1. Introduction and Who Guideline applies to

Recurrent urinary tract infections (UTIs) account for a significant proportion of referrals to Urology. The majority of men will be investigated via the One Stop Male LUTS (lower urinary tract symptoms) clinic. A minor proportion of men (neuropathic patients, transplant patients, immunocompromised patients and previous reconstructed urinary tract) should have obstruction excluded and will be seen in the recurrent UTI clinic. Women attending the recurrent UTI clinic will comprise both the pre- and post-menopausal cohort.

The following guideline covers management and treatment options within the Urology Department with the aim of a Consultant Urologist or Specialist Registrar seeing new patients, organising investigations (if required) and initiating treatment/management strategies. The majority of patients will then be placed on a patient initiated follow up (PIFU) pathway or be followed up by a Nurse Specialist (who may then also place them on a PIFU pathway).

2. Guideline Standards and Procedures

Primary Care Management

There is guidance for the management of recurrent UTIs in primary care including information on the prescribing of Methenamine. All referrals to Urology will be triaged against this guidance. The guideline is also available on the UHL Policies and Guidelines page for any other clinical specialities seeking to manage patients with recurrent UTIs.

Lower Recurrent Urinary Tract Infection Management in Adults UHL LLR Guideline.pdf (leicestershospitals.nhs.uk)

Secondary Care Managament

First consultant clinic attendance

Urine dip and post void residual on arrival (will be requested on triage of the referral)

Please assess and consider

1. Topical vaginal oestrogens in the peri- and post-menopausal cohort
2. Over the counter D-mannose
3. Over the counter cranberry tablets
4. Check USS KUB (should be done in primary care, request if not)
5. Consider flexible cystoscopy if red flags including pain, microscopic haematuria, recurrent visible haematuria, previous synthetic mesh e.g. TVT/TOT
6. Check recent HbA1C

Nurse led follow up 1

1. Check all of the above done, if no better then consider Methenamine
2. Consider flexible cystoscopy if not done already

Nurse led follow up 2

3. If no better on Methenamine, then check urine pH
    - If >5.5 then consider over the counter Vitamin C (1g BD)

- If pH <5.5 and no better, then consider prophylactic antibiotics for 6 months and/or book consultant OPA to discuss next steps

Consultant clinic attendance 2
Consider the following options

1. Prophylactic antibiotics for 6 months (based on previous sensitivities) – patients/GP should be told that this is a finite 6 month course and then should stop. Patient can be placed onto a PIFU pathway.
2. Intravesical Ialuril (especially if no obvious growth or sensitivities) (see Appendix 1)
3. Intravesical gentamicin (this can only be initiated by a Consultant Urologist in suitable patients following mandatory discussion with a Consultant Microbiologist) (see Appendix 2)
4. Trials (if available)

If better at any stage, then patient can be placed onto a patient initiated follow up pathway for the next 12 months.

3. Education and Training

None; there is pre-existing expertise in the management of this condition and delivery of treatments.

4. Monitoring Compliance

What will be measured to monitor compliance	How will compliance be monitored	Monitoring Lead	Frequency	Reporting arrangements
Biannual audit of cases seen in the clinic	Select 10 cases will be audited against the guideline.	Miss Ravindra	Biannual	Local audit meeting

5. Supporting References

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6. Key Words

Recurrent urinary tract infections

Recurrent UTIs

Urinary tract infection

CONTACT AND REVIEW DETAILS

Guideline Lead (Name and Title) Miss Pravisha Ravindra Consultant Urological Surgeon	Executive Lead
Details of Changes made during review:	

Appendix 1

Intravesical Ialuril for recurrent cystitis

1. *Rationale for use*

There are a small number of patients that experience repeated frequent urinary tract infections that result in systemic upset which require oral or parenteral antibiotics to achieve symptom relief. These patients are repeat attenders to both primary and secondary care for treatment and their quality of life is poor due to the symptoms they experience and the repeated need to seek medical treatment.

2. *Evidence for use*

Endovesical instillations of hyaluronic acid (HA) and chondroitin sulphate (CS) have been used for glycosaminoglycan (GAG) layer replenishment in the treatment of interstitial cystitis, overactive bladder, radiation cystitis, and for prevention of rUTI. A meta-analysis (n=143) based on two RCTs and two non-RCTs found significantly decreased UTI rates per patient/year and significantly longer mean UTI recurrence times for HA and HA-CS therapy compared to control treatment. In addition, subgroup analysis of the two RCTs using HA-CS reported a significantly decreased UTI rate per patient-year, significantly longer mean UTI recurrence time and a significantly better pelvic pain and urgency/frequency (PUF) total score.

