RECURRENT URINARY TRACT INFECTIONS

CHI Formulary Indication Review

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Council of Health Insurance

INDICATION UPDATE

ADDENDUM- October 2023

To the CHI Original Recurrent Urinary Tract Infections Clinical Guidance- Issued February 2020

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- IDF-FR-P-05-01-UpdatedIndicationReview&IDFUpdates

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- IDF-FR-WI-01-01SearchMethodologyGuideForNewIndications

Abbreviations

AUA	American Urological Association
BAUN	British Association of Urological Nurses
BAUS	British Association of Urological Surgeons
BBD	Bowel and Bladder Dysfunction
BID	Twice Daily
CADTH	Canadian Agency for Drugs and Technologies in Health
CAUTI	Catheter-Associated Urinary Tract Infection
CHI	Council of Health Insurance
cIAI	Complicated Intrabdominal Infection
CNS	Central Nervous System
CoR	Class of Recommendation
CrCl	Creatinine Clearance
CSU	Catheter Specimen of Urine
CUA	Canadian Urological Association
cUTI	Complicated Urinary Tract Infection
D	Day(s)
EAU	European Association of Urology
EMA	European Medicines Agency
ESBL	Extended Spectrum Beta-Lactamase
FDA	Food and Drug Administration
GAG	Glycosaminoglycan
HABP	Hospital-Acquired Bacterial Pneumonia
HAS	Haute Autorité de Santé
HTA	Health Technology Assessment
ID	Infectious Diseases
IQWIG	Institute for Quality and Efficiency in Health Care
IV	Intravenous
LE	Level of Evidence

MRSA	Methicillin-Resistant Staphylococcus Aureus
NICE	National Institute for Health and Care Excellence
NLUTD	Neurogenic Lower Urinary Tract Dysfunction
PBAC	Pharmaceutical Benefits Advisory Committee
RBUS	Renal and Bladder Ultrasonography
RCT	Randomized Clinical Trial
rUTI	Recurrent Urinary Tract Infections
SFDA	Saudi Food and Drug Authority
SPIDS	Saudi Pediatric Infectious Diseases Society
SS	Single Strength
SUFU	Society of Urodynamics, Female Pelvic Medicine & Urogenital Reconstruction
TMP-SMX	Trimethoprim-Sulfamethoxazole
US	Ultrasound
UTI	Urinary Tract Infection
VABP	Ventilator-Associated Bacterial Pneumonia
VCUG	Voiding Cystourethrogram
VRE	Vancomycin-Resistant Enterococcus
VUR	Vesicoureteral Reflux

Executive Summary

Recurrent urinary tract infections (rUTIs) are defined as two episodes of acute bacterial cystitis with related symptoms occurring within the past six months or three episodes within 12 months. This condition is significantly more prevalent among females. The symptoms are those of an acute urinary tract infection (UTI), which include cloudy or bloody urine, dysuria, and increase in urgency and frequency of urination[1]. Recurrence should not be confused with relapse which is defined as infection of the same pathogen resulting from inadequate treatment as per guidelines.

Roughly one out of every three women experiences an uncomplicated UTI before reaching the age of 24. The lifetime prevalence of at least one symptomatic UTI in women has been approximated to exceed 50%, with approximately 26% of women experiencing a recurrence within six months following treatment for their initial UTI[1].

UTIs continue to pose a significant challenge for the healthcare system in the Kingdom of Saudi Arabia (KSA). They constitute 10% of all infections in the country and rank as the second most frequent cause for emergency department admissions. Approximately 4% of patients with UTI require hospitalization for additional treatment. Another concerning aspect is the rate of readmission, with approximately 10% being readmitted within one week of their discharge, often due to ineffective treatment[2].

Antimicrobial therapy remains the primary treatment approach for managing recurrent urinary tract infections.

CHI issued Recurrent Urinary Tract Infections clinical guidance after thorough review of renowned international and national clinical guidelines in February 2020. Updating clinical practice guidelines (CPGs) is a crucial process for maintaining the validity of recommendations.

This report functions as an addendum to the prior CHI Recurrent Urinary Tract Infections clinical guidance and seeks to offer guidance for the effective management of Recurrent Urinary Tract Infections. It provides an **update on the Recurrent Urinary Tract Infections Guidelines** for CHI Formulary with the ultimate objective of updating the IDF (CHI Drug Formulary) while addressing **the most updated best available clinical and economic evidence related to drug therapies.**

Main triggers for the update are summarized, being **the issuance of updated versions of previously reviewed guidelines** namely the European Association of Urology (EAU) Urological Infections Guidelines **2023**. Moreover, **new guidelines are added to the report** such as the American Urogynecologic Society Best-Practice Statement: Recurrent Urinary Tract Infection in Adult Women **2018**, Saudi Urinary Tract Infection management protocol updated in **2020-2021**, British Association of

Urological Surgeons (BAUS) and Nurses (BAUN) Consensus Document: Management of the Complications of Long Term Indwelling Catheters **2021**, the AUA/SUFU Guideline on Adult Neurogenic Lower Urinary Tract Dysfunction: Treatment and Follow-up **2021**, EAU-ESPU guidelines recommendations for daytime lower urinary tract conditions in children **2020,** and Diagnosis and management of community-acquired urinary tract infection in infants and children: Clinical guidelines endorsed by the Saudi Pediatric Infectious Diseases Society (SPIDS) **2021.**

After carefully examining clinical guidelines and reviewing the SFDA drug list, it is advisable to include the SFDA registered drug **Imipenem + Cilastatin + Relebactam** (Recarbrio®) in the CHI formulary. Additionally, there have been **no withdrawals** of drugs from the treatment of recurrent UTIs. Finally, there have been some changes and updates to some of the listed drugs in terms of drug information and prescribing edits since February 2020.

All recommendations are well supported by reference guidelines, Grade of Recommendation (GoR), Level of Evidence (LoE) and Strength of Agreement (SoA) in all tables reflecting specific drug classes' role in Recurrent Urinary Tract Infections management.

Below is a table summarizing the major changes based on the different Recurrent Urinary Tract Infections guidelines used to issue this report:

Table 1. General Recommendations for the Management of Recurrent Urinary Tract Infections

Management of Recurrent Urinary Tract Infections		
General Recommendations	**Level of Evidence/Grade of Recommendation**	**Reference**
Treatment of asymptomatic bacteriuria is harmful in patients with recurrent urinary tract infections	Level of evidence 1b	EAU 2023 Guidelines[3]
Use continuous or post-coital antimicrobial prophylaxis to prevent recurrent UTI when nonantimicrobial interventions have failed. Counsel patients regarding possible side effects.	Strength rating: Strong	EAU 2023 Guidelines[3]
There is no consensus about the optimal duration of continuous antimicrobial prophylaxis with duration of three to twelve months.	Not graded	EAU 2023 Guidelines[3]

The choice of agent should be based on the local resistance patterns. Post-coital prophylaxis should be considered in pregnant women with a history of frequent UTIs before onset of pregnancy, to reduce their risk of UTI.		
For patients with good compliance self-administered short-term antimicrobial therapy should be considered	Strength rating: Strong	EAU 2023 Guidelines[3]
The choice of antibiotic should consider specific patient factors (allergies, renal function), complicating factors such as abnormal genitourinary anatomy, immunosuppression, and chronic catheterization, are present and uropathogen sensitivity.	Not graded	American Urogynecologic Society 2018[4]
First line therapy for acute cystitis in women with recurrent UTI: Nitrofurantoin monohydrate/macrocrystals (93% estimated clinical efficacy), Trimethoprim/sulfamethoxazole (TMP-SMX) (93% efficacy), and Fosfomycin trometamol (91% efficacy)	Not graded	American Urogynecologic Society 2018[4]
Initial treatment, for acute UTI in women with rUTI and complicating factors, until culture results are available to guide therapy (consider only if local resistance <20%) are the following options: Fluoroquinolones (ciprofloxacin and levofloxacin), Aminopenicillin (ampicillin) plus a beta-lactam inhibitor (clavulanic acid), Cephalosporins group 3a (parenteral: cefotaxime, ceftriaxone, ceftizoxime, cefmenoxime, cefodizime), and Aminoglycosides	Not graded	American Urogynecologic Society 2018[4]
Empirical treatment in severe cases or initial failure for acute UTI in women with rUTI and complicating factors, are the following options: Fluoroquinolone (if not used for initial therapy), Piperacillin plus a	Not graded	American Urogynecologic Society 2018[4]

β-lactam inhibitor, Cephalosporin group 3b (parenteral, ie, cefoperazone, ceftazidime), and Carbapenem.		
Not recommended for empirical treatment for acute UTI in women with rUTI and complicating factors, are the following options: Aminopenicillins (ie, ampicillin, amoxicillin, bacampicillin), TMP-SMX, and Fosfomycin trometamol	Not graded	American Urogynecologic Society 2018[4]
Antibiotic irrigation of the bladder for prophylaxis and/or treatment provides some potential advantages over oral and parenteral routes. These include direct drug delivery to the site of infection and bypass of gastrointestinal tract which avoids collateral consequences and side effects such as gastrointestinal upset. Gentamicin has been the antibiotic most studied for bladder irrigation. However, there is limited current evidence to support the safety of gentamicin bladder instillations.	Not graded	American Urogynecologic Society 2018[4]
Recurrent cystitis: ○ **Relapse** (referral to the ID Consultant is mandatory): ▪ Relapse is a new episode of bacteriuria with a microorganism that is **same** from the original one. ▪ Assess for pharmacologic reason for treatment failure. ▪ Longer treatment (for 2–6 weeks, depending on length of initial course).	Not graded	Saudi Guidelines 2020-2021[5]
○ **Reinfection** (referral to the ID Consultant is mandatory): ▪ Reinfection is a new episode of bacteriuria with microorganism that is **different** from the original one.	Not graded	Saudi Guidelines 2020-2021[5]

▪ If patient has two or fewer UTIs in 1 year, use patient-initiated therapy for symptomatic episodes (3-day treatment regimens). ▪ If patient has three or more UTIs in 1 year and they are temporally related to sexual activity, use post-intercourse prophylaxis with TMP/SMZ SS, cephalexin 250 mg, or nitrofurantoin 50–100 mg. ▪ If patient has three or more UTIs in 1 year that are not related to sexual activity, use daily or 3 times/week prophylaxis with TMP/SMZ SS, cephalexin 250 mg, or nitrofurantoin 50–100 mg.		
Cystoscopy should be considered in catheterized patients who report unexplained visible hematuria even if it is related to catheter changes, recurrent urinary tract infections and those reporting new bladder symptoms. Prophylactic antibiotics are usually ineffective. Consider US/Cystoscopy to rule out stones and washout of debris	Not graded	BAUS and BAUN Guidelines 2021[6]
In patients with neurogenic lower urinary tract dysfunction (NLUTD) who perform clean intermittent catheterization with recurrent urinary tract infection, clinicians may offer oral antimicrobial prophylaxis to reduce the rate of urinary tract infections following shared decision making and discussion regarding increased risk of antibiotic resistance.	Conditional Recommendation; Evidence Level: Grade C	AUA/SUFU Guideline 2021[7]
A single daily prophylactic dose of any of the following options is recommended for recurrent UTI in infants and children: • Nitrofurantoin: dose: 1-2mg/kg/day.	Not graded	SPIDS 2021 Guidelines[8]

• Trimethoprim/sulfamethoxazole: dose is based on trimethoprim at 2mg/kg/day. • Amoxicillin and cephalosporins should not routinely be used in prophylaxis because of the increased risk of development of resistant organisms. However, these regimens can be used in infants less than two months of age or in patients who cannot tolerate or developed adverse effects related to the use of trimethoprim or nitrofurantoin.		
First line prophylaxis options for recurrent UTI in non-pregnant females are: nitrofurantoin, trimethoprim, or Methenamine	Not graded	NHS 2022 Guidelines [9]

At the end of the report, a **key recommendation synthesis section** is added highlighting the latest updates in **Recurrent Urinary Tract Infections clinical and therapeutic management.**

Section 1.0 Summary of Reviewed Clinical Guidelines and Evidence

This section is divided into two parts: the first includes recommendations from **updated versions of guidelines** mentioned in the previous CHI Recurrent Urinary Tract Infections report, and the second includes **newly added guidelines** that have helped generate this report.

