FROM GUIDELINES TO INNOVATION: NAVIGATING THE FUTURE OF UTI CARE

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OBJECTIVES

- Enhance understanding of current treatment guidelines
- Analyze prophylactic measures available to prevent recurrent UTIs
- Examine recent advancements in UTI treatment, focusing on new medications and their mechanisms of action

HISTORY

- Are the most common infection worldwide
- In the United States in 2025 there was roughly 8.1 million office visit due to UTIs
- 68% of hospital UTIs are catheter-related
- 3.1-7.5 infections per 1000 catheter-days (varies by hospital unit type)
- Associated with significant healthcare costs-est. annual cost exceeding $4.8 billion in the U.S.

CHALLENGES IN DIAGNOSIS AND MANAGEMENT

- Heterogeneity
  - Variation in clinical presentation
  - Etiology
  - Disease course
  - Patient characteristics (age, gender, comorbidities, etc.)
- Low adherence to guideline recommended treatment
- Overdiagnosis and antibiotic overprescribing

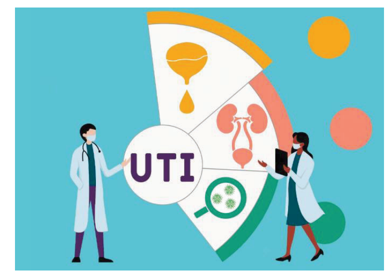


Image source: https://namhyafoods.com/blogs/news/effective-ways-to-reduce-uti-pain-a-comprehensive-guide

- https://youtu.be/dXty9q22Ik0?si=TKUBZ_G-LG1CAUa5

Asymptomatic bacteriuria

Antibiotics give no benefit in this situation and can cause harm!

Asymptomatic bacteriuria is COMMON

Population	Prevalence
Healthy premenopausal women	1–5%
Women 70–90 years old	11–16%
Female long-term care residents	25–50%
Male long-term care residents	15–50%
Females with diabetes	9–29%
Males with diabetes	1–11%
People receiving hemodialysis	25%
People with long-term indwelling urinary catheters	> 90%

AHRQ Safety Program for Improving Antibiotic Use-Acute Care

Symptoms of UTIs

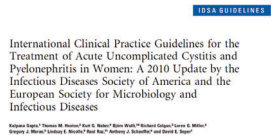
Uncomplicated Urinary Tract Infection	Complicated Urinary Tract Infection
Dysuria	Fever
Frequency	Systemic illness (chills, rigors, hemodynamic instability)
Urgency	Flank Pain
Confined to the bladder -No fever unless by a non-UTI cause	Costovertebral angle tenderness


Complicated Urinary Tract Infections (cUTI): Clinical Guidelines for Treatment and Management

CHALLENGES IN DIAGNOSIS AND MANAGEMENT

OLD DEFINITION
Uncomplicated UTI: Acute cystitis in a healthy non-pregnant afebrile woman with no diabetes and no urologic abnormalities
Acute Pyelonephritis
Complicated UTI: everything else

"NEW" DEFINITION
Complicated UTI: Infection beyond the bladder • Pyelonephritis • CAUTI • Bacteremia from UTI • Septic shock due to UTI
Uncomplicated UTI: Everything else (women and men)


IDSA GUIDELINES

International Clinical Practice Guidelines for the Treatment of Acute Uncomplicated Cystitis and Pyelonephritis in Women: A 2010 Update by the Infectious Diseases Society of America and the European Society for Microbiology and Infectious Diseases


Complicated Urinary Tract Infections (cUTI): Clinical Guidelines for Treatment and Management

Published July 17, 2025

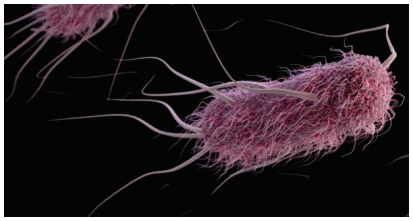
BACTERIA AND TREATMENT

COLONIZERS VS TRUE INFECTION

COMMON COLONIZERS/CONTAMINANTS (DO NOT CAUSE INFECTION-NORMALLY)

- Lactobacillus spp.
- Staphylococcus epidermidis
- Streptococci (Alpha/Nonhemolytic)
- Candida spp (Yeast)
- *S. aureus* (usually contaminant unless indwelling catheter)

