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New Drugs for the Treatment of Uncomplicated Urinary Tract Infections

Kathy Sentena, PharmD, Oregon State University Drug Use Research and Management Group

Urinary tract infections (UTI) are common, with at least one infection per year occurring in 10-20% of women, and less than 1% of men, in the United States (U.S.).[1,2] Increasing rates of resistance to antibiotics used for the treatment of UTI has elevated the need for new therapies to eradicate bacteria associated with these infections. Recently, there have been 3 new Food and Drug Administration (FDA) approvals for antibiotics to treat uncomplicated urinary tract infections (uUTIs): gepotidacin, pivmecillinam and sulopenem/probenecid. This newsletter will focus on the evidence and place in therapy for these new treatment options.

Background

Urinary tract infections are designated as uncomplicated or complicated based on infection location. Per the newly released Infectious Diseases Society of America (IDSA) complicated UTI guidelines, uUTIs are confined to the bladder and occur in afebrile women or men.[3] A complicated UTI is infection extending beyond the bladder, including pyelonephritis, febrile UTI, UTI causing bacteremia, catheter-associated UTI, and prostatitis.[3] The European Association of Urology (EAU) has recommended new nomenclature for the definitions of UTI which are localized (i.e., cystitis without any signs of systemic infection in either sex) and systemic UTI (i.e., an infection with signs and symptoms of systemic infection with or without localized symptoms that may originate from any site in the urinary tract of either sex, including pyelonephritis and prostatitis).[4]

Patients presenting with uUTI are most often treated empirically. The most causative organism for uUTIs is *Escherichia coli (E. coli)*, accounting for approximately 75%-95% of infections.[1] Additional bacteria associated with uUTI are *Proteus mirabilis (P. mirabilis), Klebsiella pneumoniae* (*K. pneumoniae*) and *Staphylococcus saprophyticus (S. saprophyticus)*.[1] Resistant uropathogens are more commonly seen in women 50 years and older, patients with recurrent uUTI, and patients with diabetes.[4] The most recent guidelines from the IDSA on uUTI, published in 2011, recommend treatment options for women based on resistance patterns and likely causative organisms (**Table 1**).[1] Patient allergies and adherence, medication availability and cost should also be considered when selecting an antibiotic.

Table 1. IDSA First-line Empiric Treatments for Uncomplicated UTI[1]

Treatment	Dose	Duration
Nitrofurantoin (slow release)	100 mg twice daily	5 days
Trimethoprim-sulfamethoxazole (TMP/SMX)	160/800 mg twice daily	3 days
Fosfomycin	3 grams	Single dose
Pivmecillinam*	400 mg twice daily*	5 days
* Previously approved in Europe prior to recent U.S. approval		

The 2025 EAU guidelines recommend that TMP/SMX only be used empirically if resistance rates in the area of use are <20% for *E. coli*.[4] The FDA issued a 2016 Safety Announcement advising against the use of fluoroquinolones for uUTIs for those who have other treatment options, due to the serious adverse events such as tendon rupture, tendinitis, and central nervous system side effects, associated with their use.[5] Guidance by the EAU also enacted stringent regulatory actions recommending against the use of fluoroquinolones.[4] They recommend that fluoroquinolones only be used when it is inappropriate to use other antibiotics. Beta-lactam antibiotics (e.g., amoxicillin/clavulanate, cefdinir, cefaclor, and cefpodoxime-proxetil) may also be considered as an alternative for treatment, but *E. coli* resistance rates can be high, especially in recurrent uUTI.