1.1 Revised Guidelines

This section contains the **updated versions** of the guidelines mentioned in the February 2020 CHI Recurrent Urinary Tract Infections Report and the corresponding recommendations:

Table 2. Guidelines Requiring Revision

Guidelines Requiring Revision	
Old Versions	**Updated versions**
1.1.1. The European Association of Urology **(EAU)** Urological Infections Guidelines **March 2018**	The European Association of Urology (**EAU**) Urological Infections Guidelines **2023**
1.1.2. Recurrent Uncomplicated Urinary Tract Infections in Women: **AUA/CUA/SUFU Guideline (2019)**	Reviewed in **2022**: **Validity Confirmed**
1.1.3. Urinary Tract Infection (Recurrent): Antimicrobial Prescribing **NICE guideline October 2018**	N/A*
1.1.4. Guidelines for the Diagnosis and Management of Recurrent Urinary Tract Infection in Women **Canadian Urological Association (CUA) 2011**	N/A*

*: *No updated versions available*

1.1.1 The European Association of Urology (EAU) Urological Infections Guidelines (March 2018)

*Please refer to **Section 1.3** of CHI Recurrent Urinary Tract Infections original clinical guidance.*

The **2023 revised edition** of EAU's 2018 Guidelines for Urinary Tract Infections introduced a set of recommendations detailed below[3].

The strength rating forms for the recommendations are influenced by the guiding principles of the GRADE methodology but do not purport to be a direct implementation of GRADE. Each strength rating form addresses several critical components, including[3]:

1. Assessing the overall quality of the evidence supporting the recommendation. The references cited in this text are graded using a classification system adapted from the Oxford Centre for Evidence-Based Medicine Levels of Evidence.
2. Evaluating the magnitude of the effect, whether it pertains to individual or combined effects.
3. Determining the certainty of the results, which includes factors like precision, consistency, heterogeneity, and other statistical or study-related considerations.
4. Weighing the balance between desirable and undesirable outcomes associated with the recommendation.
5. Considering the influence of patient values and preferences on the proposed intervention.
6. Gauging the certainty surrounding these patient values and preferences.

These key elements serve as the foundation upon which panels base their decisions when assigning a strength rating to each recommendation. The strength of each recommendation is expressed using the terms **'strong'** or **'weak'**. This determination hinges on factors such as the trade-off between the desirable and undesirable consequences of different management strategies, the quality of the available evidence (including the level of certainty in the estimates), and the nature and variability of patient values and preferences.

The recommendations listed below are assigned the strengths defined in the preceding lines[3]:

- Recurrent UTIs are defined by this guideline as recurrences of uncomplicated and/or complicated UTIs, with a frequency of at least three UTIs/year or two UTIs in the last six months.

- Treatment of asymptomatic bacteriuria is harmful in patients with recurrent urinary tract infections. (Level of evidence 1b)
- Based on limited evidence intravesical glycosaminoglycan (GAG) therapy can reduce the number of UTIs per patient per year and prolong the time interval between rUTI episodes. (Level of evidence 2)
- Advise patients on the use of local or oral probiotic containing strains of proven efficacy for vaginal flora regeneration to prevent UTIs. (Strength rating: Weak)
- Use endovesical instillations of hyaluronic acid or a combination of hyaluronic acid and chondroitin sulphate to prevent recurrent UTIs in patients where less invasive preventive approaches have been unsuccessful. Patients should be informed that further studies are needed to confirm the results of initial trials. (Strength rating: Weak)
- Use continuous or post-coital antimicrobial prophylaxis to prevent recurrent UTI when nonantimicrobial interventions have failed. Counsel patients regarding possible side effects. (Strength rating: Strong)
- For patients with good compliance self-administered short-term antimicrobial therapy should be considered. (Strength rating: Strong)
- The table below shows the non-antimicrobial prophylaxis options for recurrent UTIs treatment:

Table 3. EAU - Non-Antimicrobial Prophylaxis Options for Recurrent Urinary Tract Infections

Non-Antimicrobial Prophylaxis	
Hormonal replacement	Topical estrogen therapy (either as a creme or a pessary) shows a trend towards rUTI prevention (Strong, LE 1b)
Immunoactive prophylaxis	Oral immunotherapy with OM-89 is an effective and safe method for the prevention of rUTIs placebo at short-term follow up (< 6 months) (Strong, LE 1a)
Probiotics prophylaxis	The highest efficacy was shown with L. rhamnosus GR-1, L. reuteri B-54, L. reuteri RC-14, L. casei shirota, and L. crispatus CTV-05 (Weak, LE 1b)
Cranberry prophylaxis	The efficacy of cranberry products remains unclear, but clinicians may recommend them for rUTI prevention in women who are informed of the weak evidence base due to their favorable benefit to harm ratio. However,

	there is no clear clinical evidence regarding the appropriate dose and treatment duration (Weak, LE 1a)
D-mannose prophylaxis	D-mannose was effective for rUTI prevention compared to placebo with comparable efficacy to antibiotic prophylaxis (Weak, LE 2)
Methenamine Hippurate	Methenamine hippurate may be effective for preventing UTI in patients without renal tract abnormalities, particularly when used for short-term prophylaxis (Strong, LE 1b)
Water intake	Increased water intake (if no contraindications exist) is an effective antimicrobial-sparing strategy to prevent rUTI in premenopausal women at high risk for recurrence who drink low volumes (< 1.5 L) of fluid daily (Weak, LE 3)

- Antimicrobials for preventing rUTIs:
    - Continuous low-dose antimicrobial prophylaxis and post-coital prophylaxis are the most effective approaches and there is no significant difference in the efficacy between them. (Strong, LE 1b)
    - There is no consensus about the optimal duration of continuous antimicrobial prophylaxis with duration of three to twelve months.
    - Differences in outcomes between antibiotics did not reach statistical significance.
    - The choice of agent should be based on the local resistance patterns.
    - Post-coital prophylaxis should be considered in pregnant women with a history of frequent UTIs before onset of pregnancy, to reduce their risk of UTI.
- The table below shows a list of antimicrobials that can be administered for the prevention of rUTIs as recommended by the EAU guidelines:

Table 4. EAU - List of Antimicrobials for the Prevention of Recurrent Urinary Tract Infections

Antimicrobials for Preventing rUTIs:
Nitrofurantoin 50 mg or 100 mg once daily
Fosfomycin trometamol 3 g every ten days
Trimethoprim 100 mg once daily
Cephalexin 125 mg or 250 mg during pregnancy

Cefaclor 250 mg once daily during pregnancy

1.2 Additional Guidelines

This section includes the added guidelines to the previous CHI Recurrent Urinary Tract Infections report, along with their recommendations.

Table 5. List of Additional Guidelines

Additional Guidelines
American Urogynecologic Society Best-Practice Statement: Recurrent Urinary Tract Infection in Adult Women **2018**
Saudi Urinary Tract Infection Management Protocol Updated in **2020-2021**
British Association of Urological Surgeons (BAUS) and Nurses (BAUN) Consensus Document: Management of the Complications of Long-Term Indwelling Catheters **2021**
The **AUA/SUFU** Guideline on Adult Neurogenic Lower Urinary Tract Dysfunction: Treatment and Follow-up **2021**
EAU-ESPU Guidelines Recommendations for Daytime Lower Urinary Tract Conditions in Children **2020**
Diagnosis and management of community-acquired urinary tract infection in infants and children: Clinical guidelines endorsed by the Saudi Pediatric Infectious Diseases Society (**SPIDS**) **2021**
NHS Guidelines for Recurrent Urinary Tract Infections in Adults: Antibiotic Prophylaxis **2022**

1.2.1 The American Urogynecologic Society Best-Practice Statement: Recurrent Urinary Tract Infection in Adult Women (2018)

The guidelines recommend the following[4]:

The choice of antibiotic should take into consideration specific patient factors (e.g., allergies, renal function), complicating factors such as abnormal genitourinary anatomy, immunosuppression, chronic catheterization, and uropathogen sensitivity.

I. **Treatment of an acute episode of rUTI in women <u>without</u> complicating factors**

- Nitrofurantoin is a key first-line agent at a dose of 100mg BID for 5 days. (93% efficacy)

- Fosfomycin is effective at a dose of 3g single dose. Clinicians may need to request sensitivity testing (91% efficacy)
- Trimethoprim-sulfamethoxazole (TMP-SMX) at a dose of 160/800 mg BID for 3 days can also be used if resistance is less than 20% in the community (93% efficacy)
- Fluoroquinolones typically for 3 days are not a first-line treatment of acute cystitis without complicating factors (90% efficacy)
- Unless there is clear evidence of sensitivity to certain β-lactams, including amoxicillin and ampicillin, these antibiotics should rarely be used because of poor efficacy thought to be due in part to the low concentration in the urine for a duration of 3 to 7 days. (89% efficacy)

Table 6 below shows the antibiotic recommendations for acute UTI treatment in women with rUTI. Nitrofurantoin, TMP/SMX, and fosfmocyin can be used to treat an acute episode – or breakthrough infection – **only if they are not being used for continuous low-dose prophylaxis** of rUTIs.