Another meta-analysis (n=800) including two RCTs and six non-RCTs found that when compared to control treatment HA, with or without CS, was associated with a significantly lower mean UTI rate per patient-year and a significantly longer time to UTI recurrence. Furthermore, HA-CS therapy was associated with significantly greater mean reductions in PUF total and symptom scores and the percentage of patients with UTI recurrence during follow-up was also lower.
As randomised controlled studies are available only for HA plus CS, the quality of evidence is higher for the combination than for HA alone.

3. *Indication for use*

On the basis of this, intravesical Ialuril will be offered to patients who have have failed (or are not suitable for) conservative measures, over the counter strategies, non-antibiotic strategies including methenamine and prophylactic antibiotics. This is a licensed indication.

4. *Prescribing and supply*

Prescribing: Prescription is issued by a Urology consultant as an outpatient script, on Nervecentre or on a paper drug chart.

Duration: The treatment regime is weekly for 4 weeks and monthly for 5 months. This is administered by the nursing team and the patient attends LGH for this. If the patient is able and willing to self-administer, the option of self-administrating at home will be facilitated.

Response criteria/monitoring: The patient is booked into the recurrent UTI clinic for a telephone follow up 3 months after completing the 9 instillations of Ialuril. For any breakthrough UTI symptoms during the course of Ialuril or once the course is completed, an MSU must be sent. Patients will be considered for a further course if needed. At each review, patients will be assessed for clinical benefits of treatment, reduction in hospital/ high level of care with sepsis admissions, adverse reactions and a decision made regarding continuation of treatment. A small number of patients who find the treatment effective, may go onto a maintenance monthly regime. This is at the direction of the supervising urology consultant. The patient will have an annual urology outpatient review to assess the utility of ongoing treatment.

Discontinuation Criteria: If no clinical benefit is demonstrated at clinic review, or any reviews thereafter, intravesical Ialuril will be discontinued and alternative treatment options considered.

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Appendix 2

Intravesical Gentamicin for recurrent UTIs

1. *Rationale for use*

There are a small number of patients that experience repeated frequent urinary tract infections that result in systemic upset which require oral or parenteral antibiotics to achieve symptom relief. These patients are repeat attenders to both primary and secondary care for treatment and their quality of life is poor due to the symptoms they experience and the repeated need to seek medical treatment.

Intravesical gentamicin offers an alternative treatment of recurrent UTIs in some patients. Direct intravesical instillation results in high concentrations at the site of infection. Antimicrobial resistance is unlikely to develop in the urinary tract due to high urinary drug concentrations and a lack of selective antibiotic pressure on the commensal flora at other sites of the body (intestines, perineum, and vagina).

The purpose of this guideline is to provide a framework to ensure that intravesical gentamicin is prescribed appropriately and used safely. In the rare occurrence of patients with gentamicin resistance/allergy, this protocol may be used to administer alternative intravesical agents, following discussion with microbiology.

2. *Evidence for use*

Patients should be made aware that this treatment has not been subject to detailed research. One study has shown that in a small group of patients (27) who have multiple symptomatic urinary tract infections refractory to conventional treatment, intravesical gentamicin is effective in reducing the frequency of infections (Abrams et al., 2017). A larger prospective trial of 63 adults with rUTIs caused by multidrug resistant pathogens who received overnight intravesical gentamicin for 6 months had a reduction in the number of urinary tract infection episodes and the degree of antimicrobial resistance (Stalenhoef et al., 2019). A systematic review by Pietropaolo et al. (2018) found intravesical antimicrobial instillation to be a relatively safe and effective method for the prophylaxis and treatment of recurrent UTIs, especially in the short term where all other forms of treatment have failed.

Longer term evidence now exists; in this study by Bilsen et al 2023, forty-four patients were included (median follow-up time 976 days) and 323 UTIs occurred during follow-up. Overall treatment satisfaction was high (median 79.2/100). All but one patient had undetectable serum aminoglycoside levels and no malignancies were found on follow-up cystoscopy. Intravesical gentamicin increased the time to first UTI, reduced the number of recurrences and the necessity for systemic antibiotics. The authors concluded that in patients with recurrent UTI, intravesical gentamicin was associated with high treatment satisfaction, and was found to be a safe and effective alternative to oral antimicrobial prophylaxis.

There is evidence for safe and efficacious use in native bladders, reconstructed bladders (including bowel augmentation or replacement) and ileal conduits (Defoor et al 2006, Marei 2021 and Abrams 2017).

3. *Unlicensed indication*

While gentamicin intravenously possesses a UK Marketing Authorisation, its use for intravesical administration in the management of recurrent UTIs is an unlicensed indication. This treatment will therefore be under the supervision of a responsible Urology consultant and subject to ongoing data collection and audit.

4. *Allowed prescribers and responsibilities*

Within UHL, intravesical gentamicin will only be initiated by a consultant urologist with a specialist interest in recurrent UTIs, following discussion with a consultant microbiologist. This discussion will be documented on ICE under the named patient's details.

