CHRONIC
URINARY TRACT INFECTION
CAMPAIGN

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CHRONIC UTI INFORMATION FOR GPs

UTI accounts for 1-3% of GP appointments. Even for simple infections rates of recurrence are high. 20-30% of patients fail initial antibiotic treatment [1] and up to 70% experience another UTI within a year [2]. Up to 1.6 million women aged 18+ in Britain suffer from chronic lower urinary tract symptoms (LUTS)[3] but NICE guidance does not exist for chronic UTI and there is no quality standard for recurrent UTI. A significant number of men and children also suffer.

Negative dipstick tests and MSUs and the failure of short courses of antibiotics are for many sufferers the first step to a diagnosis of interstitial cystitis, painful bladder syndrome, urethral syndrome or overactive bladder. But numerous studies have shown dipsticks and MSUs to be unreliable.[4, 5]

IC, PBS, US, OAB: A DIAGNOSIS THAT IS FAILING CHRONIC UTI SUFFERERS

There is no widely accepted cause, cure or care pathway for these conditions.[6] Surgical interventions are painful, invasive and carry an inherent risk.[7] A 2016 analysis of 36 RCTs evaluating 1,822 participants found that bladder instillations are no better than placebo.[8] Patients are offered CBT, painkillers, anti-depressants and advised to learn to live with it.[9]

INFECTION — NOT INFLAMMATION

Burgeoning evidence suggests chronic LUTS are caused by untreated bacterial infections – not inflammation - and there is emerging evidence that chronic LUTS can be treated successfully with long-term narrow-spectrum first-generation anti-biotics. In a recent study 84% of patients reported feeling "much better" or "very much better" with this approach.[10] Effective early intervention is key to preventing chronic UTI. [11, 12, 13]

NICE GUIDANCE PRIORITISES TEST RESULTS OVER SYMPTOMS BUT THESE TESTS ARE INACCURATE

Compared with enhanced testing, standard urine culture missed 67% of uropathogens overall and 50% in participants with severe urinary symptoms and was unable to differentiate between the urine of healthy controls and overactive bladder patients.[14, 15]

Dipstick tests were just 56% sensitive to leukocyte esterase and 10% sensitive to nitrites in a study of patients with chronic LUTS without dysuria.[16] Urine culture missed 20% of infections in a 2017 GP-led study which concluded: **"The woman that is visiting you with typical urinary complaints has an infection. There is nothing more to explore."**[17] Another study found 19% of infants with a UTI will be misdiagnosed due to low bacterial counts.[18]

TREATING PERSISTENT OR RECURRENT UTI

- Believe your patient and treat according to symptoms, not just their test results
- Prescribe longer courses of antibiotics. Short courses are only effective for simple, uncomplicated UTI and repeated ineffective courses can promote microbial resistance [31]
- Ensure antibiotics are taken promptly and encourage your patient to return immediately if their symptoms persist
- Do not discount low CFU counts. In the presence of significant symptoms the concept of a threshold below which infection is discounted does not make sense
- Advise your patient on how to provide a concentrated clean-catch sample but do not discount 'contaminated' samples yielding weak mixed growth. Many UTIs are polymicrobial [32, 33], while urothelial cells are a marker of chronic infection [34]
- Don't send patients away with painkillers to see if things settle down or suggest their symptoms may be caused by stress
- Refer to a secondary facility specialising in treating chronic UTI

KASS: NO LONGER THE GOLD STANDARD

The Kass Criteria[19] was never validated for UTI. It originates from 60-year-old research on a small study of pregnant women with acute pyelonephritis. The threshold for infection (≥10^5 CFUs/mL of a known uropathogen) is disputed and 10^2 is stated in US and European guidelines.[20] Kass himself warns sufferers typically over-hydrate, diluting their urine. In requiring strong growth of a single uropathogen, Kass assumes "healthy" urine is sterile but RNA sequencing and quantitative PCR testing has disproved this.[21, 22, 23] Standard cultures are highly sensitive to E. coli but detect as little as 12% of other clinically significant species.[24]

A DISEASE MODEL FOR CHRONIC UTI

It is now known that uropathogens utilise biofilms – microbial communities protected by an extra-cellular matrix – and undergo morphological changes increasing resistance to both the immune response and to antibiotics.[25, 26]

Uropathogens in chronic or recurrent UTI colonise the urothelium, creating bacterial reservoirs which reinfect the urine when urothelial cells are shed days, weeks or months later. The colonised urothelium is weakened by the inflammatory process, leading to an increased rate of apoptosis. Prolonged inflammation of the mucosa also leads to remodelling, causing increased susceptibility to recurrent UTI.[27, 28]

Sub-lethal levels of ciprofloxacin promoted urothelial colonization and biofilm formation in murine studies,[29] and other research found it caused genetic changes conferring multi-drug resistance.[30]

FURTHER INFORMATION

This document and further information, including links to research is available at **cutic.co.uk**.

An international research effort is improving understanding and treatment of chronic UTI. The Hultgren Laboratory at Washington University School of Medicine in the U.S. and the British UCL Biofilm Centre are two such centres.

This information has been compiled by the Chronic Urinary Tract Infection Campaign (CUTIC). CUTIC is a patient group campaigning to raise awareness about chronic UTI, improve testing and treatment for sufferers, and challenge the belief that chronic lower urinary tract symptoms are caused by inflammation rather than bacterial infection.