Table 6. Antibiotic Recommendations by the American Urogynecologic Society for the Treatment of rUTIs in Women Without Complicating Factors

Antibiotic Regimens for Acute Cystitis Treatment			Estimated Clinical Efficacy
First-line antibiotics			
Nitrofurantoin monohydrate/ macrocrystals	100 mg BID x 5 days	Avoid if early pyelonephritis suspected; Minimal resistance; Minimal risk of collateral damage.	93% (84–95)
Trimethoprim/ sulfamethoxazole	160/800 mg BID x 3 days	Efficacy shown in numerous clinical trials; Avoid if resistance prevalence known to be >20%.	93% (90–100)
Fosfomycin trometamol	3 g single dose	Minimal resistance; Minimal risk of collateral damage; Avoid if early pyelonephritis suspected;	91%

		Lower efficacy than other agents; In vitro activity against VRE, MRSA, and ESBL gram-negative rods supported with clinical studies.	
Second-line antibiotics			
Fluoroquinolones	Dose varies by regimen; typically, 3-day regimen	Resistance prevalence high in some areas; High risk for collateral damage.	90% (85–98)
β-Lactams	Dose varies by regimen; typically for 3–7 days	Do not use ampicillin or amoxicillin for empirical treatment; Lower efficacy than other available agents due to high resistance and decreased concentration in the bladder; Requires close follow-up.	89% (74–98)
Self-initiated regimens			
Nitrofurantoin monohydrate/ macrocrystals	100 mg BID x 5 days	See above	
Trimethoprim/ sulfamethoxazole	160 mg/800 mg BID x 3 days	See above	
Fosfomycin trometamol	3 g	See above	

II. Treatment of an acute episode of rUTIs in women <u>with</u> complicating factors

For acute UTI in women with rUTI and complicating factors, the recommended regimens for initial, empiric therapy are:

- Initial treatment until culture results are available to guide therapy (consider only if local resistance <20%)
    - Fluoroquinolones (ciprofloxacin and levofloxacin)

- Aminopenicillin (ampicillin) plus a beta-lactam inhibitor (clavulanic acid)
- Cephalosporins group 3a (parenteral: cefotaxime, ceftriaxone, ceftizoxime, cefmenoxime, cefodizime).
- Aminoglycosides

- Empirical treatment in severe cases or initial failure:
  - Fluoroquinolone (if not used for initial therapy)
  - Piperacillin plus a β-lactam inhibitor
  - Cephalosporin group 3b (parenteral; ie, cefoperazone, ceftazidime)
  - Carbapenem
- Not recommended for empirical treatment
  - Aminopenicillins (ie, ampicillin, amoxicillin, bacampicillin)
  - TMP-SMX
  - Fosfomycin trometamol

III. Antibiotic prophylaxis

The recommended antibiotic regimens that can be used for prophylaxis according to the American Urogynecologic Society are detailed in table below.

Table 7. American Urogynecologic Society Antibiotic Regimens for Prophylaxis Against Urinary Tract Infections

Continuous Low-Dose Regimens	
Trimethoprim daily	100 mg
Trimethoprim/sulfamethoxazole daily	40mg/200mg
Trimethoprim/sulfamethoxazole every 3 d	40mg/200mg
Nitrofurantoin monohydrate/macrocrystals daily	50mg
Nitrofurantoin monohydrate/macrocrystals daily	100mg
Cephalexin daily	125mg
Cephalexin daily	250mg
Fosfomycin every 10 d	3g
Postcoital Prophylaxis	
Trimethoprim/sulfamethoxazole	40mg/200mg
Trimethoprim/sulfamethoxazole	80mg/400mg

Nitrofurantoin monohydrate/macrocrystals	50-100mg
Cephalexin	250mg

- Ibuprofen may be used as an adjunct for symptoms of acute bacterial cystitis. However, in women with rUTI, there is no evidence that ibuprofen should be used in lieu of an antibiotic.
- There is insufficient evidence to recommend Chinese herbal medicine (CHM) as rUTI treatment.
- Antibiotic irrigation of the bladder for prophylaxis and/or treatment provides some potential advantages over oral and parenteral routes. These include direct drug delivery to the site of infection and bypass of gastrointestinal tract which avoids collateral consequences and side effects such as gastrointestinal upset. Gentamicin has been the antibiotic most studied for bladder irrigation. However, there is limited current evidence supporting the safety of gentamicin bladder instillations.
- Although there is not sufficient data to recommend intravesical Colistin, it may be considered in a patient who has very limited treatment options.
- Vaginal estrogen should be used whenever possible in hypoestrogenic women with rUTI because it clearly decreases UTI recurrence.
- Methenamine hippurate may be effective for preventing UTI, specifically when used for short-term prophylaxis. Additionally, it has an acceptable side effect profile with low reported adverse events.
- There is no strong evidence supporting the role of probiotics in rUTI prevention. Robust, placebo-controlled studies are needed in patients with rUTI using optimal probiotic agents.
- The preponderance of evidence does not support routine use of cranberry products in the care of women with rUTI.
- There is limited evidence supporting routine use of the simple sugar D-mannose in women with rUTI.
- Although vitamin C has a theoretical effect based on acidification of urine, there is insufficient evidence to support its use for UTI prevention in women with rUTI.
- Nonantibiotic intravesical instillations, including hyaluronic acid and chondroitin sulfate, are promising; however, they do not yet have sufficient clinical evidence for use.

- Immunostimulants and vaccinations are likely to play a future role in rUTI prevention, although there is insufficient evidence to recommend clinical use at this time.

1.2.2 Saudi Urinary Tract Infection Management Protocol (Updated in 2020-2021)

The guideline recommends the following[10]:

For the management of recurrent cystitis:

1. **Relapse** (referral to the ID consultant is mandatory):

Relapse is a new episode of bacteriuria with microorganism that is **same** from the original one:

- Assess for pharmacologic reason for treatment failure.
- Longer treatment (for 2–6 weeks, depending on length of initial course)

2. **Reinfection** (referral to the ID consultant is mandatory):

Reinfection is a new episode of bacteriuria with microorganism that is **different** from the original one:

- If patient has two or fewer UTIs in 1 year, use patient-initiated therapy for symptomatic episodes (3-day treatment regimens).
- If patient has three or more UTIs in 1 year and they are temporally related to sexual activity, use post-intercourse prophylaxis with TMP/SMZ SS, cephalexin 250 mg, or nitrofurantoin 50–100 mg.
- If patient has three or more UTIs in 1 year that are not related to sexual activity, use daily or 3 times/week prophylaxis with TMP/SMZ SS, cephalexin 250 mg, or nitrofurantoin 50–100 mg.

1.2.3 British Association of Urological Surgeons (BAUS) and Nurses (BAUN) Consensus Document: Management of the Complications of Long-Term Indwelling Catheters (2021)

The guideline recommends the following[6]:

- Patients with recurrent catheter-associated UTI (CAUTI) need investigation that includes an ultrasound (US) and cystoscopy. Recurrent UTI in non-catheterized patients is defined as repeated UTI with a frequency of 2 or more UTIs in the last 6 months or 3 or more UTIs in the last 12 months. There is no recognized definition for recurrent CAUTI. Where possible, a closed drainage

system is preferable – patients with pre-connected sealed junctions are less likely to have UTI than those with catheters without similar junctions.

- Health care professionals need to trouble shoot with patients when they are experiencing recurrent catheter problems such as blockages.
- Cystoscopy should be considered in catheterized patients who report unexplained visible hematuria even if it is related to catheter changes, recurrent urinary tract infections and those reporting new bladder symptoms.
- Urine dipstick of CSU not recommended.
- Consider US/Cystoscopy to rule out stones and washout of debris.
- Routine antibiotic prophylaxis to prevent CAUTI inpatients with indwelling catheters is not recommended but may be appropriate in some cases. It should only be considered for patients who have a history of symptomatic UTI after catheter change or who experience trauma during catheterization.
- The treatment of CAUTI should be along the lines of treatment for other complicated UTIs. Optimal duration of treatment has not been systematically studied. However, for general guidance, it is recommended that treatment be continued for 7 days in cases where symptoms are primarily restricted to the lower urinary tract and 14 days in cases with fever, bacteremia, organ impairment or sepsis.

1.2.4 AUA/SUFU Guideline on Adult Neurogenic Lower Urinary Tract Dysfunction: Treatment and Follow-up (2021)

The American Urological Association (AUA) and the Society of Urodynamics, Female Pelvic Medicine & Urogenital Reconstruction (SUFU) published in 2021 a joint clinical guideline for the treatment and follow-up of adult neurogenic lower urinary tract dysfunction (NLUTD)[7].

The grading system used is detailed in table 10.

Table 8. AUA/SUFU Grade of Recommendations

Grade	Definition
A	High
B	Moderate
C	Low
Clinical Principles and Expert Opinions	In instances of insufficient evidence, additional guidance is provided as Clinical Principles and Expert Opinions.

The guidelines recommend the following:

- In NLUTD patients who perform clean intermittent catheterization with recurrent urinary tract infection, clinicians may offer oral antimicrobial prophylaxis to reduce the rate of urinary tract infections following shared decision making and discussion regarding increased risk of antibiotic resistance. (Conditional Recommendation; Evidence Level: Grade C)
- In NLUTD patients who perform clean intermittent catheterization with recurrent urinary tract infection, clinicians may offer bladder instillations to reduce the rate of urinary tract infections. (Expert Opinion)
- Clinicians may counsel NLUTD patients with recurrent urinary tract infection who use various forms of catheter management that cranberry extract has not been demonstrated to reduce the rate of urinary tract infections. (Conditional Recommendation; Evidence Level: Grade B)
- In NLUTD patients who have undergone lower urinary tract reconstruction utilizing bowel, and who also develop gross hematuria or symptomatic recurrent urinary tract infection, clinicians should perform cystoscopy. (Moderate Recommendation; Evidence Level: Grade C)

1.2.5 EAU-ESPU Guidelines Recommendations for Daytime Lower Urinary Tract Conditions in Children (2020)

The European Association of Urology (EAU) and the European Society for Pediatric Urology (ESPU) published joint clinical recommendations for the management of daytime lower urinary tract conditions in children[11]. The levels of evidence and strengths of recommendations are outlined in tables 3 and 4.

The guidelines recommend the following:

- Use antibiotic prophylaxis if there are recurrent infections. (Level of evidence: 2, strength rating: Weak)

1.2.6 Diagnosis and Management of Community-Acquired Urinary Tract Infection in Infants and Children: Clinical Guidelines Endorsed by the Saudi Pediatric Infectious Diseases Society (2021)

This clinical statement from the Saudi Pediatric Infectious Diseases Society (SPIDS) provides evidence-based guidance on the most effective diagnosis and management of community-acquired urinary tract infection (UTI) in infants and children[8]. The main recommendations related to **recurrent** UTIs are detailed below:

- SPIDS defined recurrent UTI as two or more episodes of symptomatic UTI within 12 months.

