University of Nebraska Medical Center
Nebraska Medicine

Novel therapies for multidrug-resistant urinary tract infections (UTIs)

Goal: With the introduction of several new antimicrobial agents for UTI treatment targeting MDROs, we gathered susceptibility data for these new agents, especially given that MIC breakpoint information has not been well established for many of these drugs and in-house susceptibility testing is not routinely available.

Key Question: How confident can we be prescribing these medications without case specific susceptibility testing?

Summary of Data on Activity in Urinary Pathogens:

- Pivmecillinam – Excellent activity against E. coli including ESBL producers (>98%). Good against *K. pneumoniae* (~90%) but lower for ESBL (80%). Good but variable other GNR (87-95%). Poor *Morganella, Serratia, Staph saprophyticus*.
- Gepotidacin – Excellent activity against all typical urinary pathogens including ESBL, FQ-resistant (>95%), and MDR pathogens.
- Sulopenem etzadroxil/probenecid – Excellent activity E. coli, ESBL *E. coli, K. pneumoniae, Proteus mirabilis* (>96%). Decreased activity ESBL *K. pneumoniae* and *Enterobacter cloacae* (80-85%).
- Tebipenem – not available yet but susceptibility rates may mirror ertapenem.
- Fosfomycin – excellent activity *E. coli* including ESBL phenotype. Poor against *K. pneumonia, Pseudomonas*. Susceptibility testing challenging in non-*E. coli*.

Pivmecillinam (Pivya):

Mechanism of Action (MOA): prodrug of amidinopenicillanic acid that is metabolized to mecillinam (beta-lactam that interferes w/ bacterial cell wall w/ high specificity against PBP-2 in the gram-negative cell wall)

Mechanism of Resistance: Cysteine biosynthesis modulation: inactivation/modification of cysB gene (which regulates cysteine biosynthesis), upregulating genes encoding proteins involved in peptidoglycan synthesis (including PBP1B, LpoB, and FtsZ)

Dose: 185 mg PO TID for 3-7 days

Cost: $830 (for a 3-day supply)

FDA Approved for: uUTI caused by susceptible isolates of *E. coli*, *Proteus mirabilis*, and *Staphylococcus saprophyticus* in women aged ≥18 years

Susceptibility Information:

U.S. data:

- Vast majority of the data is from Europe; other countries include Canada, Sri Lanka, Mauritius. Review of the literature is here.
- US study 216 uUTI compared 7 days cephalexin to pivmecillinam showing comparable high rates of clinical efficacy and improved microbiologic eradication.
- US susceptibility study of mecillinam with 3303 urinary isolates 2017-2020:
    - All Enterobacterales: 94.9%
        - *E. coli* (n = 1,869): 97.5% overall and 98.2% for ESBL+ (n = 224)
    - *Klebsiella pneumoniae* (n = 348): 87.1% overall and 80.0% for ESBL+ (n = 155)
    - *Proteus mirabilis* (n = 307): 87.3%
    - *Enterobacter cloacae* (n = 301): 97.4%
    - *Citrobacter freundii* (n = 154): 98.1%
    - *Klebsiella aerogenes* (n = 154): 93.5%
    - *Klebsiella oxytoca* (n = 170): 90.0%

Large European meta-analysis in vitro activity against:

- ***E. coli***
    - Non-ESBL, non-AmpC, non-CRE: most report susceptibility rates >95% (n = 1,886,945)
        - Few <90% but none <80%
    - ESBL or AMP-C isolates (n = 4,679): most >90%, no studies report rates <82.5%
    - Carbapenemase-producers (n = 3,909) varied by enzyme:
        - OXA-48-like carbapenemase-producers (n=1198): 92.6%
        - NDM-producers (n=391): 76.2%
        - VIM-producers (n=34): 17.6%
        - KPC-producers (n=17): 0%
- **Non-E coli**:
    - Non-multidrug-resistant ***C. freundii* and *E. cloacae*** - susceptibility rates:
        - >95% when using agar dilution and CLSI *E. coli* breakpoints
        - ~88% when using disk diffusion and EUCAST breakpoints
    - **Klebsiella** varies among species, with rates ranging from 81.8% to 93.5%, lower for ESBL-producers
    - ***Proteus mirabilis*** exhibits variable susceptibility, possibly due to discrepancies in testing methodologies, with rates ranging between 73.2% and 95.8%
    - Limited effectiveness against ***Morganella morganii, Proteus vulgaris*, and *Serratia marcescens*** (30-60% suscepitbility)
    - Active against ***Salmonella spp***. and carries an indication for treatment in Europe
    - ***Staph saprophyticus*** - demonstrates *in vitro* resistance to mecillinam, though some reports indicate it is clinically effective in treating UTI due to this organism. Expert opinion is it can be considered, though lower rates of clinical cure and higher rates of bacterial persistence should be expected

