



CHRONIC UTI INFORMATION FOR MEDICAL PROFESSIONALS

In 2008 it was estimated that nearly 45% of the world's population were affected by lower urinary tract symptoms (LUTS), and this is expected to rise.¹ Even in acute, uncomplicated urinary tract infections (UTIs), rates of recurrence are high; 25-35% of patients have symptomatic or microbiological recurrence following standard antibiotic treatment² and up to 70% experience another UTI within a year.³ Up to 1.7 million women aged 18+ in Britain suffer from chronic LUTS.⁴

To date, we do not have NICE guidance for chronic UTI.

It affects men, women and children and has a significant impact on quality of life, yet it is poorly understood.

Recurrent UTI symptoms are often treated with short courses of antibiotics. When negative urine dipsticks and midstream urine cultures (MSUs) are encountered, many patients are denied antibiotic therapy and are referred onto specialists where further diagnoses of interstitial cystitis (IC), painful bladder syndrome (PBS), urethral syndrome (US) or overactive bladder (OAB) are proposed on the basis of these negative urine tests. This is despite the fact that numerous studies have shown dipsticks and MSUs to be unreliable.^{5, 6, 7, 8, 9}

The MSU culture misses up to 90% of patients with a chronic UTI. The urine dipstick misses 60% of chronic urinary tract infections.^{5,6}

The dipstick test is positive for nitrite in <18% and positive for leucocytes in <40% of acute UTIs with positive MSU culture.^{5,6,7}

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

These are diagnosed after a UTI has been ruled out using the gold standard urine dipstick and MSU culture testing. There is no widely successful cure or care pathway for these refractory conditions.¹⁰ Surgical interventions such as cystoscopy, biopsy, urethral dilatation, cystodistension, bladder laser, botox injections, urodynamics and instillations are invasive, painful and often repeated when seeking a diagnosis. All of these procedures carry an inherent risk and are of no benefit to the patient.¹¹

A 2016 analysis of 36 RCTs evaluating 1,822 participants found that bladder instillations are no better than placebo.¹² Patients are offered CBT, painkillers, anti-depressants and often told they have to accept and live with it as a part of their ageing process.¹³

TREATING PERSISTENT OR RECURRENT UTI

- Believe in your patient's history and treat according to symptoms, not just their test results
- Prescribe longer courses of antibiotics until symptoms are cleared. Short courses are only effective for simple, uncomplicated UTI and repeated ineffective courses can promote microbial resistance²⁶
- Ensure antibiotics are taken promptly and encourage your patient to return early if their symptoms persist
- Do not discount low CFU counts or mixed growths and treat the symptomatic patients promptly. In the presence of significant symptoms the quantification of the bacterial counts on MSU culture are no longer accepted as a valid method of validating or disproving an infection, no matter how low the threshold is set.
- Advise your patient on how to provide a concentrated clean-catch urine sample but do not dismiss mixed growth as contamination as UTIs are polymicrobial^{7, 30} and urothelial cells are a marker of chronic infection⁸
- Encourage the patient to drink normally, as dilute samples often lead to negative results.
- Treat early on the basis of acute symptoms as tests are unreliable and inaccurate and remember that analgesia is not a substitute to antibiotics. Stress does not cause a UTI and not treating or believing a patient will certainly result in stress.
- In the presence of recurrent UTI symptoms, refer patients to a centre with a special interest in recurrent or chronic UTI and not to a general gynaecology, urogynaecology or urology clinic.

INFECTION — NOT INFLAMMATION

Burgeoning evidence suggests chronic and recalcitrant LUTS are missed bacterial infections which result in chronic inflammation, bladder symptoms and neuropathic pain. Effective early intervention is the key to preventing a chronic UTI.^{14, 15, 16}

NICE GUIDANCE PRIORITISES TEST RESULTS OVER SYMPTOMS BUT THESE TESTS ARE INACCURATE Standard urine culture misses 90% of patients with a chronic urinary tract infection.^{5, 6}

A study published in 2018 using urine specimens obtained via the clean-catch MSU method and utilising the UK microbiological protocols which are tailored to acute UTI, failed to detect a variety of bacterial species, including recognised uropathogens. The gold standard MSU culture was unable to differentiate between patients with LUTS and the controls.⁵ Evidence shows that it is not appropriate to rely on these tests for chronic UTI.