- Renal and bladder ultrasonography (RBUS) is a noninvasive, safe, and easy test that can detect renal and urinary bladder abnormalities. This is recommended to be performed in rUTI.
- Voiding cystourethrogram (VCUG) the radiological test of choice to diagnose and grade the severity of vesicoureteral reflux (VUR) (grade 1 through 5). VCUG can also identify the anatomy of male urethra, obstructive uropathies, and other abnormalities of the bladder. This is recommended to be performed in rUTI.
- The guidelines **do not recommend routine antibiotic prophylaxis** in infants and children with normal urinary system or mild VUR (Grade I and II) after the first UTI because such cases do not benefit from the prophylaxis therapy.
- The guidelines suggest an individualized decision for antibiotic prophylaxis after the assessment of the possible risks and benefits.
- SPIDS recommends antibiotic prophylaxis in following conditions:
    - Children with moderate to high-grade reflux (Grade III to IV)
    - Uncircumcised males with any grade of VUR
    - Children with BBD and any grade of VUR
- SPIDS choice of antibiotic prophylaxis:
    - The choice of antibiotics depends on the local antimicrobial susceptibility pattern. It is also recommended to check the previous urine culture and susceptibility results and to choose antibiotics accordingly.
    - A single daily prophylactic dose of any of the following options is recommended:
        - Nitrofurantoin: dose: 1-2 mg/kg/day.
        - Trimethoprim/sulfamethoxazole: dose is based on trimethoprim at 2mg/kg/day.
        - Amoxicillin and cephalosporins should not routinely be used in prophylaxis because of the increased risk of development of resistant organisms. However, these regimens can be used in infants less than two months of age or in patients who cannot tolerate or developed adverse effects related to the use of trimethoprim or nitrofurantoin.

1.2.7 NHS Guidelines for Recurrent Urinary Tract Infections in Adults: Antibiotic Prophylaxis (2022)

NHS Nottinghamshire has issued clinical practice guidelines for the management of recurrent UTIs and the main recommendations are summarized below[9]:

Referrals to urology are required for patients with recurrent UTIs and the following factors:

- All men
- Frank hematuria, even in the context of confirmed UTI
- Neurological disease e.g., spinal cord injury, spina bifida
- Pneumaturia or faecaluria
- Proteus on repeat urine cultures
- Suspected stone
- Obstructive symptoms, or structural/functional abnormality, causing >200ml residual urine on bladder scan
- In pregnancy:
- All recurrent UTIs in pregnancy should be discussed with the Obstetrics team.

Management of Initial Presentation of Recurrent UTI in non-pregnant females:

- Conservative Measures (poor quality or inconclusive evidence):
    - Drink plenty
    - Avoid use of scented washes/wipes
    - For sexually active women:
        - Advise post-coital voiding
        - Avoid use of contraceptive diaphragm and spermicide
    - Perineal hygiene i.e., wiping front to back.
    - Avoid using flannels. A clean unscented disposable wipe is preferable.
    - Over-the-counter products – limited evidence but some women may find useful:
        - D-mannose (1g twice daily. Available without prescription)
        - Cranberry tablets (Follow individual product instructions. Available without prescription. Contraindicated in patients on Warfarin)

- Standby Antibiotics:
    - This option limits antibiotic exposure and risk of resistance emerging and may be the more suitable option for patients with <1 UTI per month. A Patient Advice Sheet and boric acid container for pre-antibiotic mid-stream urine should be provided to the patient. A urine specimen should be obtained when the patient becomes symptomatic, but patients can self-initiate antibiotics whilst awaiting the culture results.
    - Prescribe a 'self-start' antibiotic according to previously known sensitivities and choose the narrowest spectrum agent available.
    - Safety-net with advice to seek medical attention if they develop fever, loin pain, or symptoms are not improving by 48 hours.
- Post Coital Antibiotics
    - For rUTIs triggered by sexual intercourse, this strategy is as effective as continuous antibiotic prophylaxis and reduces antibiotic exposure and the risk of resistance emerging.
- Continuous Antibiotic Prophylaxis
    - Continuous antibiotic prophylaxis is strongly associated with the development of antimicrobial resistance.
    - A 6-month trial of a low-dose nightly antibiotic may be beneficial if rUTIs are occurring ≥1 per month and are not triggered by sexual intercourse.
    - Patients should be counselled at an early stage that antibiotic prophylaxis is not usually a lifelong treatment. Documenting and triggering a review date in the patient's record and on the repeat prescription is recommended to avoid prolonged courses of antibiotics without review.
- Continuous Urinary Antiseptic Prophylaxis (Methenamine hippurate)
    - Methenamine hippurate is a urinary antiseptic agent that is converted to formaldehyde in an acidic urine environment which is directly toxic to bacteria
    - Methenamine hippurate was found to be non-inferior to prophylactic antibiotics for reducing the incidence of symptomatic UTIs over a 12-month period

- Continuous methenamine prophylaxis avoids the risks of long-term prophylactic antibiotic treatment, including the development of antibiotic resistance and adverse effects such as C. difficile infection
- Methenamine may now be offered as a first-line alternative to continuous antibiotic therapy for UTI prevention in women. It may be initiated in primary care in women without urinary tract abnormalities or neuropathic bladder (Amber 3 classification).
- Methenamine should NOT be used for the treatment of UTIs
- There is some evidence that methenamine works in an acidic urine environment. In the ALTAR study, the value of urinary acidification was not explored. Therefore, routine dipstick testing is currently not advised in this guideline until further evidence is available.

- Choice of Agents for Prophylaxis:
  - The choice of agent should be based on patient preference, consideration of the patient's co-morbidities, renal function and any contra-indicating factors. If prescribing antibiotics, the choice of antibiotic should be based on confirmed culture and sensitivity results (wherever possible). The antibiotics licensed for the prophylaxis of UTIs are trimethoprim and nitrofurantoin.
  - The risk of adverse effects, as well as common side-effects such as rashes, oral/vaginal thrush, and gastrointestinal upset, should be discussed with the patient.

Table 9. NHS 2022 First Line Prophylaxis Options for rUTI

Drug	Dose	Cautions and Monitoring
Trimethoprim	200 mg one dose post-coital (off-label) or 100 mg nightly	• Hyperkaliemia: caution when prescribing medications such as spironolactone, ACE inhibitor or angiotensin inhibitors. • Renal Impairment: Avoid if eGFR <15ml/min. Discuss with a renal physician if eGFR <30ml/min. It may increase serum creatinine. • Patients should be counselled on the risk of blood disorders and advised to seek attention if fever, sore throat, purpura, mouth ulcers, bruising or bleeding occurs.

Nitrofurantoin	100 mg immediate release one dose post-coital (off-label) Or 50 mg nightly	• Avoid if renal function eGFR <45ml/min. Consider checking renal function prior to commencing continuous prophylaxis, especially in the elderly. • Avoid if G6PD deficiency. • Use with caution in anemia, diabetes, vitamin B or folate deficiencies. • Monitor full blood count, renal function, and liver function tests every 3-6 months. • Advise the patient on the risk of pulmonary and hepatic fibrosis and the symptoms to report if they develop during treatment. Reactions can develop acutely or insidiously. • Advise the patient on the risk of peripheral and optic neuropathy and the symptoms to report if they develop during treatment.
Methenamine	1 g twice a day	• Check baseline LFTs, U&Es and eGFR. • Not for the treatment of UTI. • Avoid in patients with a history of febrile UTI or previous urosepsis. • Contra-indications: Gout, metabolic acidosis, severe dehydration. • Renal impairment: Avoid if eGFR <10ml/min. • Hepatic impairment: Avoid. • Pregnancy: Preferable to avoid as inadequate evidence of safety. • Uncommonly can cause epigastric discomfort and skin reactions.

- Second line options:
    - If resistance to first-line antibiotics and methenamine, used as single agents, is not tolerated or contra-indicated, other antibiotic agents may be considered after discussion with Urology and/or an Infection Specialist if the patient is not under urology.
    - Broader spectrum agents such as cefalexin, ciprofloxacin and co-amoxiclav have a higher risk of C. difficile diarrhoea and selection for

resistance, so they should not be routinely used for prophylaxis and be reviewed with a trial of stopping after 6 months.

- In addition, MHRA has issued an alert restricting the use of Fluoroquinolone antibiotics, e.g., ciprofloxacin.

Table 10. NHS 2022 Second Line Prophylaxis Drug Options for rUTI

Drug	Dose	Cautions and Monitoring
Cefalexin	500 mg one dose post-coital or 125 mg nightly	Higher risk of selection for resistant infections Higher risk of C. difficile infection
Pivmecillinam	200 mg one dose post-coital or 200 mg nightly	Unknown safety profile and potential carnitine deficiency with prolonged use Note the BNF pivmecillinam dosing for "chronic or recurrent bacteriuria" is not applicable for recurrent symptomatic urinary tract infections.

Managing 'breakthrough' UTIs on a continuous prophylactic agent:

- Antibiotic prophylaxis:
  - The first breakthrough infection should be treated according to culture and sensitivity results if available, with the original prophylaxis being held and then restarted once the infection has resolved if the culture confirms susceptibility to the prophylactic agent.
  - If the culture shows resistance to the prophylactic agent, or multiple breakthrough UTIs occur (≥2 UTIs in 6 months), prophylaxis has therefore proved ineffective and should be stopped or changed to an alternative prophylactic agent (antibiotic or methenamine)
  - Consider referral to Urology at this point if you have not already been referred.
- Methenamine prophylaxis
  - The breakthrough infection should be treated according to culture and sensitivity results if available.
  - Methenamine prophylaxis should be continued alongside the antibiotic course for the breakthrough infection if there has been a good response.

- If multiple breakthrough UTIs occur (≥2 UTIs in 6 months), methenamine should be stopped or changed to an alternative prophylactic agent (antibiotic)
- Consider referral to Urology at this point if not already been investigated.

Managing a patient who has had a prolonged course of a continuous prophylactic agent:

- Antibiotic prophylaxis - Identifying patients for review:
  - Patients should be reviewed after 6 months of prophylactic antibiotics with a view to stopping.
  - 12 months is a suggested trigger for audit purposes for patients on long-term antibiotic prophylaxis.
  - Patients who have urine cultures confirming resistance to the prophylactic agent they are on should have their prophylaxis stopped (exposure to antibiotic without benefit) and a clinical review to discuss ongoing management and/or the need for referral.
- Methenamine prophylaxis - Identifying patients for review:
  - Patients should be reviewed after 6 months of prophylactic methenamine with a view to stopping.
  - If the patient starts to suffer from recurrent UTIs again and methenamine was effective previously, this can be restarted. Consider referral for investigation (if the patient has not already been investigated)

Stopping continuous prophylaxis is recommended:

- A prolonged period of a prophylactic agent may allow bladder epithelial healing, reducing the risk of future UTIs when antibiotics are then stopped.
- The proportion of patients who will return to suffering recurrent UTIs after stopping continuous prophylaxis may be around 50%
- This means a significant number of patients are able to stop continuous prophylaxis without a return of symptoms and therefore avoid the risks of resistance emerging and side-effects.
- One option is to provide ‘standby’ antibiotics when stopping continuous prophylaxis which may give sufficient reassurance to patients for a trial off prophylaxis.

