Information for GPs

The Truth about Chronic Urinary Tract Infections

The majority of GPs will have come across the following scenarios relating to UTI:

- patients who present with UTI symptoms, yet whose test results show negative for infection.
- patients who present with UTI symptoms and return low leukocytes counts, elevated epithelial cells and mixed bacterial growth. This is commonly reported as 'possible contamination' or 'sterile pyuria'.
- patients whose test results show positive for infection, yet who repeatedly fail to respond to antibiotics.
- patients who respond to the standard short course of antibiotics, only for their symptoms to return not long after completing the course.

A potential cause of the above illogical outcomes is a chronic embedded UTI (cUTI). These conditions are largely unrecognised.

If the above scenarios are familiar to you or your practice colleagues, we urge you to read the following information which we hope will give a clearer picture of a condition which, at its worst, is utterly debilitating and destroys quality of life.

Is There a Problem with MSU and Dipstick Urine Tests?

Researchers have known for years that there are substantial problems with current MSU cultures and dipstick tests. The literature has described deficiencies in standard laboratory cultures since the 1980s; the inaccuracy of the urinary test strips routinely used in clinics and hospital settings has been known for over 10 years. Although these test methods are considered the 'gold standard' diagnostic tools, long-term research into both, conducted at University College London (UCL), has established that a negative test result still carries a 50% chance of a UTI. Thus, half of all patients displaying appropriate UTI symptoms, but whose test results show negative, will have a genuine infection that goes undiagnosed and therefore untreated.

The existing 'gold standard' tests are founded on criteria set by EH Kass in 1960, which he based on results from a significantly narrow sample of people suffering from acute pyelonephritis. The limitations of the Kass criteria, and the consequences of those limitations, are explained below by the late Dr Paul Schreckenberger, Director of the Clinical Microbiology Laboratory at Loyola University Medical Center, Chicago:

> *"That's another myth—the fact that infections are present only when the bacteria are present at 10^5 or greater. And that was never the intent of Kass' original report. The amount of bacteria present in urine in people that have UTI varies throughout the 24-hour clock. When you get up in the morning and the urine has been concentrated during the night, sure it can be 10^5. But at 11 o'clock when you've had your coffee and urinated a few times, it can be 10^2 and that's also significant. But labs aren't culturing at 10^2 and so I think we miss a lot of true urinary tract infections by setting these cut-off limits based on another dogma [ieKass] that we think needs to be trashed. We basically have to relearn everything about the urinary tract because we were misled. Our beliefs were unfounded. We are now, with the new science,*

> *realising everything we were taught is probably wrong. The clinicians that we work with are quite distraught over this …"* (American Society for Microbiology, 114th General Meeting, 2014)

The issue of UTI testing was debated in the UK Parliament at the end of October 2016. Please click here to see the short report of the debate:
https://hansard.parliament.uk/commons/2016-10-28/debates/ED698119-52F3-4B8B-8B4B-5EDE7106FBE1/ChronicUrinaryTractInfections

The debate was subsequently reported in the November 2016 Pulse journal. If you missed this article, please click here to read more:
http://www.pulsetoday.co.uk/clinical/prescribing/gp-guidance-on-uti-testing-should-undergo-nice-review-says-health-minister/20033257.article

Is There a Problem with NICE Guidelines for UTI?

We say yes, there are significant problems. NICE acknowledged this in 2015 with the publication of Quality Standard 90-7, which admitted that their guidance in this area was inadequate and indicated a priority need for evidence based guidance to be developed. At present NO treatment guidelines exist for the 30% of patients (4 out of 5 of whom are women) who fail to respond to the standard regimes for simple or recurrent UTI. That a situation affecting such a substantial group should exist is deplorable. That so many of these patients should ultimately be diagnosed as incurable—and often even referred for psychological/psychiatric assessment—shows how crucial it is to reverse the present lack of understanding.

Is There a Problem with Short-Courses of Antibiotics to Treat UTI?

Yes, researchers say there are serious concerns about short-course antibiotic treatments for those with rUTI and cUTI. As you will know first-hand, the standard short-courses of antibiotics (3, 5 or maximum 7 days) work well for most people with an uncomplicated UTI. However, they frequently fail to resolve infections that are recurrent or that have become chronic. Some leading researchers in the field consider that these short-courses (as well as prophylactic courses) may even be a contributory factor in the development of rUTI and cUTI.

What are these Researchers Saying?