KASS CRITERIA: NO LONGER THE GOLD STANDARD

The current microbiological criteria to diagnose UTI is the Kass Criteria.¹⁷ It was never validated for all UTIs. It originates from 60-year-old research on a small sample of pregnant women with acute pyelonephritis. The threshold for infection ($\geq 10^5$ /mL of a single species of a known uropathogen) has been disputed and thresholds as low as 10^2 CFUs/mL are now reported in some US and European guidelines.¹⁸

Kass also made an erroneous assumption that mixed growth is likely contamination. It is now known that the urinary microbiome is complex and a normal bladder hosts up to 400 different species of organisms.^{5, 19} Advanced second-generation sequencing techniques and quantitative PCR testing have validated the presence of an array of bacteria as part of a healthy bladder biome with increased numbers in chronically-infected bladders. Despite this enhanced information, much research needs to be done in order to identify the causative agent/agents.^{20, 21, 22} Standard culture media are highly sensitive to *E. coli* but detect as little as 12% of other clinically significant species.²²

A DISEASE MODEL FOR CHRONIC UTI

It is now known that uropathogens utilise microbial communities protected by an extra-cellular matrix. These biofilms undergo morphological changes, increasing resistance to both the immune response and to antibiotics.^{23, 24}

Uropathogens in chronic or recurrent UTI colonise the urothelium, creating intracellular 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, resulting in an increased

susceptibility to recurrent UTIs.^{16, 25}

Sub-lethal levels of ciprofloxacin promoted urothelial colonization and biofilm formation in murine studies.¹⁴ Other researchers found it caused genetic changes conferring multi-drug resistance.²⁶

TREATMENT OF CHRONIC UTI

Antibiotics are only effective against actively dividing microbes. Bacteria embedded in the bladder wall are dormant and do not divide. These “persisters” are not targeted by most antibiotics which act at extracellular level. Tissue-penetrating antibiotics do not have the capability to kill dormant microbes hence they evade antibiotic attack.²⁷

An observational study in 2018 reported 10 year data from a specialist centre on 624 patients with CUTI treated successfully with long-term, full-dose, narrow-spectrum, first-generation antibiotics. The lengthy full-dose regime manages to suppress the bacterial activity as they emerge from the shed urothelium, thereby preventing reinfection of young and deeper cells.

In this study, **84% of patients rated their condition as “much better”** and of those, **64% rated their condition as “very much better.”** On average it took 383 days of continuous treatment to achieve symptom resolution.²⁸

A further study from the same centre, reported the consequences of cessation of treatment in 221 patients following an unprecedented closure in 2015. 199 patients reported deterioration in their symptoms, 11 patients required hospital admission due to severe urosepsis, one patient developed a renal abscess and there were other serious medical consequences as a result of this. Symptom scores increased after cessation and recovered on re-initiating treatment, providing a proof of concept that the treatment with antibiotics was indeed needed to keep CUTI at bay.²⁹

KEY MESSAGES

- Tests to diagnose UTI are highly unreliable and often falsely-negative
- Chronic UTI is on the rise and all clinicians need to be updated
- Symptoms and history are the key to a diagnosis
- Early diagnosis and prompt treatment is the key to preventing chronic UTI
- It is no longer acceptable to deny patients treatment on the basis of faulty diagnostics

www.cutic.co.uk for this document, references, links to research and further information