Sulopenem/probenecid (Orlynvah®)

Sulopenem/probenecid is a recently approved combination tablet for uUTI caused by *E. coli, K. pneumoniae* or *P. mirabilis* in adult women who have limited or no alternative oral antibacterial treatment options.[6] Sulopenem is a penem antibacterial, specifically a broad-spectrum thiopenem ß-lactam antibiotic with efficacy against multi-drug resistant bacteria.[6] Probenecid is added to increase sulopenem serum concentrations and extend its half-life. The dose is sulopenem 500 mg/probenecid 500 mg as one tablet twice daily for 5 days, with food if possible to minimize gastrointestinal (GI) upset.[6]

Sulopenem/probenecid is not indicated for treatment of complicated UTIs, for complicated intra-abdominal infections or as step-down treatment after intravenous (IV) antibacterial treatment for these conditions.[6]

One randomized controlled trial (RCT) was used for the approval of sulopenem/probenecid (n=1579).[7] Study participants were randomized to receive sulopenem 500 mg /probenecid 500 mg given orally twice daily for 5 days or ciprofloxacin 250 mg orally twice daily for 3 days. Adult women, 18 years of age or older with a positive urinalysis and 2 or more symptoms of uUTI (e.g., urinary frequency, urgency, dysuria, or suprapubic pain) were included in the study.[7] *E. coli* was the most common causative organism, occurring in approximately 85% of patients.[7]

The primary endpoint was overall response, which combined clinical (resolution of patient reported UTI symptoms and no new UTI symptoms) and microbiological response (reduction of all baseline uropathogens to less than 10^3 CFU/mL in the urine) on day 12.[7] The overall response was compared in 2 subsets by testing ciprofloxacin microbiological susceptible mMITT (mMITT-S) and microbiological non-susceptible MITT (mMITT-R) ciprofloxacin patient urine samples from the modified intent to treat (mITT) population. Superiority of sulopenem/probenecid to ciprofloxacin was based on the mMITT-R population and noninferiority was based on the comparison of sulopenem/probenecid to ciprofloxacin in the mMITT-S population.[7]

Results for the primary endpoint of clinical and microbiologic response demonstrated superiority of sulopenem/probenecid at 12 days compared to ciprofloxacin in the subset of patients in the mMITT-R group with an absolute difference (AR) of 26.6% (95% confidence interval [CI], 15.1 to 37.4; p-value not reported).[7] Sulopenem/probenecid was not noninferior to ciprofloxacin in the mMITT-S subset; however, sulopenem/probenecid was noninferior to ciprofloxacin in the mMITT population overall.[7] Authors attributed this result to a higher proportion of patients with post-treatment asymptomatic bacteriuria (ASB) in the sulopenem/probenecid group, and noted that this group did not have a higher rate of clinical relapse.

A recent double-blind, randomized, noninferiority trial compared sulopenem/probenecid to amoxicillin/clavulanate in adult women (n=2222) with uUTI.[8] The primary end point was overall success, defined as combined clinical cure and microbiological cure at day 12. Sulopenem/probenecid overall success occurred in 60.9% of patients compared to 55.6% of patients treated with amoxicillin/clavulanate (mean difference [MD] 5.4%; 95% CI, -0.8 to 11.5; noninferiority criteria met).[8]

The most common adverse events associated with sulopenem/probenecid were diarrhea, nausea, vulvovaginal mycotic infections, headache and vomiting.[6] Sulopenem/probenecid compared to amoxicillin/clavulanate was found to have more frequent, treatment-emergent, mild adverse events.[8] Individuals with hypersensitivity, blood dyscrasias, or uric acid kidney stones, should not take sulopenem/probenecid. Serious adverse reactions associated with sulopenem/probenecid are hypersensitivity reactions, which are associated with all ß-lactam antibiotics.

Sulopenem/probenecid inhibits ornithine aminotransferase (OAT) 1/3 which can increase drug concentrations of medications that use this enzyme system for elimination.[6] Use with ketorolac is contraindicated and use with ketoprofen is not recommended.[6]

Gepotidacin (Blujepa®)

Gepotidacin is a new antibiotic approved in March of 2025 for the treatment of uUTI infections in female adult patients and pediatric patients 12 years of age and older who weigh at least 40 kg with the following susceptible organisms: *E. coli, K. pneumoniae, C. freundii* complex, *S. saphrophyticus*, and *E. faecalis*.[9] Gepotidacin works by a different mechanism of action than other antibiotics. It is a triazaacenaphtheylene bacterial type II topoisomerase inhibitor, which blocks deoxyribonucleic acid (DNA) replication by the inhibition of DNA gyrase and topoisomerase IV.[9] The dose of gepotidacin is two 750 mg (1500 mg) tablets twice daily for 5 days, taken after a meal.[9] Gepotidacin should not be used in patients with complicated UTI.