The urology consultant will:

- Document consent for the treatment in the notes
- Provide the patient with written and verbal information about the treatment
- Ensure that the patient has adequate training to administer the treatment
- Prescribe gentamicin for so long as it is needed
- Send a standard letter to the patient's GP on commencement of the regime including the rationale for treatment, treatment regime, potential complications and contact numbers

5. Eligible patients

- Patients with an intact bladder who suffer repeated, difficult to treat, urinary tract infections - >6 proven UTIs in any 12 month period, or at least 1 infection requiring hospital admission in any 12 month period with a background of recurrent UTIs.
- Patients with a bladder augmented with, or replaced by, a bowel segment
- Patients with an ileal conduit
- Patients need to be able to competently self-catheterise

These guidelines should only be used when all conventional measures to reduce the frequency of urinary tract infections have either failed or not applicable/tolerated, including a trial of non-antibiotic prophylaxis, low dose antibiotic prophylaxis (for 6 months), intravesical Ialuril, cranberry tablets, conservative measures, probiotics, D mannose and topical vaginal oestrogen.
Discussion has taken place with the consultant microbiologist to ensure that no other oral antimicrobial treatment options are available or recommended and that the organism is sensitive to the intravesical agent being used.

The patient should be made aware by the clinicians that the treatment may be of limited benefit and has not be subject to extensive detailed research but there is emerging evidence of its success. They should then take part in a full discussion and decide for themselves whether they want to use this treatment. This discussion must be documented in the patient's notes along with the patients consent to proceed.

The patient's technique in performing ISC should he checked and found to be satisfactory. If this is not the case, then the patients should be taught ISC by a urology nurse specialist.

Consideration must also be given to whether there are any relatives in the immediate household with an allergy to the antimicrobial agent being used and any necessary precautions.

6. Dosing and method of administration

Dosing: Gentamicin 80mg instilled intravesically once daily (at night) for 8 weeks. The frequency will then be reduced to twice every week for the next 8 weeks, then to once per week for 8 weeks and then treatment stopped (6 month treatment duration in total).

Duration: The initial therapeutic course is intended to be 6 months in the absence of complications or change in circumstances.

Administration: Gentamicin 80mg diluted in 50ml sterile sodium chloride 0.9% should be instilled in the bladder nightly, after completion of a conventional bladder washout, and the catheter withdrawn, leaving the solution in the bladder overnight. The solution will be voided spontaneously in the morning, or to be removed by routine ISC.

Monitoring: Gentamicin levels will be checked one week after initiation of intravesical gentamicin, and treatment discontinued if gentamicin levels are >1mg/L. These will be rechecked at 3m, 6m and at annual reviews, along with serum creatinine. Consideration of any audiology issues will also be checked at these reviews. For any breakthrough UTI symptoms during the course of intravesical gentamicin or once the course is completed, an MSU must be sent.

7. Prescribing and supply

Prescribing: Prescription is issued by a Urology consultant as an outpatient script, on Nervecentre or on a paper drug chart. Gentamicin 80mg/2mls injction (for intravesical use) should be prescribed in multiples of 5 (30 ampoules a month). Sodium chloride 0.9% 20ml ampoules should be prescribed in multiples of 20 (100 ampoules/month). Equipment to facilitate intravesical administration will be provided by the specialist nurse and the patient's GP will be requested to prescribe subsequent supplies.

Response criteria: Patients will be reviewed at Day 7, 1 month, 3 months and at 6 months after starting treatment. Once treatment has stopped, patients will be placed onto a PIFU pathway. At each review, patients will be assessed for clinical benefits of treatment, reduction in hospital/ high level of care with sepsis admissions, adverse reactions and a decision made regarding continuation of treatment. A small number of patients, who find the treatment effective, may undergo a further 6 month regime followed by a monthly maintenance regime. This is at the direction of the supervising urology consultant following a further discussion with a consultant microbiologist (discussion will be documented on ICE under the named patient details). These patients will have an annual urology outpatient review to assess the utility of ongoing treatment and side effects.

Discontinuation criteria: If no clinical benefit is demonstrated at clinic review, or any reviews thereafter, intravesical gentamicin will be discontinued and alternative treatment options considered. If gentamicin resistance or adverse effects develop at any time during treatment, then intravesical gentamicin will be discontinued.

8. Adverse drug reactions

Gentamicin may cause local irritation in the bladder. Ototoxicity and nephrotoxicity are unlikely adverse effects. The Medicines and Healthcare products regulatory agency (MHRA) yellow card scheme should be used to report any adverse effects which are serious, medically significant or result in harm from intravesical gentamicin.

9. Audit

An audit of all patients commenced on intravesical gentamicin will be undertaken within the urology department. Data recorded will include efficacy of treatment, number/type of hospital admissions due to UTIs, number of episodes of symptomatic UTIs, courses of adjunct oral antibiotics, side effects (including nephrotoxicity and ototoxicity) and the development of any gentamicin resistance.

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