1. Irwin, D., Kopp, Z., Agatep, B., Milsom, I., Abrams, P. (2011) Worldwide prevalence estimates of lower urinary tract symptoms, overactive bladder, urinary incontinence and bladder outlet obstruction. *BJU International*, 108 (7), 1132-8
2. Milo, G., Katchman, E. A., Paul, M., Christiaens, T., Baerheim, A., Leibovici, L. (2005). Duration of antibacterial treatment for uncomplicated urinary tract infection in women. *The Cochrane Database of Systematic Reviews*. 2005(2), CD004682.
3. Foxman, B. (2010). The epidemiology of urinary tract infection. *Nature Reviews Urology*, 7(12), 653-660.
4. Berry, S. H., Elliott, M. N., Suttorp, M., Bogart, L. M., Stoto, M. A., Eggers, P., Nyberg, L., Clemens, J. Q. (2011). Prevalence of symptoms of bladder pain syndrome/interstitial cystitis among adult females in the U.S. *Journal of Urology*, 186(2), 540-544.
5. Sathiananthamoorthy, S., Malone-Lee, J., Gill, K., Tymon, A., Nguyen, T.K., Gurung, S., Collins, L., Kupelian, A. S., Swamy, S., Khasriya, R., Spratt, D.A., Rohn, J. (2019). Reassessment of routine midstream culture in diagnosis of urinary tract infection. *Journal of Clinical Microbiology*, 57(3), e01452-18.
6. Gill, K., Kang, R., Sathiananthamoorthy, S., Khasriya, R., Malone-Lee, J. (2018). A blinded observational cohort study of the microbiological ecology associated with pyuria and overactive bladder symptoms. *International Urogynecology Journal*, 29(10), 1493-1500.
7. Khasriya, R., Malone-Lee, J. (2010). 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 Urology*, 183(5), 1843-1847.
8. Swamy, S., Gorny, M., and Malone-Lee, J. (2014). Fallacies and misconceptions in diagnosing urinary tract infection. *Futuremedicine.com*. <https://doi.org/10.2217/fmeb2013.13.276> 9
9. Kupelian, A.S., Horsley, H., Khasriya, R., Amussah, R.T., Badiani, R., Courtney, A.M, Chandhyoke, N.S., Riaz, U., Savlani, K., Moledina, M., Montes, S.D., O'Connor, D., Visavadia, R., Kelsey, M.C., Rohn, J.L., Malone-Lee, J. (2013) 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*, 112(2), 231-8.
10. NICE Evidence Summary ESUOM26 (February 2014) Interstitial Cystitis: dimethyl sulfoxide bladder instillation: nice.org.uk/guidance/esuom26
NICE Evidence Summary ESUOM43 (April 2015) Interstitial Cystitis: Oral pentosan polysulfate sodium.
11. Santucci, R. A., Payne, C. K., Anger, J. T., Saigal, C. S. (2008). Office dilation of the female urethra: a quality of care problem in the field of urology. *Journal of Urology*, 180(5), 2068-2075.
12. Ford, A., Ballard, P., Ramage, C., Ogah, J. (2016) Cochrane Review: Intravesical treatments for painful bladder syndrome/ interstitial cystitis.
13. Cozean, N., Cozean, J. (2016). The interstitial cystitis solution: a holistic plan for healing painful symptoms, resolving bladder and pelvic floor dysfunction, and taking back your life. Fair Winds Press.
14. Goneau, L.W., Hannan, T. J., Macphee, R. A., Schwartz, D. J., Macklaim, J. M., Gloor, G. B., Razvi, H., Reid, G., Hultgren, S. J., Burton, J. P. (2015). Subinhibitory antibiotic therapy alters recurrent urinary tract infection pathogenesis through modulation of bacterial virulence and host immunity. *Journal of the American Society for Microbiology*, 6(2), e00356-15.
15. O'Brien, V.P., Hannan, T. J., Schaeffer, A. J., Hultgren, S. J. (2015). Are you experienced? Understanding bladder innate immunity in the context of recurrent urinary tract infection. *Current Opinion in Infectious Diseases*, 28(1), 97-105.
