New Antibiotics for UTI and uUGC: Gepotidacin

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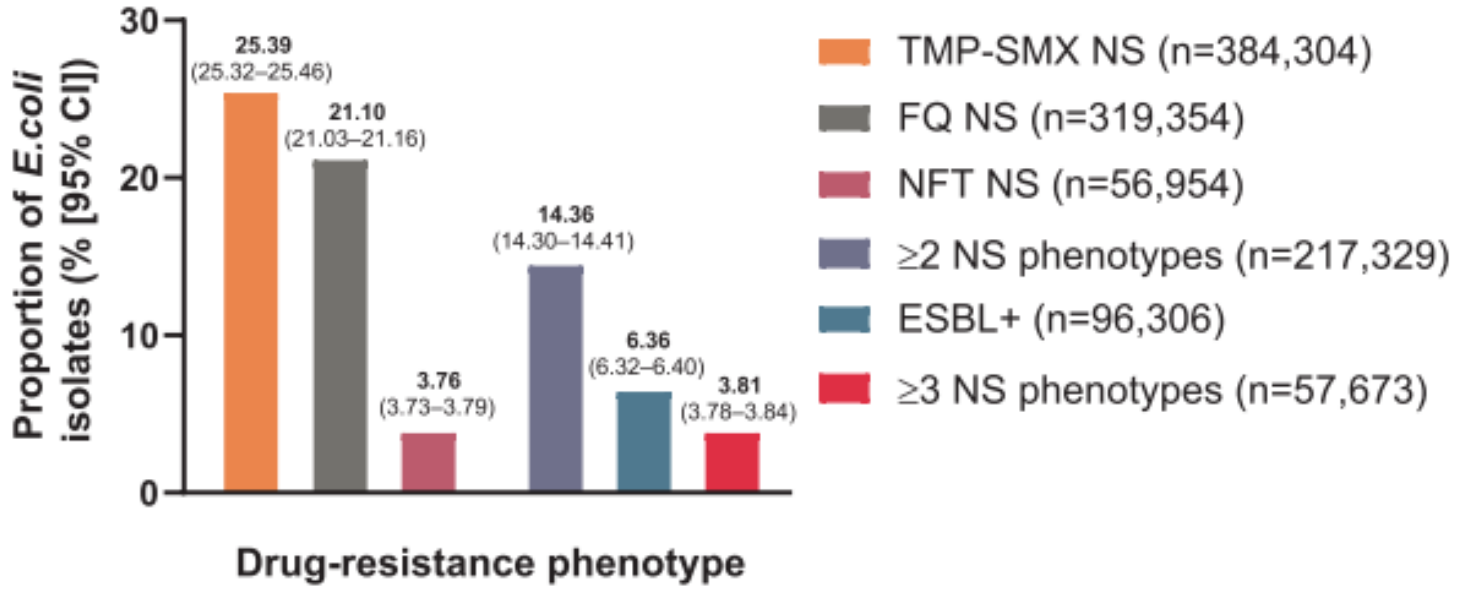
Resistance is Common and Rising

- Urine cultures from women in US outpatient facilities
- 1.5 million *E.coli* isolates



Kaye, et al. CID 2021. DOI: 10.1093/cid/ciab560

New Drug Check-List

- Spectrum
- Indications & Evidence
- Resistance
- Safety, side-effects
- Practical aspects
- Role

New Antibiotic: Gepotidacin

- First in class: triazaacenaphthylene antibiotic
  - Inhibits bacterial DNA replication – inhibition of DNA gyrase and topoisomerase (via distinct binding sites)
- Developed for uUTI and uncomplicated urogenital gonorrhea
- Available PO only

Gepotidacin - Spectrum

- *E.coli*
- *Klebsiella pneumoniae*
- *Citrobacter freundii*
- *Staph saprophyticus*
- *Enterococcus faecalis*
- *Neisseria gonorrhoeae*

Gepotidacin – Indications & Evidence

- FDA approval March 2025
  - uUTI in female adult and pediatric patients > 12 yo & >40 kg
  - 1500 mg PO BID x 5 days
- Evidence: EAGLE-2 & EAGLE-3, phase 3 randomized, multicenter, double-blind, non-inferiority trials (gepo vs. nitro)
  - Female, non-pregnant, ≥12yo, ≥40kg
  - 2+: dysuria, frequency, urgency, lower abdm pain; & positive UA
  - Primary end-point: therapeutic response at test-of-cure (day 10-13)
  - Both stopped early for efficacy