Scott Hultgren, Professor of Molecular Biology, Washington University, St Louis, suggests that the typical short-course Trimethoprim that women receive is ineffective in resolving these infections. He states:

> *"Ten days of trimethoprim-sulfamethoxazole (SXT) therapy reduces urinary recurrences and eradicates fecal colonization, whereas 3 days of SXT treatment has no effect over a twenty-eight-day observation period despite clearing fecal colonization acutely. Interestingly, SXT is unable to eradicate bacteria from the bladder reservoir even after a 10-day treatment regimen, thus demonstrating that the bladder reservoir can persist even in the face of long-term antibiotic therapy."* [1]

Hultgren has found this common pattern of recurrent UTI to be caused by uropathogenic escherichia coli (UPEC). He has demonstrated that, very early on during the initial acute UTI, a UPEC forms bacterial reservoirs inside the bladder, which then go on to re-infect the host:

> *"UPEC utilizes complex mechanisms to subvert innate defenses to persist and cause disease. The ability of UPEC to invade into superficial cells of the bladder has been shown to be a critical mechanism in the ability of UPEC to establish a persistent infection"* [2]

His research has also implicated prophylactic antibiotics in the development of antibiotic-resistant strains of UPEC, which women with rUTI are so often prescribed:

> *"Patients with chronic urinary tract infections are commonly treated with long-term prophylactic antibiotics that promote the development of antibiotic-resistant forms of uropathogenic Escherichia coli (UPEC), further complicating treatment."* [3]

Other researchers are finding that for some infectious diseases, much higher antibiotic doses are required to eradicate bacteria completely. For example: Professor Sun NyuntWai, Umeå University, Belgium, speaking of cholera, says:

> *"Antibiotics are no problem if the dosage is right. But if it isn't high enough, bacteria counterattack with an alternative strategy,"* [4]

From a Research Gate publication:

> *"Sub-lethal concentrations of antibiotics increase mutation frequency in the cystic fibrosis pathogen Pseudomonas aeruginosa"* [5]

References:

1. http://www.ncbi.nlm.nih.gov/pubmed/12438384/
2. http://www.pnas.org/content/101/5/1333.full.pdf
3. http://www.ncbi.nlm.nih.gov/pubmed/22089451
4. http://sciencenordic.com/weak-antibiotic-doses-undermine-our-body%E2%80%99s-defences
5. https://www.researchgate.net/publication/233837375_Sub-lethal_concentrations_of_antibiotics_increase_mutation_frequency_in_the_cystic_fibrosis_pathogen_Pseudomonas_aeruginosa

Is There a Treatment for Chronic Urinary Tract Infection?

Professor Malone-Lee at the Lower Urinary Tract Symptoms (LUTS) Clinic, Whittington Hospital, London, provides a tertiary clinical service for patients referred because they suffer from recalcitrant LUTS, recurrent UTI, chronic bladder pain/interstitial cystitis (IC), all of which are resistant to management

under known guidelines. These people typically describe symptoms, despite routine urinalyses which are consistently negative.

Through 20 years' experience in this field, Malone-Lee has developed a treatment protocol for these recalcitrant infections. The regime consists of bespoke long-term, first generation antibiotics and is successful in the majority of cases. Patients that do not fully recover generally find their conditions much more manageable, and their health and quality of life significantly enhanced.

Does the Treatment Result in Antibiotic Resistance?

Please read the empirical comments below from Professor Malone-Lee, Emeritus Professor of Medicine UCL, which bears out many of the findings detailed in the above section.

Notes on the dangers of using low-dose antibiotics:

> *"I am very nervous about low dose antibiotic regimes. I have had suspicions of mischief for some years but my worst fears have now been confirmed by murine experiments conducted in the USA. The trouble is that low dose antibiotic regimes appear to be a sure way of generating a difficult ingrained infection. Tom Hannan, in the USA has published data from working with mice. Their studies have shown that the biology is such that the low dose regimes generate immune and microbial strategies that encourage the evolution of quite significant deep colonisation that can be very difficult to sort out. This is the reason why we insist on tolerable high dose regimes using first-generation antimicrobials."*

Notes on why his treatment of long-term, standard dose antibiotics doesn't lead to antibiotic resistance:

> *"Contrary to popular expectation, we experience few problems with antibiotic resistance. There are Darwinian reasons for this because bacterial resistance results from evolution. The bacteria divide very slowly so that replication and variation are minimal. The antibiotic doses provide a lethal selection pressure that favours extinction, as opposed to evolution. For resistance to evolve the correct balance of variation, replication and selection must exist. Our approach is designed to subvert those elements."*