MIC Breakpoint Information:

- Tested as mecillinam, can currently be tested using disk diffusion (10 µg mecillinam disk)
- CLSI breakpoints only for *E. coli* causing uUTIs (disk and MIC); no CLSI QC ranges or automated AST options are available – see table below
- EUCAST offers broader guidance (*E. coli, Citrobacter* spp., *Klebsiella* spp., *Raoultella* spp., *Enterobacter* spp., *P. mirabilis*, for uUTI only) with defined QC and higher-dose assumptions, but these breakpoints are not harmonized with CLSI/FDA dosing in the US – see table below
- NM Micro lab has not validated testing; if requested would be sent to a reference lab

Mecillinam *in vitro* antimicrobial susceptibility testing breakpoints[b]

Standards	Breakpoints						Approved organisms	Specimen type
	MIC (µg/mL or mg/L)[a]			Zone diameter (mm) (10 µg disk)				
	S	I	R	S	I	R		
CLSI M100-Ed35 (2025)	≤8	16	≥32	≥15	12–14	≤11	*E. coli*	Urine
EUCAST 2025 v15.0	≤8	-	>8	≥15	-	<15	*Citrobacter* spp. *E. coli* *Enterobacter* spp. *Klebsiella* spp. *P. mirabilis* *Raoultella* spp.	Urine (uncomplicated UTI only)
FDA	CLSI M100 standard recognized							

MIC50/90 for *E. coli* with agar dilution testing (4)

	MIC50 range (µg/mL or mg/L)[a]	MIC90 range (µg/mL or mg/L)[a]	Overall MIC range (µg/mL or mg/L)[a]
E. coli (excluding ESBL, AmpC, CRE)	0.25–0.5	2–4	0.06 to >128
ESBL *E. coli*	1–2	4–8	0.06 to >128

Gepotidacin (Blujepa):

MOA: Triazaacenaphthylene inhibitng type II topoisomerases, including bacterial topoisomerase II (DNA gyrase) and topoisomerase IV, preventing DNA replication

Mechanism of Resistance:

- Mutations in the genes encoding DNA gyrase subunits (gyrA and gyrB) and topoisomerase IV (parC and parE)
- Unlike fluoroquinolones, which rely on a water-metal ion bridge easily disrupted by single-point mutations, gepotidacin's structural orientation enables it to retain potency even in the presence of common quinolone-resistance mutations

Dose: 1500mg (2 tabs) PO q12 hours for 5 days

Cost: $1700 (for a 5-day supply)

FDA Approved for: uUTI caused by the following susceptible microorganisms: *E. coli*, *K. pneumoniae*, *Citrobacter freundii* complex, *S. saprophyticus*, and *Enterococcus faecalis* (higher doses for cUTI reportedly led to excessive QTc prolongation)

Susceptibility Information:

Large Systematic Review primarily including data from US and North America although some isolates from Europe, Asia, and Latin America

- Enterobacterales resistance (total n = 23,711):
  - *E. coli*: 0-0.1%, intermediate: 0-0.2% of cases
  - *K. pneumoniae*: 0-3.4%, intermediate: 3.5-8%
  - *Proteus mirabilis*: 0%, intermediate: 5.2-11.1%
  - *Enterobacter cloacae*: 0-6.8%, intermediate: 0- 6.6%
  - ESBL Enterobacterales: 0-0.6%, intermediate: 0-1.1%
  - MDRO Enterobacterales (n=323; resistant to ≥3 antibacterial other classes): 0%, intermediate: 0-7.4% with MDR E. coli resistant 0%, intermediate 0.8-1%
- Non- Enterobacterales resistance:
  - *E. faecalis*: 0-0.8%
  - *S. saprophyticus*: 0-34.3% (1 study 34.3%; 3 studies 0-6.9%)
- Resistance in isolates resistant to other urinary agents:
  - FQ-R Enterobacterales: 0%, 0-11.1% intermediate
  - ESBL FQ-R Enterobacterales: 0%, 0-14.3% intermediate
  - Augmentin-R Enterobacterales: 0%, 0-10% intermediate
  - Similar results for resistance to Ampicillin, Mecillinam, Fosfomycin, Nitrofurantoin, & TMP-SMX