- Consider referring patients who relapse after stopping continuous prophylaxis, if not already been investigated.
- Longer term prophylaxis with an antibiotic or methenamine may be helpful in those patients whose UTIs are suppressed when on prophylaxis and recur when prophylaxis is discontinued after 6 months.

Section 2.0 Drug Therapy in Recurrent Urinary Tract Infections

This section comprises three subsections: the first one contains the newly recommended drugs, the second one covers drug modifications, and the third one outlines the drugs that have been withdrawn from the market.

2.1 Additions

After February 2020, there have been no new drugs that have received FDA or EMA approval for the management of rUTIs. Nevertheless, the antimicrobial combination of Imipenem + Cilastatin + Relebactam was registered by the SFDA list and submitted to the CHI for evaluation. Hence, relevant information pertaining to this drug can be found below.

2.1.1 Imipenem + Cilastatin + Relebactam

This section includes pertinent information regarding the use of Imipenem + Cilastatin + Relebactam (Recarbrio®) in complicated Urinary Tract Infections[13].

Table 11. Drug Therapy with Imipenem + Cilastatin + Relebactam

SCIENTIFIC NAME **Imipenem + Cilastatin + Relebactam**	
SFDA Classification	Prescription
SFDA Approval	Yes
US FDA	Yes in 2019, for complicated urinary tract infections, including pyelonephritis in patients who have limited or no alternative treatment options.
EMA	Yes in 2020, for infections caused by bacteria classed as aerobic gram-negative bacteria when other treatments might not work

MHRA	Yes
PMDA	Yes
Indication (ICD-10)	N39.0
Drug Class	Antibiotic
Drug Sub-class	Carbapenem with beta-lactamase inhibitor
ATC Code	J01DH56
Pharmacological Class (ASHP)	Carbapenems
DRUG INFORMATION	
Dosage Form	Vial
Route of Administration	Intravenous use
Dose (Adult) [DDD]	IV: 1.25 g every 6 hours. Switch to an appropriate oral regimen once symptoms improve if culture and susceptibility results allow. Total duration of therapy ranges from 5 to 14 days and depends on clinical response and the antimicrobial chosen to complete the regimen
Maximum Daily Dose Adults	N/A
Dose (pediatrics)	N/A
Maximum Daily Dose Pediatrics	N/A
Adjustment	**RENAL IMPAIRMENT:** CrCl ≥90 mL/minute: No dosage adjustment necessary. CrCl 60 to 89 mL/minute: 1 g every 6 hours. CrCl 30 to 59 mL/minute: 750 mg every 6 hours. CrCl 15 to 29 mL/minute: 500 mg every 6 hours. CrCl <15 mL/minute: Do not administer unless hemodialysis is instituted within 48 hours. End-stage renal disease on hemodialysis: 500 mg every 6 hours; administer after hemodialysis and at intervals timed from the end of that hemodialysis session. Peritoneal dialysis: Use is not recommended (inadequate data). **HEPATIC IMPAIRMENT:**

	There are no dosage adjustments provided in the manufacturer's labeling; however, hepatic impairment is not likely to have any effect on exposure.
Prescribing edits	ST, AGE, MD, PA
AGE (Age Edit): the safety and efficacy of Imipenem + Cilastatin + Relebactam HCl in children aged less than 18 years have not been established	
CU (Concurrent Use Edit): N/A	
G (Gender Edit): N/A	
MD (Physician Specialty Edit): Infectious Disease Specialist	
PA (Prior Authorization): this drug is indicated only as a last resort for adult patients' treatment with enterobacteria infections, sensitive to the imipenem/cilastatin/relebactam combination, and for whom recourse to other beta-lactams and carbapenems (meropenem or imipenem-cilastatin) cannot be considered in case of resistance, in particular through KPC-type carbapenemase production. It is given as IV 1.25 g every 6 hours. Switch to an appropriate oral regimen once symptoms improve if culture and susceptibility results allow. Total duration of therapy ranges from 5 to 14 days and depends on clinical response. This drug should be prescribed after consultation with an infectious disease specialist.	
QL (Quantity Limit): N/A	
ST (Step Therapy): Recommended for complicated urinary tract infections, including pyelonephritis in patients who have limited or no alternative treatment options.	
EU (Emergency Use Only): N/A	
PE (Protocol Edit): N/A	
SAFETY	
Main Adverse Drug Reactions (Most common and most serious)	**Most common (>10% frequency):** Hematologic & oncologic: Anemia (11%) Hepatic: Increased serum aspartate aminotransferase (12%)
Drug Interactions	**Category X**: • BCG (Intravesical) • Cholera Vaccine • Fecal Microbiota (Live) (Oral and rectal)
Special Population	**Older Adult** Refer to adult dosing.

Pregnancy	Imipenem and cilastatin cross the placenta. Due to pregnancy-induced physiologic changes, some pharmacokinetic parameters of imipenem/cilastatin may be altered. Information specific to relebactam has not been located.
Lactation	Imipenem is present in breast milk. Excretion of relebactam is not known.
Contraindications	Severe hypersensitivity (eg, anaphylaxis) to cilastatin, imipenem, relebactam, or any component of the formulation.
Monitoring Requirements	Periodic renal function tests; signs of hypersensitivity/anaphylaxis.
Precautions	**Concerns related to adverse effects:** - CNS effects: Carbapenems have been associated with CNS adverse effects, including confusional states and seizures (myoclonic); use caution with CNS disorders (eg, brain lesions, history of seizures) and adjust dose in renal impairment to avoid drug accumulation. Drug accumulation may increase seizure risk. - Hypersensitivity reactions: Serious hypersensitivity/anaphylactic reactions, some fatal, have been reported with beta-lactams. Carefully inquire about previous hypersensitivity reactions to penicillins, carbapenems, cephalosporins, other beta-lactams, and other allergens. Discontinue treatment and institute supportive care if a hypersensitivity reaction occurs. - Superinfection: Prolonged use may result in fungal or bacterial superinfection, including Clostridioides difficile-associated diarrhea (CDAD); CDAD has been observed >2 months postantibiotic treatment.

	Disease-related concerns: Renal impairment: Use with caution in patients with renal impairment; dosage adjustment required. Increased seizure risk has been reported in patients with significant renal dysfunction. Do not use in patients with CrCl ≤15 mL/minute unless hemodialysis is instituted within 48 hours.
Black Box Warning	N/A
REMS	N/A

Clinical Trials – Imipenem + Cilastatin + Relebactam

This antibiotic demonstrates in vitro activity against a broad spectrum of pathogens, encompassing multidrug-resistant (MDR) Pseudomonas aeruginosa and carbapenem-resistant Enterobacterales (CRE) like Klebsiella pneumoniae carbapenemase. However, it's important to note that the inclusion of relebactam does not reinstate the effectiveness of imipenem when dealing with metallo-β-lactamase (MBL)-producing Enterobacterales and carbapenem-resistant Acinetobacter baumannii[14].

Imipenem + Cilastatin + Relebactam has demonstrated excellent efficacy and tolerability in real-world clinical practice. Notably, in pivotal phase II and III clinical trials, imipenem/cilastatin/relebactam demonstrated noninferiority when compared to piperacillin/tazobactam in patients with HABP/VABP and to imipenem/cilastatin in patients with cUTIs and cIAIs. It also exhibited effectiveness in treating infections that were not susceptible to imipenem[15,16].

Imipenem/cilastatin/relebactam was generally well tolerated, with a safety profile consistent with that of imipenem/cilastatin. The available evidence suggests that imipenem/cilastatin/relebactam is an effective and well-tolerated option for treating gram-negative infections in adults, including those who are critically ill or at high risk, and it holds promise as a treatment for infections caused by carbapenem-resistant pathogens[15,16].

Health Technology Assessment (HTA) – Imipenem + Cilastatin + Relebactam

After conducting a comprehensive analysis of several HTA bodies, including the National Institute for Health and Care Excellence (NICE), the Canadian Agency for Drugs and Technologies in Health (CADTH), the Haute Autorité de Santé (HAS), the Institute for Quality and Efficiency in Health Care (IQWIG), and the Pharmaceutical Benefits Advisory Committee (PBAC), it was found that **only HAS has provided recommendations regarding the use of Imipenem + Cilastatin + Relebactam for the treatment of complicated UTI**

Table 12. Imipenem + Cilastatin + Relebactam HTA Analysis

MEDICATION	AGENCY	DATE – HTA RECOMMENDATION
Imipenem + Cilastatin + Relebactam	NICE	N/A
	CADTH	N/A
	PBAC	N/A
	IQWIG	N/A
	HAS[17]	**Positive opinion for reimbursement** in the market authorization (MA) indications, only as a last resort for patients' treatment with enterobacteria infections, sensitive to the imipenem/cilastatin/relebactam combination, and for whom recourse to other beta-lactams and carbapenems (meropenem or imipenem-cilastatin) cannot be considered in case of resistance, in particular through KPC-type carbapenemase production. **Negative opinion for reimbursement** in other situations.

It is worth noting that Imipenem + Cilastatin + Relebactam currently lacks generic alternatives, which means that there are no identical, lower-cost versions of the drug available. The overall cost of treatment with Imipenem + Cilastatin + Relebactam remains relatively higher than other antibiotics prescribed for complicated UTI.