Wagenlehner, et al. Lancet. 2024. https://doi.org/10.1016/S0140-6736(23)02196-7

	EAGLE-2		EAGLE-3	
	Gepotidacin (n=320)	Nitrofurantoin (n=287)	Gepotidacin (n=277)	Nitrofurantoin (n=264)
Primary outcome				
Therapeutic success	162 (50·6%)	135 (47·0%)	162 (58·5%)	115 (43·6%)
Treatment difference (95% CI)*	4·3% (–3·6 to 12·1)	..	14·6% (6·4 to 22·8)	..
Z statistic for non-inferiority (boundary)†	3·5554 (2·065)	..	5·8838 (2·098)	..
One-sided p value for superiority (boundary)‡	0·1445 (0·019)	..	0·0003 (0·018)	..
Therapeutic failure	158 (49·4%)	152 (53·0%)	115 (41·5%)	149 (56·4%)
Clinical success, microbiological failure	48 (15·0%)	52 (18·1%)	26 (9·4%)	52 (19·7%)
Clinical failure, microbiological success	70 (21·9%)	59 (20·6%)	38 (13·7%)	36 (13·6%)
Clinical failure, microbiological failure	40 (12·5%)	41 (14·3%)	51 (18·4%)	61 (23·1%)
Use of another antibiotic for uncomplicated UTI§	5 (1·6%)	12 (4·2%)	18 (6·5%)	14 (5·3%)
Secondary outcomes				
Clinical success	210 (65·6%)	187 (65·2%)	188 (67·9%)	167 (63·3%)
Treatment difference (95% CI)*	1·2% (–6·3 to 8·7)	..	4·4% (–3·5 to 12·3)	..
Clinical failure	110 (34·4%)	100 (34·8%)	89 (32·1%)	97 (36·7%)
Clinical improvement (without resolution)	81 (25·3%)	74 (25·8%)	49 (17·7%)	67 (25·4%)
Clinical worsening (or no change from baseline)	9 (2·8%)	15 (5·2%)	19 (6·9%)	16 (6·1%)
Unable to determine¶	20 (6·3%)	11 (3·8%)	21 (7·6%)	14 (5·3%)

Wagenlehner, et al. Lancet. 2024. https://doi.org/10.1016/S0140-6736(23)02196-7

Gepotidacin - Resistance

- Enterobacterales and *N. gonorrhoeae* with elevated MIC have rarely emerged in clinical trials
- Cross-resistance, not identified
- Barrier to resistance should be high…

Keam. Drugs 2025. https://doi.org/10.1007/s40265-025-02214-9

Gepotidacin – Safety & Side-effects

- Most frequent side-effects
  - diarrhea (16%)
  - nausea (9%)
- Serious AE: acetylcholinesterase inhibition (rare)
- QTc prolongation observed with IV
- Avoid CrCl < 30 & severe liver impairment
- Substrate of CYP3A4

Keam. Drugs 2025. https://doi.org/10.1007/s40265-025-02214-9

Gepotidacin – Practical aspects

- Still quite new
  - don’t know which pharmacies stock it or cost but $$$$
- Susceptibility testing info is unknown but feasible
- Potential for significant drug-drug interactions

Gepotidacin – Role

- Cystitis due to uropathogens with resistance to other oral drugs

	Spectrum	Indications & Evidence	Resistance	Safety, side-effects	Practical aspects	Role
Gepotidacin	Common UTI pathogens	uUTI	Rare, no cross	Well tolerated QTc prolong	Unknowns	Cystitis if other PO not possible, yes ESBL

Gepotidacin – Indications & Evidence

- FDA approval December 2025
  - Uncomplicated urogenital gonorrhea (uUGC) in patients ≥ 12 yo
  - 3000 mg PO q12 x 2 doses
- Evidence: EAGLE-1, phase 3 randomized, multicenter, double-blind, non-inferiority trials (gepo vs. CTX + azithro)
  - ≥12yo, ≥45kg
  - Uncomplicated urogenital infection (discharge or positive test)
  - Primary end-point: micro success (Cx eradication at TOC day 4-8)

Wagenlehner, et al. Lancet. 2024. https://doi.org/10.1016/S0140-6736(23)02196-7

	Micro-ITT population		Microbiologically evaluable population	
	2 × 3000 mg gepotidacin (N=202)	500 mg ceftriaxone plus 1 g azithromycin (N=204)	2 × 3000 mg gepotidacin (N=187)	500 mg ceftriaxone plus 1 g azithromycin (N=186)
Microbiological success, n (% [95% CI])	187 (92·6% [88·0 to 95·8])	186 (91·2% [86·4 to 94·7])	187 (100% [98·0 to 100])	186 (100% [98·0 to 100])
Treatment difference, % (95% CI)*	−0·1% (−5·6 to 5·5)	..	0·0% (−2·6 to 2·7)	..
One-sided p value for superiority	0·5072	..	..	..
Microbiological failure	15 (7·4%)	18 (8·8%)	0	0
Bacterial persistence	0	0	0	0
Unable to determine†	15 (7·4%)	18 (8·8%)	NA	NA
Use of other systemic antimicrobials‡	0	2 (1·0%)	NA	NA

Ross JDC, et al. Lancet. 2025. https://doi.org/10.1016/S0140-6736(25)00628-2