COMMON BACTERIA THAT CAUSE INFECTION

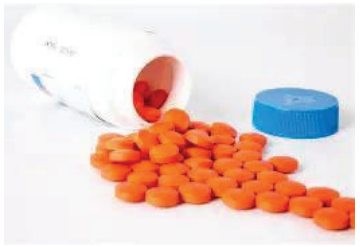


- E.coli
- Klebsiella pneumoniae
- Staphylococcus saprophyticus
- Proteus mirabilis

Other Less common:

- Pseudomonas aeruginosa
- Citrobacter freundii
- Serratia marcescens

UNCOMPLICATED UTI TREATMENT



First Line
- Nitrofurantoin 100 mg twice daily x 5 days
- TMP-SMX 160/800 mg twice daily x 3 days

Alternative
- Fosfomycin 3 g x1 Dose
- Cephalosporin 500mg twice daily for 3-7 days
- Pivmecillinam 400mg twice daily 3-7 days
- Gepotidacin 1500mg twice daily for 5 days

- **Do NOT use amoxicillin empirically**

Kalpana Gupta, Thomas M. Hooton, Kurt G. Naber, Björn Wullt, Richard Colgan,... David E. Soper, International Clinical Practice Guidelines for the Treatment of Acute Uncomplicated Cystitis and Pyelonephritis in Women: A 2010 Update by the Infectious Diseases Society of America and the European Society for Microbiology and Infectious Diseases, *Clinical Infectious Diseases*, Volume 52, Issue 5, 1 March 2011, Pages e103–e120, https://doi.org/10.1093/cid/ciq257

COMPLICATED UTI TREATMENT

Condition of the Patient	Preferred	Alternative
Sepsis with or without shock**	Third or fourth generation cephalosporins,* carbapenems,# piperacillin-tazobactam, fluoroquinolones&	Novel beta lactam-beta lactamase inhibitors,+ cefiderocol, plazomicin, or older aminoglycosides%
Without sepsis, IV route of therapy	Third or fourth generation cephalosporins,* piperacillin-tazobactam, or fluoroquinolones&	Carbapenems,# newer agents (novel beta lactams-beta lactamase inhibitors,+ cefiderocol, plazomicin), or older aminoglycosides%
Without sepsis, oral route of therapy	Fluoroquinolones& or trimethoprim-sulfamethoxazole	Amoxicillin-clavulanate or oral cephalosporins (see **Table 3.1**)

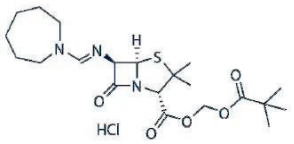
Complicated Urinary Tract Infections (cUTI): Clinical Guidelines for Treatment and Management

NEW UTI MEDICATIONS

2024-PRESENT

PIVMECILLINAM

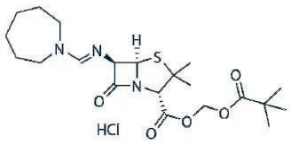
- Trade name: Pivya™
- FDA approved in April 2024
- Treatment of female adults with uUTI caused by
  - *E.coli*
  - *Proteus mirabilis*
  - *Staphylococcus saprophyticus*



- NOT active against Pseudomonas aeruginosa
- Oral prodrug of mecillinam (a beta-lactam), which targets the penicillin-binding protein 2 (PBP2)
- Excretion: Primarily renal: high urinary concentrations make it especially effective for UTIs

PIVMECILLINAM

- Narrow Spectrum -> less disruption of normal flora compared to broader antibiotics
- Less resistance rates-> especially against E.coli
- Well Tolerated-> mild side effects
- Suitable for outpatient treatment
- Drug interactions: Methotrexate and valproic acid
- Avoid in patients with penicillin allergy



Dose
- 185mg orally three times a day for 3-7 days (FDA approval notice)
- 400mg orally twice daily for 3-7 days (IDSA guidelines)

SULOPENEM ETZADROXIL/PROBENECID

- FDA Approved October 2024
  - Approval based on the SURE 1 and REASSURE clinical trials
  - Trade name: Orlynvah™
- Prodrug (oral formulation) converted into active drug (sulopenem)
- Combined with probenecid to enhance its PK
- Penem beta-lactam
- Active against
  - E.coli
  - Klebsiella pneumoniae
  - Proteus mirabilis
- Dose
  - 500mg sulopenem etzadroxil and 500mg probenecid (1 tablet) every twelve hours for 5 days
- Avoid in persons with penicillin allergy or gout
- Contraindicated with ketorolac

https://www.fda.gov/drugs/news-events-human-drugs/fda-approves-new-treatment-uncomplicated-urinary-tract-infections-adult-women-who-have-limited-or-no