Conclusion Statement – Imipenem + Cilastatin + Relebactam

Imipenem + Cilastatin + Relebactam is recommended only as a **last resort** for complicated urinary tract infections, including pyelonephritis (cUTI) in patients who have limited or no alternative treatment options. The drug is relatively tolerable and effective. It is important to note that there is currently no existing data or specific recommendations from health technology assessment (HTA) organizations regarding the use of Imipenem + Cilastatin + Relebactam for conditions other than those addressed in the HAS HTA analysis. Nevertheless, **it is advisable to consider adding Imipenem + Cilastatin + Relebactam to the CHI formulary while exercising caution in patients with a history of seizures or kidney impairment.**

2.2 Modifications

Below are the modifications made to the list of recurrent UTI drugs since the CHI report in February 2020, reflecting the changes and updates:

Table 13. Prescribing Edits (PE) Modifications

Drugs	PE modifications
Fluoroquinolones	**Fluoroquinolones: Ciprofloxacin and Levofloxacin were both added** **"Step Therapy (ST)"** was added: second line therapy for the treatment of acute cystitis in women with rUTI (consider only if local resistance <20%)
Ampicillin	**"ST"**: second line therapy for the treatment of acute cystitis in women with rUTI. NOTE: Lower efficacy than other available agents due to high resistance and decreased concentration in the bladder. Requires close follow-up. Not recommended alone as empiric therapy.
Ampicillin + Sulbactam	**"ST"**: second line therapy for the treatment of acute cystitis in women with rUTI. NOTE: Lower efficacy than other available agents due to high resistance and decreased concentration in the bladder. Requires close follow-up.
Amoxicillin	**"ST"**: second line therapy for the treatment of acute cystitis in women with rUTI. NOTE: Lower efficacy than other available agents due to high resistance and decreased concentration in the bladder. Requires close follow-up. Not recommended alone as empiric therapy.
Amoxicillin + Clavulanic acid	**"ST"**: second line therapy for the treatment of acute cystitis in women with rUTI. NOTE: Lower efficacy than other available agents due to high resistance and decreased concentration in the bladder. Requires close follow-up.
Cefotaxime	Initial treatment until culture results are available to guide therapy for acute UTI in women with rUTI and complicating factors
Ceftriaxone	Initial treatment until culture results are available to guide therapy for acute UTI in women with rUTI and complicating factors

Ceftizoxime	Initial treatment until culture results are available to guide therapy for acute UTI in women with rUTI and complicating factors
Ceftazidime	**"ST"**: recommended as empirical treatment in severe cases or initial failure
Aminoglycosides	**Aminoglycosides: Gentamicin and Amikacin** Initial treatment until culture results are available to guide therapy for acute UTI in women with rUTI and complicating factors
Piperacillin tazobactam	**"ST":** recommended as empirical treatment in severe cases or initial failure
Nitrofurantoin, Fosfomycin, and Sulfamethoxazole + Trimethoprim	They are recommended as a self-initiated regimen **"ST":** recommended as first line therapy for treatment of acute cystitis in women with rUTI

2.3 Delisting

No medications have been withdrawn or are no longer recommended for the treatment of recurrent UTI since February 2020.

Section 3.0 Key Recommendations Synthesis

- Treatment of asymptomatic bacteriuria is harmful in patients with recurrent urinary tract infections. (Level of evidence 1b)[3].
- Continuous or post-coital antimicrobial prophylaxis should be used to prevent recurrent UTI when nonantimicrobial interventions have failed. Patients should be counseled regarding possible side effects. (Strength rating: Strong). There is no significant difference in the efficacy between the two treatment strategies. (Strong, LE 1b)[3].
    - There is no consensus about the optimal duration of continuous antimicrobial prophylaxis with duration of three to twelve months[3].
    - The choice of agent should be based on the local resistance patterns[3].
    - Post-coital prophylaxis should be considered in pregnant women with a history of frequent UTIs before onset of pregnancy, to reduce their risk of UTI[3].
- For patients with good compliance, self-administered short-term antimicrobial therapy should be considered. (Strength rating: Strong)[3].
- The choice of antibiotic should consider specific patient factors (allergies, renal function), complicating factors such as abnormal genitourinary anatomy, immunosuppression, and chronic catheterization, are present and uropathogen sensitivity[4].
- First line therapy for acute cystitis in women with recurrent UTI: Nitrofurantoin monohydrate/macrocrystals (93% estimated clinical efficacy), Trimethoprim/sulfamethoxazole (93% efficacy), and Fosfomycin trometamol (91% efficacy)[4].
- Initial treatment, for acute UTI in women with rUTI and complicating factors, until culture results are available to guide therapy (consider only if local resistance <20%) are the following options: Fluoroquinolones (ciprofloxacin and levofloxacin), Aminopenicillin (ampicillin) plus a beta-lactam inhibitor (clavulanic acid), Cephalosporins group 3a (parenteral: cefotaxime, ceftriaxone, ceftizoxime, cefmenoxime, cefodizime), and Aminoglycosides[4].
- Empirical treatment in severe cases or initial failure for acute UTI in women with rUTI and complicating factors, are the following options: Fluoroquinolone (if not used for initial therapy), Piperacillin plus a β-lactam inhibitor, Cephalosporin group 3b (parenteral; ie, cefoperazone, ceftazidime), and Carbapenem[4].

- Not recommended for empirical treatment for acute UTI in women with rUTI and complicating factors, are the following options: Aminopenicillins (ie, ampicillin, amoxicillin, bacampicillin), TMP-SMX, and Fosfomycin trometamol[4].
- Antibiotic irrigation of the bladder for prophylaxis and/or treatment provides some potential advantages over oral and parenteral routes. These include direct drug delivery to the site of infection and bypass of gastrointestinal tract which avoids collateral consequences and side effects such as gastrointestinal upset. Gentamicin has been the antibiotic most studied for bladder irrigation. However, there is limited current evidence supports the safety of gentamicin bladder instillations[4].
- For acute UTI in women with rUTI and complicating factors, the recommended regimens for initial, empiric therapy are[4]:
    - Initial treatment until culture results are available to guide therapy (consider only if local resistance <20%)
        - Fluoroquinolones (ciprofloxacin and levofloxacin)
        - Aminopenicillin (ampicillin) plus a beta-lactam inhibitor (clavulanic acid)
        - Cephalosporins group 3a (parenteral: cefotaxime, ceftriaxone, ceftizoxime, cefmenoxime, cefodizime).
        - Aminoglycosides
    - Empirical treatment in severe cases or initial failure:
        - Fluoroquinolone (if not used for initial therapy)
        - Piperacillin plus a β-lactam inhibitor
        - Cephalosporin group 3b (parenteral; ie, cefoperazone, ceftazidime)
        - Carbapenem
    - Not recommended for empirical treatment
        - Aminopenicillins (ie, ampicillin, amoxicillin, bacampicillin)
        - TMP-SMX
        - Fosfomycin trometamol
- Antibiotic irrigation of the bladder for prophylaxis and/or treatment provides some potential advantages over oral and parenteral routes. These include direct drug delivery to the site of infection and bypass of gastrointestinal tract which avoids collateral consequences and side effects such as gastrointestinal upset. Gentamicin has been the antibiotic most studied for bladder irrigation.

However, there is limited current evidence supports the safety of gentamicin bladder instillations[4].

- Although there are not sufficient data to recommend intravesical Colistin, it may be considered in a patient who has very limited treatment options[4].

Recurrent cystitis:

Relapse (referral to the ID Consultant is mandatory[10]:

  - Relapse is a new episode of bacteriuria with microorganism that is same from the original one
  - Assess for pharmacologic reason for treatment failure.
  - Longer treatment (for 2–6 weeks, depending on length of initial course)

Reinfection (referral to the ID Consultant is mandatory)[10]:

  - Reinfection is a new episode of bacteriuria with microorganism that is different from the original one
  - If patient has two or fewer UTIs in 1 year, use patient-initiated therapy for symptomatic episodes (3-day treatment regimens).
  - If patient has three or more UTIs in 1 year and they are temporally related to sexual activity, use post-intercourse prophylaxis with TMP/SMZ SS, cephalexin 250 mg, or nitrofurantoin 50–100 mg.
  - If patient has three or more UTIs in 1 year that are not related to sexual activity, use daily or 3 times/week prophylaxis with TMP/SMZ SS, cephalexin 250 mg, or nitrofurantoin 50–100 mg.

- Cystoscopy should be considered in catheterized patients who report unexplained visible hematuria even if it is related to catheter changes, recurrent urinary tract infections and those reporting new bladder symptoms. Prophylactic antibiotics are usually ineffective. Consider US/Cystoscopy to rule out stones and washout of debris[6].
- In NLUTD patients who perform clean intermittent catheterization with recurrent urinary tract infection, clinicians may offer oral antimicrobial prophylaxis to reduce the rate of urinary tract infections following shared decision making and discussion regarding increased risk of antibiotic resistance. (Conditional Recommendation; Evidence Level: Grade C)[7].

Section 4.0 Conclusion

This report serves as **an annex to the previous CHI Recurrent Urinary Tract Infections report** and aims to provide recommendations to aid in the management

of Recurrent Urinary Tract Infections. It is important to note that these recommendations should be utilized to support clinical decision-making and not replace it in the management of individual patients with Recurrent Urinary Tract Infections. Health professionals are expected to consider this guidance alongside the specific needs, preferences, and values of their patients when exercising their judgment.

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Section 6.0 Appendices

Appendix A. Prescribing Edits Definition

I. Prescribing Edits (ensure consistent use of abbreviations, e.g., CU, ST)

Some covered drugs may have additional requirements, rules, or limits on coverage. These requirements and limits may include:

Prescribing edits Tools	Description
AGE (Age):	Coverage may depend on patient age
CU (Concurrent Use):	Coverage may depend upon concurrent use of another drug
G (Gender):	Coverage may depend on patient gender
MD (Physician Specialty):	Coverage may depend on prescribing physician's specialty or board certification
PA (Prior Authorization):	Requires specific physician request process
QL (Quantity Limits):	Coverage may be limited to specific quantities per prescription and/or time period
ST (Step Therapy):	Coverage may depend on previous use of another drug
EU (Emergency Use only):	This drug status on Formulary is only for emergency use
PE (Protocol Edit):	Use of drug is dependent on protocol combination, doses, and sequence of therapy

Appendix B. Recurrent Urinary Tract Infections Scope

Recurrent Urinary Tract Infections Scope

<table>
<tr><th>Section</th><th>Rationale/Updates</th></tr>
<tr><td>Section 1.1.1
The European Association of Urology (EAU) Guidelines on Urological Infections: March 2023[18]</td><td>
The GRADE Working Group grades of recommendation and levels of evidence are detailed in tables below

Table GRADE Working Group Grades of Recommendation
<table>
<tr><th>Grade</th><th>Definition</th></tr>
<tr><td>High certainty: (⊕⊕⊕⊕)</td><td>Very confident that the true effect lies close to that of the estimate of the effect.</td></tr>
<tr><td>Moderate certainty: (⊕⊕⊕)</td><td>Moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.</td></tr>
<tr><td>Low certainty: (⊕⊕)</td><td>Confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.</td></tr>
<tr><td>Very low certainty: (⊕)</td><td>Very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.</td></tr>
</table>

Table. GRADE Working Group Levels of Evidence
<table>
<tr><th>Level of Evidence</th><th>Definition</th></tr>
<tr><td>1</td><td>Two systematic reviews including non-randomized controlled trials (RCTs) and two RCTs describe comparable rates of post-biopsy infection in patients with and without antibiotic prophylaxis.</td></tr>
<tr><td>2</td><td>Be informed about local antimicrobial resistance.</td></tr>
<tr><td>3</td><td>Banned by European Commission due to side effects.</td></tr>
<tr><td>4</td><td>Contradicts principles of Antimicrobial Stewardship.</td></tr>
<tr><td>5</td><td>Fosfomycin trometamol (3 RCTs), cephalosporins (2 RCTs), aminoglycosides (2 RCTs).</td></tr>
<tr><td>6</td><td>Only one RCT comparing targeted and augmented prophylaxis.</td></tr>
</table>
</td></tr>
</table>

