Treatment of Recurrent Urinary Tract Infections: A guide *with evidence*

Acute bacterial cystitis is defined by the American Urological Association (AUA)/Canadian Urological Association (CUA)/ Society of Urodynamics, Female Pelvic Medicine & Urogenital Reconstruction (SUFU) as "A culture-proven infection of the urinary tract with a bacterial pathogen associated with acute-onset symptoms such as dysuria in conjunction with variable degrees of increased urinary urgency and frequency, haematuria, and new or worsening incontinence". These can be classed as uncomplicated (occurring in a urinary tract with no factors that would promote a Urinary tract infection (UTI)) vs complicated (occurring in a patient at higher risk for a UTI with factors that could potentially decrease treatment efficacy). These can be further classified into persistent and recurrent. Persistent UTIs are those where a bacterium is not eradicated in the urine two weeks after sensitivity adjusted treatment.[1]

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How do we define recurrent urinary tract infections (UTIs)?

According to the European Association of Urology (EAU), recurrent UTIs can be defined as more than 2 in 6 months or more than 3 in 12 months.[2] UTIs are more common in females, with a lifetime incidence of 50-60%, with males having a lifetime incidence of 13-14%.[3,4] This would make a UTI occurring in a man more suspicious and likely to be investigated. UTIs present with the symptoms described above. Dysuria is discomfort or burning passing urine, abdominal pain, flank pain, or fatigue may also be present with UTIs.

Conservative management

Treatment of urinary tract infections, as with many conditions, starts first with lifestyle modifications. Some of these include but are not limited to: good hygiene, good sexual hygiene- voiding pre and post intercourse, double voiding if a UTI may be brewing, wiping from front to back, avoiding constipation, increasing one's fluid intake (at least two litres of water a day). Increasing fluid intake was the subject of a 2020 systematic review by Scott et al which showed low evidence for the same; however, given the minimal potential for harm, this should be encouraged.[5]

Women can be referred to the British Association of Urological Surgeons (BAUS) information leaflet on UTIs, which is very informative.[6] If infections are not settling despite treatments and patients are experiencing pain or haematuria, then they should be screened for any sources of recurrent infection. Sources of recurrent infections include urological pathologies including but not limited to: urethral strictures, bladder stones, vesicoureteric reflux, cystoceles, hydroureter/hydronephrosis and kidney stones.

Supplements

Cranberry products: Cranberry products were the subject of a recent randomised study in which patients taking cranberry or cranberry with vitamin C were shown to have increased oxalate excretion. Oxalate excretion is a risk factor for renal stone development, so cranberry products should be avoided in patients with a history of renal stones.[7] A recent systematic review and meta-analysis of randomised controlled trials (RCT's) by Fu et al. 2017 found cranberry products to be beneficial- particularly cranberry tablets (low-quality evidence). The AUA/CUA/SUFU guideline recommends cranberry tablets (Grade C evidence (low level of certainty)).[1] EAU makes no recommendation regarding cranberry- but fails to mention Fu's review in their guideline.[2] NICE remain equivocal on this recommendation stating non-pregnant women may wish to try cranberry as a self-care treatment.[8]

D-mannose: This supplement works by inhibiting bacterial adherence to urothelial cells. This mechanism of action is interesting as roughly 80% of UTI's are caused by E. Coli, which are thought to use pilli to adhere to the bladder wall. **One RCT showed that 2 grams of D-mannose daily was significantly superior to placebo and as effective as 50 mg nitrofurantoin in preventing recurrent UTIs.**[9] AUA/CUA/SUFU currently advises they cannot recommend d-mannose due to the limited evidence available for it.[1] EAU advises that this RCT is "indicative but not sufficient for a recommendation", whereas NICE advises that some women "may wish to try D-mannose, as a self-care treatment".[2,8]

Vaginal oestrogens: Vaginal oestrogens are definitely recommended for preventing recurrent UTIs in postmenopausal and some perimenopausal women. These recommendations stem from a 2008 Cochrane review by Perotta et al., which showed good evidence for the same, with oestrogen creams noted to be superior.[10] AUA/CUA/SUFU endorses oestrogens (Grade B evidence (moderate level of certainty)).[1] EAU also recommends oestrogens (low level of evidence).[2] NICE also recommends oestrogens with the caveat of warning patients

Formulation	Composition	Strength and Dosage
Vaginal tablet	oestradiol hemihydrate*	10 mcg per day for 2 weeks, then 10 mcg 2–3 times weekly
Vaginal ring	17β-oestradiol	2 mg ring released 7.5 mcg per day for 3 months (changed by patient or provider)
Vaginal cream	17β-oestradiol	2 g daily for 2 weeks, then 1 g 2-3 times per week
	Conjugate equine oestrogen	0.5 g daily for 2 weeks, then 0.5 g twice weekly

Figure 1. Commonly used vaginal oestrogen therapy[1]

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regarding possible side effects of breast tenderness and vaginal bleeding. Patients can remain on oestrogens but should be reviewed at least once a year by their general practitioner.[8] Figure 1. Details the different oestrogen regimens