Notes on managing multi-resistant microbes using narrow spectrum antibiotics at a double dose:

> *"Patients with complex chronic urinary infections typically present with a history of multiple antibiotic exposure. Cultures, when positive, reveal multi-resistant strains. The history shows that hammering at these infections with advanced, powerful antibiotic is not making much ground.*

"The multi-resistant microbes require a protected environment, infused with powerful antibiotics in order to thrive. Evolution is always parsimonious. The multi-resistant microbes invest substantial metabolic effort into generating multiple enzymes for destroying antibiotics. Thus they are at a disadvantage if the environment does not merit such a spectrum of enzymes. Other less resistant microbes will then have an advantage. Thus if powerful broad-spectrum antibiotics are not in the environment the multi-resistant bacteria will struggle to compete with more common microbes.

"Ideally we should like to respond to this type of situation by not using antibiotics, but usually we are challenged by a rising infection in the urinary tract. Thus we take an alternative approach: We use first generation, narrower spectrum antibiotics to seek a way of dampening the infection. If the patient is at home, in their own environment, our expectation is that harmless commensals will start to assert dominance in the microbiome of the bladder.

"We can usually get greater purchase from the first generation antibiotic by using higher doses than normal. Because these drugs have been around for so many years they tend to be benign, as selection has weeded out the trouble makers. This approach requires a certain amount of dogged persistence and patience but our results are encouraging. Wherever possible we try to augment the regime by using Methenamine, though that is not always tolerated.

"The trick that we have frequently used to abort so-called multi-resistant infections depends on the antibiotic levels we can achieve in the tissue. A resistant bug will become sensitive when we double the antibiotic dose."

Current International Research

Chronic UTI Group, University College London (UCL), UK
Headed by Dr Jennifer Rohn and Emeritus Professor James Malone-Lee
www.ucl.ac.uk/nephrology/research

The Chronic UTI Group focuses on the microbial diversity and host/pathogen interactions of recalcitrant and recurrent urinary tract infection, with a special interest in how chronic/recurrent UTI differs from uncomplicated acute UTI. They are investigating how protected bacterial reservoirs might facilitate recurrence and antibiotic resistance. The team is currently working on a novel therapeutic treatment for cUTI which is soon to enter clinical trials. It involves encapsulated antibiotics in multi-layered microcapsules, designed to be targeted into the bladder to deliver a high, penetrative dose of therapeutic agent. The Chronic UTI Group research encompasses microbiology, molecular cell biology, immunology, tissue engineering, metagenomics, high-resolution imaging and biofilm biology.

The Center for Women's Infectious Disease Research (cWIDR), Washington University School of Medicine, USA, Headed by Professor Scott Hultgren
http://cwidr.wustl.edu/research.htm

The Center for Women's Infectious Disease Research (cWIDR) is investigating common and often overlooked infections affecting women, such as acute and chronic urinary tract infections, interstitial cystitis and sexually transmitted diseases. The research combines women's health, microbiology, immunology and infectious diseases, and has made significant progress with acute, recurrent and chronic UTI with the discoveries and understanding of uropathogenic E. coli (UPEC), intracellular bacterial communities (IBC) and biofilm infection.

The Marshall Centre for Infectious Diseases Research and Training, Perth, Western Australia
Headed by Professor Barry Marshall
(2005 Nobel Prize recipient for his discovery that stomach ulcers are caused by bacteria, not stress, and can be cured by antibiotics.)
www.ic-bps.com

After receiving letters over the years by people diagnosed with Interstitial Cystitis (IC)/Painful Bladder Syndrome (PBS), Professor Barry Marshall decided it was time to take on a much neglected area of research at his research centre. The first stage of research commenced in late 2016. His team's mission is: *"To evaluate the current knowledge about IC-BPS (Interstitial Cystitis Bladder Pain Syndrome), establish baseline measurements in normal persons and then find abnormalities in patients which might generate hypotheses, suggest causes and ultimately result in a cure."*

Loyola Urinary Education and Research Collaborative, Chicago, USA
Headed by Professor Alan Wolfe
www.ssom.luc.edu/luerec

The Loyola research team was the first to publish the discovery of the female urinary microbiota (FUM) in 2014 and continues to make in-roads in developing an understanding of the urinary microbiota and how it relates to health and disease. Once they have a clear understanding of the urinary microbiota, they hope to develop treatments for various LUTS conditions and syndromes that are, at present, not well understood.

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