7	Originally introduced to use alternative antibiotics in case of fluoroquinolone resistance.
8	Various schemes: fluoroquinolone plus aminoglycoside (3 RCTs); and fluoroquinolone plus cephalosporin (1 RCT).
9	Significantly inferior to targeted and augmented prophylaxis

The guidelines recommendations are summarized below:

This table shows the non-antimicrobial prophylaxis options for recurrent UTIs treatment:

Table Non-Antimicrobial Prophylaxis Options for Recurrent Urinary Tract Infections

Non-Antimicrobial Prophylaxis	
Hormonal replacement	Topical estrogen therapy (either as a creme or a pessary) shows a trend towards rUTI prevention (Strong, LE 1b)
Immunoactive prophylaxis	Oral immunotherapy with OM-89 is an effective and safe method for the prevention of rUTIs placebo at short-term follow up (< 6 months) (Strong, LE 1a)
Probiotics prophylaxis	The highest efficacy was shown with L. rhamnosus GR-1, L. reuteri B-54, L. reuteri RC-14, L. casei shirota, and L. crispatus CTV-05 (Weak, LE 1b)
Cranberry prophylaxis	The efficacy of cranberry products remains unclear, but clinicians may recommend them for rUTI prevention in women who are informed of the weak evidence base due to their favorable benefit to harm ratio. However, there is no clear clinical evidence regarding the appropriate dose and treatment duration (Weak, LE 1a)
D-mannose prophylaxis	D-mannose was effective for rUTI prevention compared to placebo with comparable efficacy to antibiotic prophylaxis (Weak, LE 2)
Methenamine Hippurate	Methenamine hippurate may be effective for preventing UTI in patients without renal tract abnormalities, particularly when used for short-term prophylaxis (Strong, LE 1b)

Water intake	Increased water intake (if no contraindications exist) is an effective antimicrobial-sparing strategy to prevent rUTI in premenopausal women at high risk for recurrence who drink low volumes (< 1.5 L) of fluid daily (Weak, LE 3)

Antimicrobials for preventing rUTIs:

- Continuous low-dose antimicrobial prophylaxis and post-coital prophylaxis are the most effective approaches and there is no significant difference in the efficacy between them. (Strong, LE 1b)
- There is no consensus about the optimal duration of continuous antimicrobial prophylaxis with duration of three to twelve months.
- Differences in outcomes between antibiotics did not reach statistical significance.
- The choice of agent should be based on the local resistance patterns.
- Post-coital prophylaxis should be considered in pregnant women with a history of frequent UTIs before onset of pregnancy, to reduce their risk of UTI.

Table List of Antimicrobials for the Prevention of Recurrent Urinary Tract Infections (rUTIs)

Antimicrobials for Preventing rUTIs:
Nitrofurantoin 50 mg or 100 mg once daily
Fosfomycin trometamol 3 g every ten days
Trimethoprim 100 mg once daily
Cephalexin 125 mg or 250 mg during pregnancy
Cefaclor 250 mg once daily during pregnancy

Recurrent UTI: Recurrences of uncomplicated and/or complicated UTIs, with a frequency of at least three UTIs/year or two UTIs in the last six months.

- One RCT investigated the effect of ABU treatment in female patients with recurrent symptomatic UTI without identified risk factors [25] and demonstrated that treatment of ABU increases the risk for a subsequent symptomatic UTI episode, compared to non-treated patients (RR 0.28, 95% CI 0.21 to 0.38; n=673). This protective effect of spontaneously developed ABU can be used as part of prevention in female patients with recurrent symptomatic UTI; therefore, treatment of ABU is not

	recommended. • Treatment of asymptomatic bacteriuria is harmful in patients with recurrent urinary tract infections. (Level of evidence 1b) • Increased water intake is an effective antimicrobial-sparing strategy to prevent rUTI in premenopausal women at high risk for recurrence who drink low volumes (< 1.5 L) of fluid daily. (Level of evidence 3) • Probiotics containing L. rhamnosus GR-1, L. reuteri B-54 and RC-14, L. casei shirota, or L. crispatus CTV-05 are effective for vaginal flora restoration and have shown a trend towards prevention of rUTIs. (Level of evidence 1b) • Based on limited evidence intravesical GAG therapy can reduce the number of UTIs per patient per year and prolong the time interval between rUTI episodes. (Level of evidence 2) • Advise pre-menopausal women regarding increased fluid intake as it might reduce the risk of recurrent UTI. (Strength rating: Weak) • Use vaginal oestrogen replacement in post-menopausal women to prevent recurrent UTI. (Strength rating: Strong) • Use immunoactive prophylaxis to reduce recurrent UTI in all age groups. (Strength rating: Strong) • Advise patients on the use of local or oral probiotic containing strains of proven efficacy for vaginal flora regeneration to prevent UTIs. (Strength rating: Weak) • Advise patients on the use of cranberry products to reduce recurrent UTI episodes; however, patients should be informed that the quality of evidence underpinning this is low with contradictory findings. (Strength rating: Weak) • Use D-mannose to reduce recurrent UTI episodes, but patients should be informed of the overall weak and contradictory evidence of its effectiveness. (Strength rating: Weak) • Use methenamine hippurate to reduce recurrent UTI episodes in women without abnormalities of the urinary tract. (Strength rating: Strong) • Use endovesical instillations of hyaluronic acid or a combination of hyaluronic acid and chondroitin sulphate to prevent recurrent UTIs in patients where less invasive preventive approaches have been unsuccessful. Patients should be informed that further studies are needed to confirm the results of initial trials. (Strength rating: Weak) • Use continuous or post-coital antimicrobial prophylaxis to prevent recurrent UTI when nonantimicrobial interventions have failed. Counsel patients regarding possible side effects. (Strength rating: Strong) • For patients with good compliance self-administered short-term antimicrobial therapy should be considered. (Strength rating: Strong)

Section 1.1.2 **American Urogynecologic Society Best-Practice Statement: Recurrent Urinary Tract Infection in Adult Women 2018**[4]	This guideline tackles some methodologies for prevention of recurrent UTIs (rUTIs), a major complication arising from acute cystitis. The recommendations of the American Urogynecology Society for the treatment of rUTIs infection are listed below: The choice of antibiotic should consider specific patient factors (allergies, renal function), complicating factors such as abnormal genitourinary anatomy, immunosuppression, and chronic catheterization, are present and uropathogen sensitivity. For the treatment of acute cystitis in women with rUTI: • Nitrofurantoin is a key first-line agent at a dose of 100mg BID for 5 days. (93% efficacy) • Fosfomycin is effective at a dose of 3g single dose. Clinicians may need to request sensitivity testing (91% efficacy) • Trimethoprim-sulfamethoxazole (TMP-SMX) at a dose of 160/800 mg BID for 3 days can also be used if resistance is less than 20% in the community (93% efficacy) • Fluoroquinolones typically for 3 days are not a first-line treatment of acute cystitis without complicating factors (90% efficacy) • Unless there is clear evidence of sensitivity to certain β-lactams, including amoxicillin and ampicillin, these antibiotics should rarely be used because of poor efficacy thought to be due in part to the low concentration in the urine for a duration of 3 to 7 days. (89% efficacy) For acute UTI in women with complicating factors, the recommended regimens for initial, empiric therapy are: • Fluoroquinolones (ciprofloxacin and levofloxacin) • Aminopenicillin (ampicillin) plus a beta-lactam inhibitor (clavulanic acid) • Cephalosporins group 3a (parenteral: cefotaxime, ceftriaxone, ceftizoxime, cefmenoxime, cefodizime). • Aminoglycosides In case of initial failure or severe cases, the use of piperacillin plus a beta-lactam inhibitor or a carbapenem or fluoroquinolones (if not used before) or cephalosporins group 3 (if not used before) is warranted. The recommended antibiotic regimens that can be used for prophylaxis

<table>
<tr><td></td><td>according to the American Urogynecologic Society are detailed in table below.

Table Antibiotic Regimens for Prophylaxis Against Urinary Tract Infections
<table>
<tr><th colspan="2">Continuous Low-Dose Regimens</th></tr>
<tr><td>Trimethoprim daily</td><td>100 mg</td></tr>
<tr><td>Trimethoprim/sulfamethoxazole daily</td><td>40mg/200mg</td></tr>
<tr><td>Trimethoprim/sulfamethoxazole every 3 d</td><td>40mg/200mg</td></tr>
<tr><td>Nitrofurantoin monohydrate/macrocrystals daily</td><td>50mg</td></tr>
<tr><td>Nitrofurantoin monohydrate/macrocrystals daily</td><td>100mg</td></tr>
<tr><td>Cephalexin daily</td><td>125mg</td></tr>
<tr><td>Cephalexin daily</td><td>250mg</td></tr>
<tr><td>Fosfomycin every 10 d</td><td>3g</td></tr>
<tr><th colspan="2">Postcoital Prophylaxis</th></tr>
<tr><td>Trimethoprim/sulfamethoxazole</td><td>40mg/200mg</td></tr>
<tr><td>Trimethoprim/sulfamethoxazole</td><td>80mg/400mg</td></tr>
<tr><td>Nitrofurantoin monohydrate/macrocrystals</td><td>50-100mg</td></tr>
<tr><td>Cephalexin</td><td>250mg</td></tr>
</table></td></tr>
<tr><td>Section 1.1.6.
Saudi Urinary Tract Infection management protocol updated in 2020-2021[10]</td><td>Recurrent cystitis:

Relapse (referral to the ID Consultant is mandatory:

• Relapse is a new episode of bacteriuria with microorganism that is same from the original one
- Assess for pharmacologic reason for treatment failure.
- Longer treatment (for 2–6 weeks, depending on length of initial course)

Reinfection (referral to the ID Consultant is mandatory):

• Reinfection is a new episode of bacteriuria with microorganism that is different from the original one
- If patient has two or fewer UTIs in 1 year, use patient-initiated therapy for symptomatic episodes (3-day treatment regimens).
- If patient has three or more UTIs in 1 year and they are temporally related to sexual activity, use post-intercourse prophylaxis with TMP/SMZ SS, cephalexin 250 mg, or nitrofurantoin 50–100 mg.
- If patient has three or more UTIs in 1 year that are not related to sexual activity, use daily or 3 times/week prophylaxis with TMP/SMZ SS, cephalexin 250 mg, or nitrofurantoin 50–100 mg.</td></tr>
</table>