GEPOTIDACIN

- FDA Approved March 2025
  - Trade Name: Blujepa™
- Novel first in class, triazaacenaphthylene antibiotic
- Inhibits bacterial DNA replication by targeting two type II topoisomerase enzymes, DNA gyrase and topoisomerase IV. This unique mechanism of action provides activity against common uropathogens including multidrug resistant strains

GEPOTIDACIN

- Treatment of female adult and pediatric patients 12 years of age and older >40kg with uUTI caused by susceptible *E.coli, Klebsiella pneumoniae, Citrobacter freundii complex, Staphylococcus saprophyticus, and Enterococcus faecalis*
- Dosing
  - 1500mg orally twice daily for 5 days
- Generally tolerated well with most common adverse event being diarrhea and nausea
- Approved for the treatment of uncomplicated gonorrhea

GEPOTIDACIN

	Minimum Inhibitory Concentrations (mcg/mL)			Disk Diffusion (zone diameter in mm)		
Pathogen	S	I	R	S	I	R
Enterobacterales[a]	≤ 16	32	≥ 64	≥ 12	8-11	≤ 7
Staphylococcus saprophyticus	≤0.25	-	-	≥ 23	-	-
Enterococcus faecalis	≤4	-	-	≥ 14		

S = susceptible; I = intermediate; R = resistant

[a] Clinical efficacy was shown for *Escherichia coli*, *Klebsiella pneumoniae*, and *Citrobacter freundii* complex.

https://www.fda.gov/drugs/development-resources/gepotidacin-oral-products

UNIQUE TREATMENT OPTIONS

HELPFUL TIPS

SINGLE DOSE AMINOGLYCOSIDES

Infectious Diseases Society of America 2024 Guidance on the Treatment of Antimicrobial-Resistant Gram-Negative Infections

Pranita D. Tamma,[1] Emily L. Heil[2], Julie Ann Justo[3], Amy J. Mathers[4], Michael J. Satlin[5], & Robert A. Bonomo,[6]

- Uncomplicated cystitis caused by extended-spectrum ß lactamase producing Enterobacterales (ESBL-E) and carbapenem-resistant Enterobacterales (CRE)
- Nearly exclusively eliminated by the renal route in their active form
- Achieve high urinary concentrations (with minimal toxicities)

SINGLE DOSE AMINOGLYCOSIDES

Antimicrob Agents Chemother. 2018 Dec 21;63(1):e02165-18. doi: 10.1128/AAC.02165-18

A Systematic Review of Single-Dose Aminoglycoside Therapy for Urinary Tract Infection: Is It Time To Resurrect an Old Strategy?

Kellie J Goodlet [a,m], Fatima Z Benhalima [a], Michael D Nailor [b]

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PMCID: PMC6325212 PMID: 30397061

Multicenter Study. Acad Emerg Med. 2024 Jul;31(7):649-655. doi: 10.1111/acem.14886. Epub 2024 Mar 7.

Prospective evaluation of single-dose aminoglycosides for treatment of complicated cystitis in the emergency department

Jordan E Jenrette [1,2], Kyle Coronato [3], Matthew A Miller [4], Kyle C Molina [3], Alexander Quinones [3], Gabrielle Jacknin [3]

Affiliations + expand

PMID: 38450896 DOI: 10.1111/acem.14886

HELPFUL TIPS IN UNIQUE SITUATIONS

Uncomplicated female cystitis

- You have an ESBL E. coli that has seemingly has no oral options.
  - Fosfomycin 3g packet one-time
- ESBL E. coli where fosfomycin fails.
  - Gentamicin 5mg/kg one-time

Fluoroquinolone-resistant Pseudomonas

- Tobramycin 5mg/kg one-time.

Recurrent male UTI, same organism, appropriate previous treatment

- Consider chronic prostatitis.
  - Fluoroquinolone (4 weeks) or TMP-SMX (6 weeks) or Doxycycline (6 weeks)
  - Fosfomycin, nitrofurantoin, and beta-lactam's poorly penetrate

Source: BJU International 116:509, 2015; New Engl J Med 366:1028, 2012; IDSA DOI: 10.1093/cid/ciad428

HELPFUL TIPS IN UNIQUE SITUATIONS

Candidal UTI (are you sure this is not colonization?)

