to require a five day course to have equivalent outcome to three days of trimethoprim-sulfamethoxazole or a fluoroquinolone. After the fluoroquinolones were approved for treatment of UTIs, there has been very little success in the discovery of new oral agents for UTIs.

Current guidelines for empirical treatment of UTIs are a bit confusing as they recommend nitrofurantoin, trimethoprim-sulfamethoxazole (when local resistance is below 20 percent), and fosfomycin as first line treatment, and fluoroquinolones when the first three are not appropriate. The second-line also includes a variety of beta-lactams which means that five different classes (at least) of antibiotics are in the mix. It is rare to have culture data for individual patients at the time of initial prescription, and it can be difficult to get meaningful regional information on resistance patterns even in a hospital setting. Guidelines for treatment of cystitis and pyelonephritis are being revised from their most recent 2011 publication date.[10]

Conceptualization of UTIs

Over the course of four decades the conceptualization of UTI has also been refined and better understood. The empty vessel flotsam on the beach model has been replaced with a more interactive one. Bacteria can, and do, invade the superficial bladder cells and move from cell to cell without a planktonic phase in the urine (we do know that they are inside of cells.) This explains late recurrence of UTIs without intercurrent symptoms—the bacteria can hide in plain sight within bladder cells for weeks to months. This also helps us to understand the confusing data that were used to distinguish upper from lower tract UTI when clinical features were ambiguous.

For about 20 percent of women with cystitis, recurrences or relapses can be regular and debilitating. Even with attention to potential risk factors such as spermicide use, these infections can be hard to manage. Various interventions including long courses of preventive antibiotics targeted women with frequent recurrent UTIs. But, over time with the combination of increased antibiotic resistance, greater awareness of cumulative antibiotic toxicity and ecological harm, the appetite for suppression has diminished. There is still no dependable formula to help these patients though many are offered empiric antibiotic refills as a pre-emptive approach when symptoms begin.

What happens to patients with cystitis symptoms who prefer to avoid, or do not have access to, antibiotics? This question has been studied despite ethical concerns about withholding known effective treatment. In fact, many clinical trials for cystitis have included placebo treatment which approximates the natural history of UTI (aside from the placebo effect itself).

It is helpful to know what these studies showed what to expect in a post-antibiotic world, or in a setting where only parenteral drugs might be effective. Most of the trials in the late 20th century and early 2000s that included a placebo showed a slower recovery but eventual relief of symptoms and bacteriuria in most patients. A 2015 study comparing immediate fosfomycin vs. ibuprofen showed superior outcomes with the antibiotic, but resolution without antibiotics in two thirds of the women receiving a short course of ibuprofen. Ironically, fosfomycin is the last single dose antibiotic still used for UTIs.

A 40-year reflection

If, in 1982, I had a crystal ball that allowed me to glimpse the medical knowledge of 2022. I would have commented that a single dose antibiotic strategy could be a flash in the pan if slightly longer courses were

more effective at minimal added risk and expense. I would have asked if our understanding of cystitis was too much influenced by the availability of reliable, easy treatment rather than a deeper understanding of the ecology, host/pathogen interaction, and potential for the emergence of resistance. I would also have taken note of how we would use UTI epidemiology as a tool to provide insight into the dissemination of enteric flora through communities, and even down to the granular level of households. I would have marveled at whole genome sequencing which would have sounded like a super electron microscope drilling down to the literal molecular level.

The opportunity to use this technology to distinguish closely related strains, to complement our understanding of commensalism, microbiota and pathogenicity would have truly been exciting. I would have commented on the potential for this mild infection to become more worrisome as waves of bacterial resistance eroded our limited breakfront of existing antibiotics.

In 1982, I was not aware of the word, secular, which derives from the French *siècle* meaning century. But secular includes long periods of time shorter than a century, and certainly as long as a career in infectious diseases. I would advise myself and my colleagues to be patient and to learn from the secular trends of newer observations and challenges that would emerge from this common, modest, and crafty infection.

And, I would freely give credit to cystitis for the deeper understanding of human health and disease, and how that can be affected by even a single dose of antibiotic.

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