Section 1.1.7. **British Association of Urological Surgeons (BAUS) and Nurses (BAUN) Consensus Document: Management of the Complications of Long Term Indwelling Catheters 2021**[6]	- Patients with recurrent CAUTI need investigation (eg US and cystoscopy). Recurrent UTI in non-catheterized patients is defined as repeated UTI with a frequency of 2 or more UTIs in the last 6 months or 3 or more UTIs in the last 12 months. There is no recognized definition for recurrent CAUTI. Where possible, a closed drainage system is preferable – patients with pre-connected sealed junctions less likely to have UTI than those with catheters without similar junctions. - Health care professionals need to trouble shoot with patients when they are experiencing recurrent catheter problems such as blockages - Cystoscopy should be considered in catheterized patients who report unexplained visible hematuria even if it is related to catheter changes, recurrent urinary tract infections and those reporting new bladder symptoms. - Urine dipstick of CSU not recommended - Prophylactic antibiotics are usually ineffective - Consider US/Cystoscopy to rule out stones and washout of debris
Section 1.1.8. **The AUA/SUFU Guideline on Adult Neurogenic Lower Urinary Tract Dysfunction: Treatment and Follow-up 2021**[7]	- In NLUTD patients who perform clean intermittent catheterization with recurrent urinary tract infection, clinicians may offer oral antimicrobial prophylaxis to reduce the rate of urinary tract infections following shared decision making and discussion regarding increased risk of antibiotic resistance. (Conditional Recommendation; Evidence Level: Grade C) - In NLUTD patients who perform clean intermittent catheterization with recurrent urinary tract infection, clinicians may offer bladder instillations to reduce the rate of urinary tract infections. (Expert Opinion) - Clinicians may counsel NLUTD patients with recurrent urinary tract infection who use various forms of catheter management that cranberry extract has not been demonstrated to reduce the rate of urinary tract infections. (Conditional Recommendation; Evidence Level: Grade B) - In NLUTD patients who have undergone lower urinary tract reconstruction utilizing bowel, and who also develop gross hematuria or symptomatic recurrent urinary tract infection, clinicians should perform cystoscopy. (Moderate Recommendation; Evidence Level: Grade C)
Section 1.1.9. **EAU-ESPU guidelines recommendations for daytime lower urinary tract conditions in children 2020** [11]	- Use antibiotic prophylaxis if there are recurrent infections. (level of evidence: 2, strength rating: Weak)

Section 1.1.10. **Diagnosis and management of community-acquired urinary tract infection in infants and children: Clinical guidelines endorsed by the Saudi Pediatric Infectious Diseases Society (SPIDS) 2021**	The guidelines recommend the following: - SPIDS defined recurrent UTI as two or more episodes of symptomatic UTI within 12 months. - Renal and bladder ultrasonography (RBUS) is a noninvasive, safe, and easy test that can detect renal and urinary bladder abnormalities. This is recommended to be performed in rUTI. - VCUG is the radiological test of choice to diagnose and grade the severity of VUR (grade 1 through 5). VCUG can also identify the anatomy of male urethra, obstructive uropathies, and other abnormalities of the bladder. This is recommended to be performed in rUTI. - The guidelines do not recommend routine antibiotic prophylaxis in infants and children with normal urinary system or mild VUR (Grade I and II) after the first UTI because such cases do not benefit from the prophylaxis therapy - The guidelines suggest an individualized decision for antibiotic prophylaxis after the assessment of the possible risks and benefits. - SPIDS recommends antibiotic prophylaxis in following conditions: o Children with moderate to high-grade reflux (Grade III to IV) o Uncircumcised males with any grade of VUR o Children with BBD and any grade of VUR - SPIDS choice of antibiotic prophylaxis: o The choice of antibiotics depends on the local antimicrobial susceptibility pattern. It is also recommended to check the previous urine culture and susceptibility results and to choose antibiotics accordingly o A single daily prophylactic dose of any of the following options is recommended: o Nitrofurantoin: dose: 1-2mg/kg/day. o Trimethoprim/sulfamethoxazole: dose is based on trimethoprim at 2mg/kg/day. o Amoxicillin and cephalosporins should not routinely be used in prophylaxis because of the increased risk of development of resistant organisms. However, these regimens can be used in infants less than two months of age or in patients who cannot tolerate or developed adverse effects related to the use of trimethoprim or nitrofurantoin.
HTA Pharmacoeconomics Analysis	Recommendations from HTA bodies should be added under each drug therapy section as they are missing from the previous/initial document.

Appendix C. MeSH Terms PubMed

C.1 PubMed Search for Recurrent Urinary Tract Infections:

Query	Filters	Search Details	Results
(((((Urinary Tract Infections[MeSH Terms]) OR (Infection, Urinary Tract[Title/Abstract])) OR (Infections, Urinary Tract[Title/Abstract])) OR (Tract Infection, Urinary[Title/Abstract])) OR (Tract Infections, Urinary[Title/Abstract])) OR (Urinary Tract Infection[Title/Abstract])	Guideline, in the last 5 years	("urinary tract infections"[MeSH Terms] OR "infection urinary tract"[Title/Abstract] OR "infections urinary tract"[Title/Abstract] OR "tract infection urinary"[Title/Abstract] OR "tract infections urinary"[Title/Abstract] OR "urinary tract infection"[Title/Abstract]) AND ((y_5[Filter]) AND (guideline[Filter]))	27

Appendix D. Treatment Algorithm

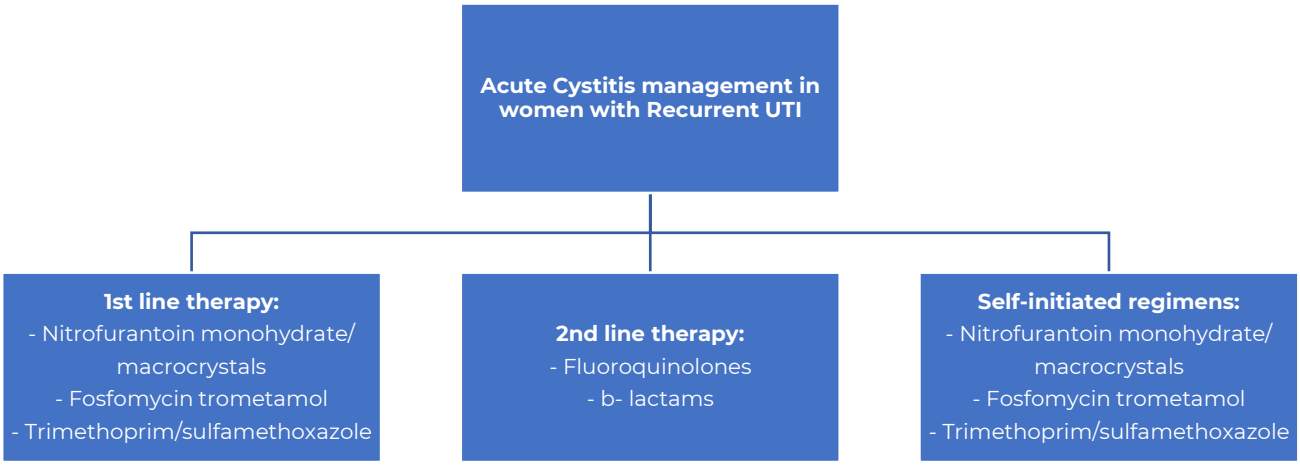

Figure 1. *Treatment Algorithm for the Management of Acute Cystitis in Women with Recurrent Urinary Tract Infections*

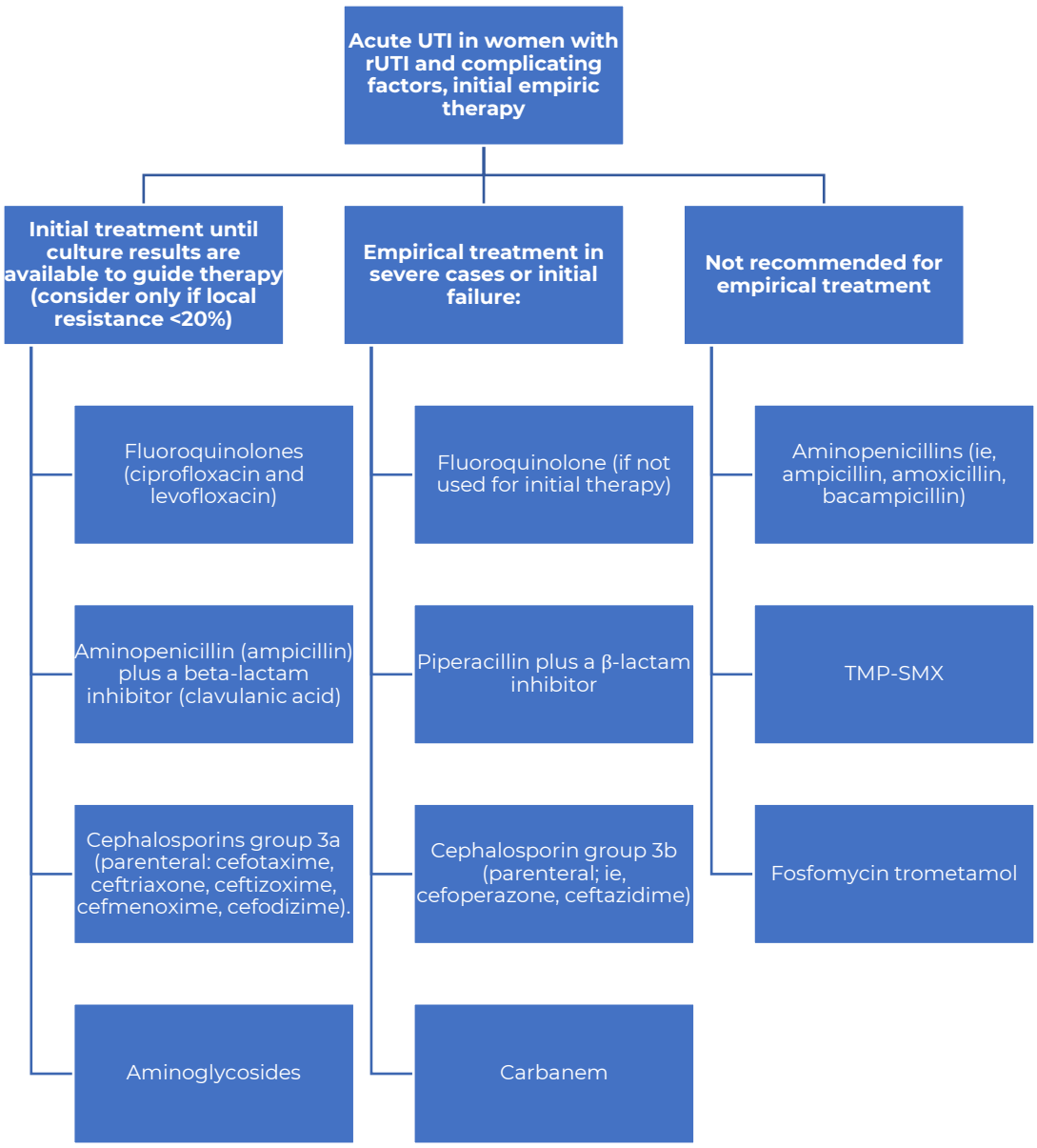

Figure 2. *Treatment Algorithm for the Management of Acute UTI in Women with Recurrent Urinary Tract Infection and Complicating Factors*