- Albicans, Dubliniensis, Tropicalis, Parapsilosis
  - Fluconazole, 14 days
- Glabrata
  - Possibly fluconazole, but if so will need to be at a larger dose, 14 days
    - Call an ID provider or pharmacist.
- Auris or Krusei
  - Fluconazole resistant, call ID
- Uncomplicated Gram-Negative Bacteremia
  - 7 days of therapy is non-inferior to 14

Source: Clin Infect Dis 62:409, 2016; Clin Infect Dis . 2019 Sep 13;69(7):1091-1098

HELPFUL TIPS

- Cefazolin = cephalexin (Keflex) and cefadroxil (Duricef)
- Ceftriaxone = cefdinir (Omnicef) and cefpodoxime (Vantin)

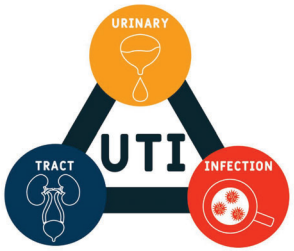
Susceptibility

	Escherichia coli (1) MIC	
Amoxicillin/clavulanate	8 ug/mL	Sensitive
Ampicillin	>=32 ug/mL	Resistant
Cefazolin	<=4 ug/mL	Sensitive
Ceftriaxone	<=1 ug/mL	Sensitive
Ciprofloxacin	>=4 ug/mL	Resistant
Gentamicin	<=1 ug/mL	Sensitive
Levofloxacin	>=8 ug/mL	Resistant
Nitrofurantoin	<=16 ug/mL	Sensitive [1]
Tetracycline	>=16 ug/mL	Resistant (C) [2]
Tobramycin	<=1 ug/mL	Sensitive
Trimethoprim/Sulfamethoxazole	>=320 ug/mL	Resistant

PREVENTION

RECURRENT UTI

- Recurrent UTI: > = 2 infections in six months or >= 3 infections in one year
- Rates increase progressively after menopause



DON'T WASTE YOUR TIME

- Avoid using for prevention of recurrent UTI
  - D-Mannose
    - Despite an encouraging initial small industry-sponsored study, a large multicenter, RCT published last year in JAMA Internal Medicine demonstrated NO BENEFIT for prevention of recurrent UTI (in a mostly post-menopausal population).
  - Vitamin C Monotherapy
    - Evidence very poor/mixed, biologically implausible and there is a risk of nephrolithiasis and GERD
  - Probiotics
    - Encouraging studies for VAGINAL (applied to the vagina) probiotics, but commercial/prescription formulations are not available yet. It is implausible that oral probiotics would be effective, and a Cochrane review concludes that there is no significant benefit compared with placebo or no treatment. Careful of oral supplements that claim to be "vaginal probiotics" or "support vaginal health".
  - "Hygiene measures"
    - Evidence is poor for existence of a correlation with or improvement with alteration of vaginal wiping or voiding after intercourse. Be very careful with this topic as it may suggest to the patient that it is their fault they have UTIs.
    - There are data that urinary incontinence, diarrhea, and constipation are associated with UTI, so these are good to address from a patient-centered perspective, but we lack data that improving these improves UTIs

Hayward et al. JAMA IM, 2024; Beerrepoot and Geerlings. Pathogens. 2016; Schwenger et al. Cochrane 2015

WHAT IS USEFUL? EVIDENCE-BASED, NON-ANTIBIOTIC PREVENTION

- "High dose" water-40-50% reduction dilutes and clears bacteriuria
  - May be limited by incontinence
  - Should start working quickly
- Vaginal estrogen-50% reduction-increases blood flow, restores microbiome
  - Likely needs a few months for efficacy
  - Benefits symptoms of genitourinary syndrome of menopause and (perhaps) overactive bladder in addition to UTI
  - Safe for (almost) all patients
- Methenamine Hippurate-50% reduction-inhibits bacterial growth
  - Should start working quickly
  - Occasional GI side effects
  - Can use down to eGFR of 30. May consider dose reduction below that
- Cranberry (controversial) ~25% reduction-may decrease bacterial binding
  - Efficacy is variable
  - Can be expensive
  - Certainty of benefit is low

Hooton et al. JAMA IM. 2018; Buck et al. Urology 2021; Harding et al. BMJ 2025; William et al. Cochrane 2023