EAGLE-2 & EAGLE-3 trials:

- Phase 3 trial demonstrating noninferiority of Gepotidacin compared w/ Nitrofurantoin revaluated susceptibility in all trial isolates:
  - *E. coli* (n = 1159): 99.9% susceptible
    - CTX-M positive isolates (n=155) 98.9% susceptible
    - QRDR mutations (FQ resistance assoc.) isolates (n=342) 94.4% susceptible
  - *Klebsiella pneumoniae* (n = 114): 96.5%
  - *Proteus mirabilis* (n = 67): 95.5%

MIC Breakpoint Information:

	Minimum Inhibitory Concentrations (mcg/mL)			Disk Diffusion (zone diameter in mm)		
Pathogen	S	I	R	S	I	R
Enterobacterales[a, b]	≤ 16	32	≥ 64	≥ 12	8-11	≤ 7
Staphylococcus saprophyticus[b]	≤0.25	-	-	≥ 23	-	-
Enterococcus faecalis[b]	≤4	-	-	≥ 14	-	-
Neisseria gonorrhoeae[c]	≤ 1	2	≥ 4	≥ 28	23-27	≤ 22

- FDA-recognized STIC (susceptibility testing interpretive criteria) for organisms associated with its approved indications, including Enterobacterales (uUTI pathogens), *Staph saprophyticus, E faecalis*, and *Neisseria gonorrhoeae* (with organism- & indication-specific MIC and disk criteria)
- A 10-µg disk diffusion test is FDA-cleared for clinical use
- Our Micro lab had not validated this drug in-house, and if this is requested, it would be sent to a reference lab

Sulopenem etzadroxil/probenecid (Orlynvah):

MOA:

- Sulopenem etzadroxil is a penem prodrug that is hydrolyzed to active sulopenem (which inhibits cell wall synthesis through binding to PBPs)
- Probenecid inhibits OAT3-mediated renal clearance of sulopenem, resulting in prolonged serum levels

Mechanism of Resistance:

- Altered PBPs, carbapenemase production, porin changes (reduced expression of outer membrane proteins), efflux pumps
- Of note, similar to other carbapenems it is unaffected by many beta lactamases

Dose: 500 mg PO BID for 5 days

Cost: ~$3,000 (for a 5-day supply)

FDA Approved for:

- uUTI caused by *E coli, Klebsiella pneumoniae*, or *Proteus mirabilis* in adult females who have limited or no alternative oral antibacterial treatment options
- In cUTI study, failed to be statistically non-inferior at microbiological test of cure with IV→PO switch vs ertapenem→PO cipro

Susceptibility Information:

SENTRY Database study including 1647 Enterobacterales and 559 anaerobic isolates collected in Europe & USA between 2018 and 2020. Primarily UTI (61%), BSI (23%), IAI (16%).

- Enterobacterales using MIC ≤1 which is the MIC breakpoint for other carbapenems (n=1647) 99.2% susceptible
    - *E. coli* (n=983) 100% susceptible
    - *Klebsiella* spp. (n=347) 98.8%
    - *Enterobacter cloacae* (n=110) 97.3%
    - *Klebsiella oxytoca, Morganella morganii, Proteus mirabilis, Klebsiella aerogenes* all 100% active but fewer isolates (all <100)
- Using the lower CLSI MIC breakpoint of ≤0.25 (n=1647) 95% susceptible
    - *E. coli* (n=983) 99.7% susceptible
        - ESBL-phenotype (n=170) 98.3 %
    - *Klebsiella* spp. (n=347) 96.8%
        - ESBL-phenotype (n=49) 83.7%
    - *Enterobacter cloacae* (n=110) 82.7% susceptible
    - *Proteus mirabilis* (n=91) 95.6% susceptible
- Activity in Serratia, Morganella, Providencia is generally decreased