Hiprex/methenamine hippurate: This acts as a bacteriostatic and requires acidic urine in order to act. This could mean getting patients to take vitamin c or drink orange juice. This is not licensed for over-the-counter dispensing in Ireland, but it is in Australia. The evidence for this medication is lacking. A Cochrane review by Lee et al. in 2012 concluded that hiprex may prevent UTIs in patients without renal tract abnormalities but not in those with abnormalities. The rate of adverse events was low but poorly described.[11] This medication is considered less suitable for prescribing, but is still an option. AUA/CUA/SUFU were unable to recommend its use based on the evidence available.[1] EAU does not mention hiprex in their guideline.[2] Based on the evidence that hiprex was inferior to nitrofurantoin for prophylaxis, NICE were unable to recommend its use.[8, 12]

OM-89: This is a less well-known form of UTI prophylaxis. This is an oral vaccine which is a form of immunoactive prophylaxis. This has been shown to be superior to placebo for reducing UTIs in female patients in RCTs, as well as having a good safety profile. AUA/CUA/SUFU could not make a recommendation on this given a 2015 RCT by Wagenlehner et al.[1, 13] EAU currently strongly advise this based on four studies, including a 2013 systematic review and meta-analysis by Beerepoot et al..However, the EAU guideline does not reference this 2015 RCT.[2, 14] NICE does not mention immunoactive prophylaxis in their guideline.[8]

Antibiotics

Prophylactic antibiotics are an effective option for preventing UTIs, with many trials proving their superiority to placebo. It should be noted that the 10 of these trials quoted in the AUA/CUA/SUFU guidelines are all older than 1995, and while the results are acceptable, they should be interpreted in light of current resistance patterns.[1] The goal is to use as few antibiotics as possible as the problem with these is, of course, antibiotic resistance. The lowest dose should be given for the shortest time needed. Antibiotic prophylaxis should be given for 6 months courses. A trial of then stopping these is reasonable. If the patient's urinary tract infections recur, then a urine sample should be sent for culture and sensitivity and depending on the sensitivity of the grown organism, the antibiotic can be changed. This is to avoid treating an organism that is not sensitive to a given antibiotic.

Trimethoprim and nitrofurantoin are the most common. Using antibiotics as single-dose prophylaxis when exposed to a trigger was shown to be as effective, with fewer adverse events. These could be taken pre- or post-coitus in those who find this is a trigger.[15] Regimens for prophylaxis between the three guidelines vary slightly. All three guidelines recommend trimethoprim and nitrofurantoin, and cephalexin (NICE recommending this as second line).[1, 2, 8] Trimethoprim should not be given in pregnancy, and care should be taken with nitrofurantoin due to the risk of pulmonary fibrosis. The rate of pulmonary or hepatic adverse events with nitrofurantoin has been reported to be 0.001% and 0.0003%, respectively. Thus, this medication should be avoided in chronic lung disease, and caution should be taken with long-term prescribing.[16] Figure 2. Details the different antibiotic regimens according to each guideline

Another method of recurrent UTI treatment for those with good compliance is self-diagnosis and treatment with short-course regimens. AUA/CUA/SUFU recommends this (Grade C evidence) but does appreciate the risk for antibiotic overuse. To avoid this, these patients should be reliable regarding symptom insight and should endeavour to send urine cultures before initiation if possible. EAU recommends this based on Schaeffer's 1999 prospective cohort study.[2, 17] NICE does not recommend this based on the risk of antibiotic overuse and lack of RCTs.[8]

Breakthrough urinary tract infections can be defined as infections occurring with 105 colony-forming units per millilitre in a urine culture with an abnormal urinalysis (positive nitrite test or greater than five white blood cells per high-powered field or both) and a clinical course compatible with a UTI.[18] These can occur in individuals despite antibiotic prophylaxis. When reviewing these patients, it is important to assess their symptoms and differentiate between cystitis-like symptoms and a true UTI with a positive mid-stream urine for culture and sensitivity. If these patients are on prophylactic antibiotics, their daily dose can be stopped, and they should be treated with a full dose course. Their prophylactic antibiotics may then be resumed depending on their antibiotic sensitivities. If these infections are persistent, further investigations could be considered, including measuring a patients flow rate of urine and the quantity of urine they have left in their bladder post-voiding (post-void residual). Ultrasound is a quick and safe method to image a patient's bladder and kidneys to assess for anomalies. Endoscopy in the form of a bladder scope (flexible cystoscopy) can also be considered. Flexible cystoscopy is not offered routinely but should be done without delay in atypical cases, for example, renal calculi, outflow obstruction or urothelial cancer.[2]

References upon request

Guideline	Antibiotic	Dose	Frequency
AUA/CUA/SUFU [1]	Trimethoprim	100mg	OD
	Co-trimoxazole	40/200mg	OD
	Co-trimoxazole	40/200mg	Thrice weekly
	Nitrofurantoin	50mg	OD
	Nitrofurantoin	100mg	OD
	Cephalexin	125mg	OD
	Cephalexin	250mg	OD
	Fosfomycin	3g	Every 10 days
EAU [2]	Trimethoprim	100mg	OD
	Nitrofurantoin	50mg	OD
	Nitrofurantoin	100mg	OD
	Cephalexin	125mg	OD
	Cephalexin	250mg	OD
	Cefaclor	250mg	OD
	Fosfomycin	3g	Every 10 days
NICE [8]	Trimethoprim	100mg	OD
	Nitrofurantoin	50mg	OD
	Nitrofurantoin	100mg	OD
	Cephalexin	125mg	OD
	Amoxicillin	250mg	OD
	Pivmecillinam	200mg	OD

Figure 2. Prophylactic antibiotic options as per guidelines