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ALTERNATIVE FORMULATIONS

- Tablet: Vagifem, Yuvafem
  - 10mcg vaginally twice weekly
  - May be more convenient and less messy but can result in higher levels of systemic estrogen
- Ring: Estring
  - 2mg/ring every 3 months releases (7.5mcg/day or ~ 50mcg/week)
  - Great option for elderly with arthritis, neuropathy, dementia
  - Could be inserted by family/caretaker but usually by PCP or gyn

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METHENAMINE HIPPURATE-BACKGROUND

- In use in its current form since at least 1970's.
- With increasing antibiotic resistance, interest in this medication has increased
- MOA: When it reaches the bladder, it slowly converts in a pH-dependent reaction into formaldehyde
  - Older formulations thought to need urinary acidifications but not supported by more modern data, where it appears effective without any purposeful alterations in urine pH.
- GI side effects are common
- Unclear duration of therapy

Morse. J Med Assoc GA 1965; Strom and Jun. Biopharm Drug Dispose 1993; Final Report. Methenamine. J am Coll Toxicol 1992

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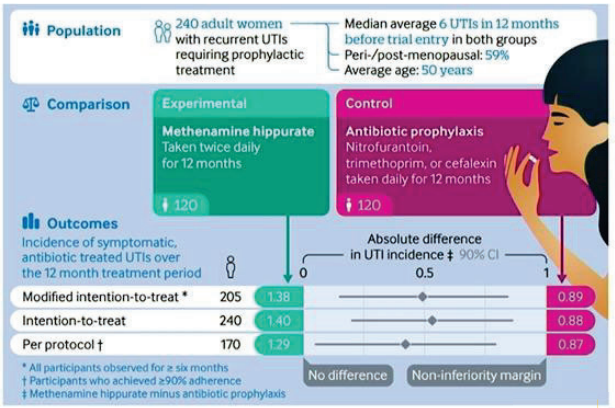

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METHENAMINE HIPPURATE

- Low potential for encouraging antibiotic resistance
- Safe to prescribe-no associations with cancer despite more than 50 years of use but duration of therapy is unknown
- Comparable reduction in UTIs compared to antibiotic prophylaxis
- Dose: 1 gm twice a day down to eGFR of 30, may dose adjust below that and watch for signs of acidemia
- Avoid concomitant use with sulfamethoxazole

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ANTIBIOTIC PROPHYLAXIS

- Patient selection matters!
- Great option for post-coital prophylaxis (especially pre-menopausal women) with clear correlation between intercourse and infection
- **Caution with elderly patients with multiple morbidities**
  - Nonspecific symptoms
  - Incontinence
  - Pre-existing antibiotic resistance
  - Polymicrobial cultures

Albert et al. Cochrane, 2004; Ahmed et al Age Ageing. 2019; Lanford et al. CID 2021

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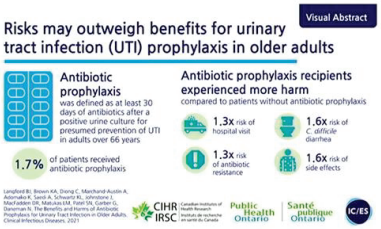
PROPHYLAXIS

Continuous antibiotic prophylaxis: patient selection matters

- 2021 matched cohort study comparing older adults (≥66 y) receiving antibiotic prophylaxis with patients with positive urine cultures who received treatment but not prophylaxis. Each prophylaxis recipient (n = 3190) was matched to 10 non-recipients.



Langford et al. CID 2023

MEDICATION FOR ANTIBIOTIC PROPHYLAXIS

- Nitrofurantoin and TMP/SMX are recommended as first-line agents
- Patients may have more GI side effects with nitrofurantoin
- More resistance development with TMP/SMX
- Cephalexin may be an alternative
- Weekly Fosfomycin an option but lacks good data on efficacy and GI side effects are common

Speirs et al. BJGP Open 2021; Price et al. Am J OG. 2016; Abbott et al. 2018, 2022

SUMMARY

- Prevalence and Impact: UTIs are extremely common, affecting over 10 million people annually in the U.S., with significant healthcare costs exceeding $4.8 billion.
- Diagnosis and Treatment: Challenges include varied clinical presentations and overdiagnosis. Treatment options range from traditional antibiotics to new medications like pivmecillinam, sulopenem, and gepotidacin.
- Prevention: Effective measures include high-dose water intake, vaginal estrogen, and methenamine hippurate, while some popular methods like D-Mannose and Vitamin C monotherapy lack strong evidence.

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