Large Canadian study of E. coli urinary isolates (n=539) from 2014-16 found no isolates with MIC values in the intermediate or resistant range (100% susceptible)

MIC Breakpoint Information:

	Minimum Inhibitory Concentrations (mcg/mL)			Disk Diffusion (zone diameter in mm)		
Pathogen	S	I	R	S	I	R
Enterobacterales[a]	≤ 0.25	0.5	≥ 1.0	≥ 19	16-18	≤ 15

- Susceptibility testing is based on testing sulopenem alone, as probenecid has no antibacterial activity and only serves to increase sulopenem exposure
- FDA-recognized breakpoints are available for sulopenem against Enterobacterales (including *E. coli, Klebsiella pneumoniae*, and *Proteus mirabilis*); testing is approved only for select Enterobacterales and not for Pseudomonas, Enterococcus, or carbapenemase-producing organisms
- Our Micro lab has not validated this drug in-house, and testing would be via send out. A 2-µg sulopenem disk is commercially available

Tebipenem (Orapenem):

MOA: binds to and inhibits PBPs, thereby inhibiting bacterial cell wall synthesis

Mechanism of Resistance:

- Carbapenemase production and efflux pumps

Dose: 600 mg IV/PO q6 hrs for 7-10 days

Cost: ?

FDA Approved for: nothing yet, coming soon for cUTI/pyelonephritis (re-submitted to FDA with better outcome data than when it was not approved in 2022; similar to sulopenem, it failed to have non-inferior results compared to imipenem at the microbiological test of cure). Large trial shows clinical equivalence to IV ertapenem in the treatment of complicated UTI.

Susceptibility Information:

Large US survey of Enterobacterales urinary isolates (n=3576) form 2019-2020:

- No interpretive criteria. See MIC distribution below.
- MIC values similar to ertapenem for *E. coli* and *Klebsiella pneumoniae* but higher for *Proteus mirabilis*.
- MIC values for tebipenem did not differ between ESBL and non-ESBL isolates

In vitro activity of tebipenem against Enterobacterales clinical isolates causing UTI in US hospitals

Organism/group (no. of isolates)	No. and cumulative % of isolates inhibited at an MIC (µg/mL)													MIC_{50}	MIC_{90}
	≤0.004	0.008	0.015	0.03	0.06	0.12	0.25	0.5	1	2	4	8	>8		
All[a] (3,576)	4 (0.1)	606 (17.1)	2,060 (74.7)	429 (86.7)	207 (92.4)	193 (97.8)	50 (99.2)	9 (99.5)	0 (99.5)	3 (99.6)	2 (99.6)	5 (99.8)	8 (100)	0.015	0.06
E. coli (2,339)	4 (0.2)	578 (24.9)	1,578 (92.3)	134 (98.1)	29 (99.3)	10 (99.7)	4 (99.9)	1 (>99.9)	0 (>99.9)	0 (>99.9)	1 (100.0)			0.015	0.015
K. pneumoniae (511)		3 (0.6)	296 (58.5)	176 (93.0)	18 (96.5)	3 (97.1)	2 (97.5)	1 (97.7)	0 (97.7)	1 (97.8)	1 (98.0)	4 (98.8)	6 (100)	0.015	0.03
P. mirabilis (235)		1 (0.4)	6 (3.0)	23 (12.8)	63 (39.6)	120 (90.6)	22 (100.0)							0.12	0.12
Non-ESBL (2,643)[b]	4 (0.2)	560 (21.3)	1,611 (82.3)	238 (91.3)	88 (94.6)	120 (99.2)	22 (100)							0.015	0.03
ESBL (442)[c]		22 (5.0)	269 (65.8)	95 (87.3)	22 (92.3)	13 (95.2)	6 (96.6)	2 (97.1)	0 (97.1)	1 (97.3)	2 (97.7)	4 (98.6)	6 (100)	0.015	0.06
MDR (222)[d]		14 (6.3)	134 (66.7)	45 (86.9)	8 (90.5)	10 (95.0)	4 (96.8)	0 (96.8)	0 (96.8)	1 (97.3)	0 (97.3)	1 (97.7)	5 (100)	0.015	0.06

Antimicrobial agent	MIC (µg/mL)			CLSI[b]		
	50%	90%	Range	%S	%I	%R
All (3,576)						
Tebipenem	0.015	0.06	≤0.004 to >8	-	-	-
Non-ESBL (2,643)						
Tebipenem	0.015	0.03	≤0.004 to 0.25	-	-	-
MDR (222)						
Tebipenem	0.015	0.06	0.008 to >8	-	-	-

MIC Breakpoint Information:

- Because tebipenem is still investigational and has not yet received FDA approval, no FDA or CLSI breakpoints exist. No disks or automated AST products are available commercially.