The approval of gepotidacin was based on 2 similar methodologically designed studies to determine efficacy.[10] Both studies were randomized, double-blind, double-dummy, phase 3, non-inferiority studies comparing gepotidacin 1500 mg twice daily for 5 days to nitrofurantoin 100 mg (slow release formulation) twice daily for 5 days (EAGLE-2 and EAGLE-3).[10] Qualifying uropathogens were: gram-negative bacilli, (*S. saprophyticus* or *Enterococcus* species) at concentrations of $\geq 10^5$ CFU/mL.[10] The average of age of participant was 52 years and 50 years in EAGLE-2 and EAGLE-3, respectively. The majority of patients in both studies had urine cultures positive for *E.coli*.[10]

The primary endpoint was therapeutic response, which combined clinical (e.g., symptom score of 0) and microbiological response (e.g., reduction of qualifying uropathogens to less than 10^3 CFU/mL in the urine). Uropathogens had to be susceptible to nitrofurantoin to be included in the microbiological intention to treat (ITT) nitrofurantoin (NTF-S) population.[10] Both studies were stopped early due to gepotidacin efficacy after interim analysis.

Gepotidacin was non-inferior to nitrofurantoin in both studies for those isolates that did not have resistance to nitrofurantoin. Gepotidacin achieved therapeutic success in 50.6% of gepotidacin patients compared to 47.0% of patients taking nitrofurantoin (treatment difference [TD] 4.3%; 95% CI, -3.6 to 12.1) in EAGLE-2.[10] In EAGLE-3, gepotidacin was noninferior and superior to nitrofurantoin (TD 14.6%; 95% CI, 6.4 to 22.8;

p=0.003/ absolute risk reduction [ARR] 14.6/number needed to treat [NNT] 7) for the combined primary endpoint.[10] In EAGLE-2 clinical success was the same between groups (65%) and microbiological success was greater in the gepotidacin group (67.9%) compared to nitrofurantoin (63.3%) in EAGLE-3.[10]

The most common adverse events associated with the use of gepotidacin are diarrhea, nausea, abdominal pain, flatulence, headache, soft feces, dizziness, vomiting and vulvovaginal candidiasis.[9] Gepotidacin should not be taken with drugs that inhibit CYP3A4 enzymes and in those with severe hepatic (Child-Pugh Class C) or renal (estimated glomerular filtration rate [eGFR] <30 ml/min) impairment due to the risk of increased concentrations of gepotidacin.[9]

Pivmecillinam (Pivya®)

Pivmecillinam was approved in April of 2024 by the FDA for uUTI.[11] Pivmecillinam is a penicillin antibacterial used for the treatment of uUTI in female patients 18 years old and older caused by susceptible isolates of *E. coli, P. mirabilis and S. saprophyticus.*[11] Pivmecillinam is given as one 185 mg tablet by mouth 3 times a day for 3-7 days as clinically indicated. Pivmecillinam is not approved for complicated UTI. Pivmecillinam has been approved in Europe for over 40 years.