16. Hannan T.J., Mysorekar, I. U., Hung, C. S., Isaacson-Schmid, M. L., Hultgren, S. J. (2010). Early severe inflammatory responses to uropathogenic *E. coli* predispose to chronic and recurrent urinary tract infection. *PLoS Pathogens*, 6(8), e1001042.
17. Kass, E.H. (1957). Bacteriuria and the diagnosis of infection in the urinary tract. *Archives of Internal Medicine*. 100(5), 709-714.
18. Stamm, W.E., Counts, G. W., Running, K. R., Fihn, S., Turck, M., Holmes, K.K. (1982). Diagnosis of coliform infection in acutely dysuric women. *New England Journal of Medicine*, 307(8), 463-468.
19. Thomas-White, K., Forster, S. C., Kumar, N., Van Kuiken, M., Putonti, C., Stares, M. D., Hilt, E. E., Price, T. K., Wolfe, A. J., Lawley, T.D. (2018). Culturing of female bladder bacteria reveals an interconnected urogenital microbiota. *Nature Communications*, 9, 1557.
20. Drake, M. J., Morris, N., Apostolidis, A., Rahnema'i, M. S., Marchesi, J. R. (2017). The urinary microbiome and its contribution to lower urinary tract symptoms. *Neurourology and Urodynamics*, 36(4), 850-853.
21. Hilt, E. E., McKinley, K., Pearce, M. M., Rosenfeld, A. B., Zilliox, M. J., Mueller, E. R., Brubaker, L., Gai, X., Wolfe, A. J., Schreckenberger, P. C. (2014) Urine is not sterile: use of enhanced urine culture techniques to detect resident bacterial flora in the adult female bladder. *Journal of Clinical Microbiology*, 52(3), 871-6.
22. Price, T. K., Dune, T., Hilt, E. E., Thomas-White, K. J., Kliethermes, S., Brincat, C., Brubaker, L., Wolfe, A. J., Mueller, E. R., Schreckenberger, P. C. (2016). The clinical urine culture: enhanced techniques improve detection of clinically relevant microorganisms. *Journal of Clinical Microbiology*, 54(5), 1216-1222.
23. Soto, S.M. (2014). Importance of biofilms in urinary tract infections: new therapeutic approaches. *Advances in Biology*, 2014, 1-13. Article ID 543974.
24. Flores-Mireles, A. L., Walker, J. N., Caparon, M., Hultgren, S. J. (2015). Urinary tract infections: epidemiology, mechanisms of infection and treatment options. *Nature Reviews Microbiology*, 13(5), 269-284.
25. O'Brien, V.P., Hannan, T. J., Yu, L., Livny, J., Roberson, E. D. O., Schwartz, D. J., Souza, S., Mendelsohn, C. L., Colonna, M., Lewis, A. L., Hultgren, S. J. (2016). A mucosal imprint left by prior *Escherichia coli* bladder infection sensitizes to recurrent disease. *Nature Microbiology*, 2, 16196.
26. Kohanski, M. A., DePristo, M. A., & Collins, J. J. (2010). Sublethal antibiotic treatment leads to multidrug resistance via radical-induced mutagenesis. *Molecular Cell*, 37(3), 311-320.
27. Wood, T. K., Knabel, S. J., & Kwan, B. W. (2013). Bacterial persister cell formation and dormancy. *Applied and Environmental Microbiology*, 79(23), 7116-7121.
28. Swamy, S., Barcella, W., De Iorio, M., Gill, K., Khasriya, R., Kupelian, A. S., Rohn, J. L., & Malone-Lee, J. (2018). Recalcitrant chronic bladder pain and recurrent cystitis but negative urinalysis: What should we do?. *International Urogynecology Journal*, 29(7), 1035-1043.
29. Swamy, S., Kupelian, A. S., Khasriya, R., Dharmasena, D., Toteva, H., Dehpour, T., Collins, L., Rohn, J. L., & Malone-Lee, J. (2019). Cross-over data supporting long-term antibiotic treatment in patients with painful lower urinary tract symptoms, pyuria and negative urinalysis. *International Urogynecology Journal*, 30(3), 409-414.
30. Wolfe, A. J., Toh, E., Shibata, N., Rong, R., Kenton, K., Fitzgerald, M., Mueller, E. R., Schreckenberger, P., Dong, Q., Nelson, D. E., & Brubaker, L. (2012). Evidence of uncultivated bacteria in the adult female bladder. *Journal of Clinical Microbiology*, 50(4), 1376-1383.