Fosfomycin (Monurol = PO, Contepo = IV):

MOA: phosphonic acid derivative inhibiting bacterial cell wall synthesis by inactivating the MurA enzyme (aka UDP-N-acetylglucosamine enolpyruvyl transferase) which is critical in cell wall creation

Mechanisms of Resistance:

- Mutations in the transport system that fosfomycin uses to enter bacterial cells (ex: glycerophosphate transport in GN bacteria, G6P transporter in GP bacteria)
- Bacterial production of enzymes that modify/inactivate the drug (fosA, fosB, fosX)

Dose:

- PO: 3g single dose
- IV: 12-24 g/day in 2-3 divided doses, 5-14 days

Cost: $2200 (for a 4-day IV course)

FDA Approved for:

- uUTI (PO formulation)
- cUTI (IV formulation)

Susceptibility Information:

2025 study from Walter Reed hospital of 1353 urine isolates 2016-17 (E. coli MIC breakpoints (≤64) were used for isolates without breakpoints). Used agar dilution method:

- *E. coli* (n=903) 95.9% susceptible (no difference between ESBL, non-ESBL)
- *E. faecalis* (n=95) 97.9% susceptible
- *K. pneumoniae* (n=139) 36.7% susceptible (no difference between ESBL, non-ESBL)
- *P. aeruginosa* (n=47) 55.3% susceptible
- *Citrobacter* (n=26) 96.2% susceptible
- *E. faecium* (n=24) 100% susceptible
- *P. mirabilis* (n=26) 92.3% susceptible
- What about ESBLs?
    - Spanish study, looked just at *E coli*:

	2017	2018	2019	2020	2021	2022
ESBL-S total isolates; n (%S)	131 (79.39)	155 (89.03)	197 (76.14)	120 (78.33)	119 (83.19)	127 (80.31)
Non-ESBL producers total isolates; n (%S)	2,019 (98.46)	2,057 (97.72)	2,120 (97.17)	1,535 (97.39)	1,764 (97.56)	1,825 (97.26)

	2017	2018	2019	2020	2021	2022
Total isolates (N) Fos-S; n (%S)	2,150 2,092 (97.30)	2,212 2,148 (97.11)	2,317 2,210 (95.38)	1,655 1,589 (96.01)	1,883 1,820 (96.65)	1,952 1,877 (96.16)

MIC Breakpoint Information:

- CLSI breakpoints apply to E. coli and Enterococcus faecalis urine isolates for uUTI only
- Use of disc diffusion and E-test in non-*E. coli* Enterobacterales and *Pseudomonas* species frequently results in inner colonies making interpretation challenging.
- Our Micro lab currently has E-tests available in-house and use beyond *E. coli* & *E. faecalis* is strongly discouraged because there are no breakpoints & in vitro results do not reliably predict clinical activity. For example, *P. aeruginosa* has intrinsic resistance mechanisms, rapid inducible resistance, and poor PK/PD correlation, making susceptibility results misleading rather than useful

TABLE 1 CLSI and EUCAST breakpoints for oral and intravenous fosfomycin

	MIC (µg/mL) by category			Zone diam (mm) by category		
Parameter	**Susceptible**	**Intermediate**	**Resistant**	**Susceptible**	**Intermediate**	**Resistant**
$EUCAST_{oral}$[a]	≤8	NA[b]	>8	≥24	NA	<24
$EUCAST_{IV}$	≤32	NA	>32	≥21[c]	NA	<21[c]
CLSI[a]	≤64	128	≥256	≥16	13–15	≤12

a | All breakpoints apply only to *E. coli*.

b | NA, not available.

c | Zone diameter breakpoints apply only to *E. coli*.