Pivmecillinam is a pro-drug of mecillinam that targets penicillin-binding protein 2 (PBP2).[11] This bacterial enzyme is not routinely targeted by other ß-lactam antibiotics and makes it effective against pathogens like *E. coli.*

Pivmecillinam was studied in 3 clinical trials for FDA approval. Only one of these trials was a comparative efficacy trial to an antibiotic, cephalexin, used for uUTI.[12] The other trials were a placebo-controlled trial and a trial comparing pivmecillinam to ibuprofen.[12,13]

Pivmecillinam 185 mg three times daily for 3 days was compared to cephalexin 250 mg four times daily for 7 days in a multi-center, double-blind RCT (n=440) in the U.S.[12] Women 18 years and with uUTI were included. The composite endpoint was clinical (i.e., no symptoms that persisted during treatment or post treatment) and microbiological cure. Microbiological cure was a negative urine culture on day 10 for presenting pathogen.[12] Microbiological cure and clinical cure was not statistically significantly different between pivmecillinam and cephalexin (**Table 2**).[12] For the combined endpoint of clinical and microbiological cure, 72% of those treated with pivmecillinam compared to 76% of patients treated with cephalexin achieved that outcome (TD -4%; 95% CI, -16 to 7; p>0.05).[12]

In a phase 3 study, pivmecillinam 185 mg three times daily was compared to ibuprofen 600 mg daily three times daily.[13] Both regimens were given for 3 days. The trial was a double-blind, double dummy, noninferiority trial. Patients were asked to record symptoms daily, including if they felt cured, in a diary. The main outcome was proportion of patients who felt cured by day 4, as recorded in their diary.[13] A key secondary outcome was the proportion of patients with a positive second urine culture at 14 days for primary pathogen.

Pivmecillinam was found to be associated with a higher number of patients who felt cured by day 4 of treatment compared to those randomized to ibuprofen. Ibuprofen was chosen as a comparator to see if symptomatic uUTI treatment could reduce antibiotic use since uUTIs are often self-limiting. The difference was not large enough to consider pivmecillinam to be more effective compared to ibuprofen (risk difference [RD] 35%; 95% CI, 27% to 43%; noninferiority not met) (**Table 2**).[13] There were fewer patients in the pivmecillinam group with a positive bacterial culture at 14 days compared to the ibuprofen group (RD -16%; 95% CI, -26% to -7%; p<0.001; ARR] 18%/NNT 6).[13]

In a double-blind, phase 3 RCT comparing 3 different doses of pivmecillinam to placebo, pivmecillinam was more effective for all doses. Pivmecillinam was given as 200 mg three times daily for 7 days, 200 mg twice daily for 7 days or 400 mg twice a day for 3 days. The trial was a double dummy design, so all patients received identical-appearing tablets. For the composite response rate of clinical and microbiological cure, the combined doses of pivmecillinam were more effective than placebo (ARR 52%/NNT 2) (**Table 2**)[11].

Table 2. Pivmecillinam for the Treatment of uUTI

Study	Outcome	Result
Pivmecillinam vs. Placebo[11]	Composite Response Rate (clinical and microbiological cure)	Combined pivmecillinam groups: 85 (62%) Placebo: 14 (10%) TD 52% (95% CI, 41 to 62)
Pivmecillinam vs. Cephalexin[12]	Clinical cure	Pivmecillinam: 102 (95.3%) Cephalexin: 102 (93.6%) P=0.58
	Microbiological cure	Pivmecillinam: 96 (89.7) % Cephalexin: 89 (81.7%) P=0.09
Pivmecillinam vs. Ibuprofen[13]	Patient reported symptoms of being cured	Pivmecillinam: 131 (73.6%) Ibuprofen: 70 (38.7%) Noninferiority criteria not met

Abbreviations: CI = confidence interval, TD = treatment difference

Oregon Health Plan Fee-for-service Policy

Prior authorizations are required for all 3 new antibiotics indicated for uncomplicated urinary tract infections:

- Gepotidacin (Blujepa®)
- Pivmecillinam (Pivya®)
- Sulopenem/probenecid (Orlymvah®)

Conclusions

Appropriate antibiotic use for the treatment of uUTI is important for symptom resolution and to minimize development of resistant organisms. New medications indicated for uUTI may be considered for women who require second line treatment options due to intolerance to first line therapies or antibiotic resistance. Evidence for all 3 new drugs is limited by small trials of short duration that show little or small magnitude of benefit over existing therapies, and they will likely be more expensive than generic first-line treatment options which cost approximately $10 per treatment course.

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