1. Milo et al. Duration of Antibacterial Treatment for Uncomplicated Urinary Tract Infection in Women. The Cochrane Database of Systematic Reviews. 2005(2):CD004682
2. Foxman B. The Epidemiology of Urinary Tract Infection. Nature Reviews Urology. 2010 7(12):653-660
3. Rand Interstitial Cystitis Epidemiology Study 2010
4. Swamy, Gorny and Malone-Lee. Fallacies and Misconceptions in Diagnosing Urinary Tract Infection. July 2014 futuremedicine.com. https://doi.org/10.2217/fmeb2013.13.276
5. Kupelian et al. Discrediting Microscopic Pyuria and Leucocyte Esterase as Diagnostic Surrogates for Infection in Patients with Lower Urinary Tract Symptoms: Results from a clinical and laboratory evaluation. BJU International 2013
6. NICE Evidence Summary ESUOM26 (February 2014) Interstitial Cystitis: dimethyl sulfoxide bladder instillation and ESUOM43 (April 2015) Interstitial Cystitis: Oral pentosan polysulfate sodium
7. Santucci et al. Office Dilation of the Female Urethra: A Quality of Care Problem in the Field of Urology. Journal of Urology. 2008 180.5: 2068–2075
8. Ford et al. Intravesical treatments for painful bladder syndrome/ interstitial cystitis. 2016 Update of Cochrane Database of Systematic Reviews 2007, Issue 4. Art. No.: CD006113
9. Cozean, N and J. The Interstitial Cystitis Solution. 2016
10. Recalcitrant chronic bladder pain and recurrent cystitis but negative urinalysis: What should we do? Swamy, S., Barcella, W., De Iorio, M. et al. Int Urogynecol J (2018)]
11. Goneau et al. Subinhibitory Antibiotic Therapy Alters Recurrent Urinary Tract Infection Pathogenesis through Modulation of Bacterial Virulence and Host Immunity. 31 March 2015. Journal of the American Society for Microbiology (6) 2 e00356-15
12. O'Brien et al. Are You Experienced? Understanding bladder innate immunity in the context of recurrent urinary tract infection. Current Opinion in Infectious Diseases. Feb 2015 28(1):97-105
13. Hannan et al. Early Severe Inflammatory Responses to Uropathogenic E. coli Predispose to Chronic and Recurrent Urinary Tract Infection. PLoS Pathogens. 2010 6(8):e1001042
14. Gill K, Kang R, Sathiananthamoorthy S, Khasriya R, Malone-Lee J. A blinded observational cohort study of the microbiological ecology associated with pyuria and overactive bladder symptoms. Int Urogynecol J. 2018. Epub 2018/02/20. doi: 10.1007/s00192-018-3558-x. PubMed PMID: 29455238.
15. Price et al. The Clinical Urine Culture: Enhanced Techniques Improve Detection of Clinically Relevant Microorganisms. Journal of Clinical Microbiology. May 2016 (54) 5
16. Khasriya and Malone-Lee. The Inadequacy of Urinary Dipstick and Microscopy as Surrogate Markers of Urinary Tract Infection in Urological Outpatients with Lower Urinary Tract Symptoms Without Acute Frequency and Dysuria. Journal of Urololgy. 2010 183(5): 1843–1847
17. Heytens et al. Women With Symptoms of a Urinary Tract Infection but a Negative Urine Culture: PCR-based quantification of Escherichia coli suggests infection in most cases. Clinical Microbiology and Infection. 2017
18. Swerkersson et al. Urinary Tract Infection in Infants: The significance of low bacterial count. Paediatric Nephrology 2016. 31:239–245
19. Kass EH. Bacteriuria and the Diagnosis of Infection in the Urinary Tract. Archives of Internal Medicine. 1957 100:709-714
20. Stamm et al. Diagnosis of Coliform Infection in Acutely Dysuric Women. New England Journal of Medicine. 1982 307(8): 463-468
21. Drake et al. The Urinary Microbiome and Its Contribution to Lower Urinary Tract Symptoms. Neurourology and Urodynamics. 2017 36:850–853
22. Hilt et al. Urine Is Not Sterile: Use of enhanced urine culture techniques to detect resident bacterial flora in the adult female bladder. Journal of Clinical Microbiology. 2014 52(3):871-6
23 and 24. Price, ibid
25. Soto. Importance of Biofilms in Urinary Tract Infections: New Therapeutic Approaches. Advances in Biology 2014. Article ID 543974
26. Flores-Mireles et al. Urinary Tract Infections: Epidemiology, mechanisms of infection and treatment options. Nature Reviews Microbiology. 2015 May: 13(5): 269–284
27. O'Brien et al. A Mucosal Imprint Left By Prior Escherichia coli Bladder Infection Sensitizes to Recurrent Disease. Nature Microbiology. 2016 Oct 31;2:16196
28. Hannan ibid
29. Goneau ibid
30. Kohanski et al. Sublethal Antibiotic Treatment Leads to Multidrug Resistance via Radical-Induced Mutagenesis. Molecular Cell. 2010 February 12 37: 311–320
31. Kohanski ibid
32. Khasriya ibid
33. Wolfe et al. Evidence of Uncultivated Bacteria in the Adult Female Bladder. Journal of Clinical Microbiology. 2012 50(4): 1376-83
34. Swamy, ibid