UWTASP tele-antimicrobial stewardship program | echo

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New Antibiotics

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Project ECHO

Disclosures

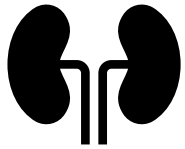
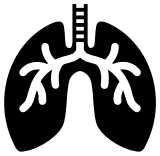
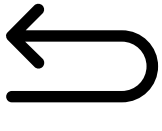
Today's speaker has no financial relationships with an ineligible company relevant to this presentation to disclose.

None of the planners have relevant financial relationship(s) to disclose with ineligible companies whose primary business is producing, marketing, selling, re-selling, or distributing healthcare products used by or on patients

All relevant financial relationships have been mitigated

The Most Common Sources of Bacteremia

Bacteremia Antibiotic Length Actually Needed for Clinical Effectiveness (BALANCE Trial), 7 vs 14 days of antibiotics

				
Urinary Tract 1523 (42%)	Intra-abdominal or hepatobiliary 679 (19%)	Lung 469 (13%)	Vascular catheter 229 (6.3%)	Skin & soft tissue 187 (5.2%)

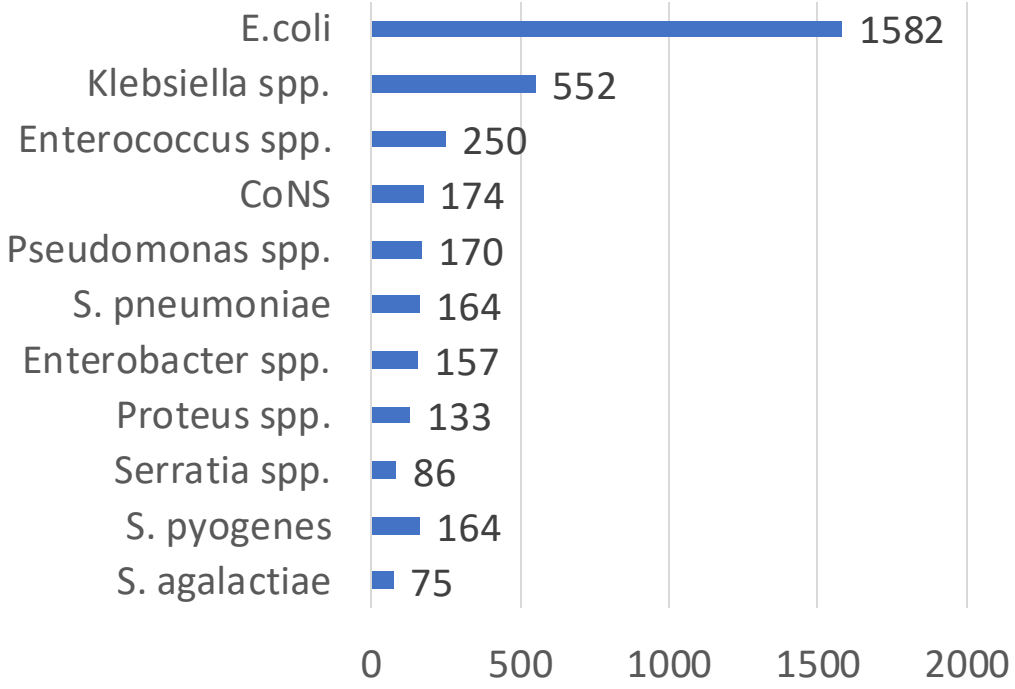
2562 monomicrobial gram-negative bacteria (71.0%)

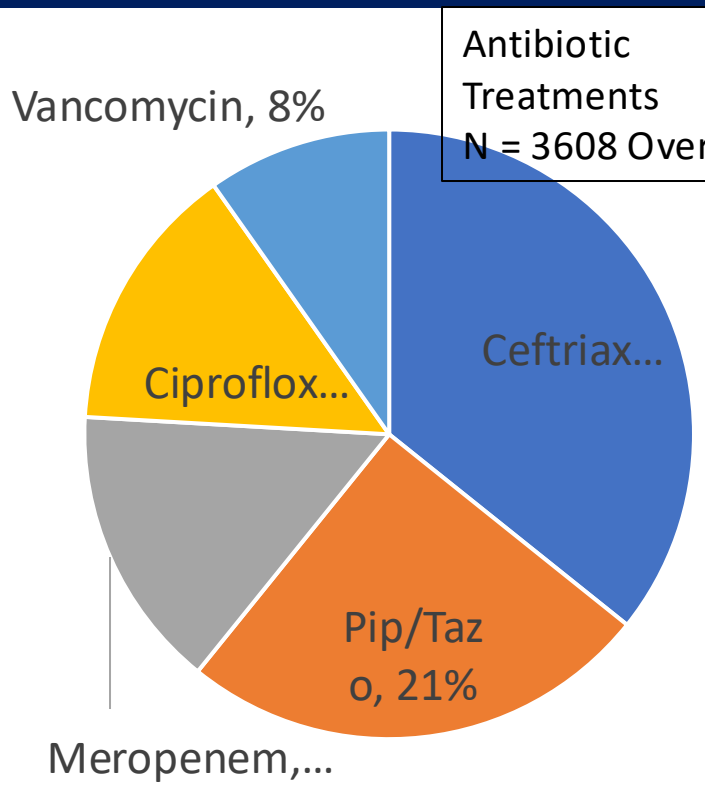
625 monomicrobial gram-positive bacteria (17.3%)

Daneman N, et al. N Engl J Med. Published November 20, 2024. doi:10.1056/NEJMoa2404991

Epidemiology of Resistance

Why do we always talk about GNs?





- Ertapenem = 5.7% (n = 206)
- Gentamicin = 1.2% (n = 42)
- Colistin = 0.4%, (n = 13)

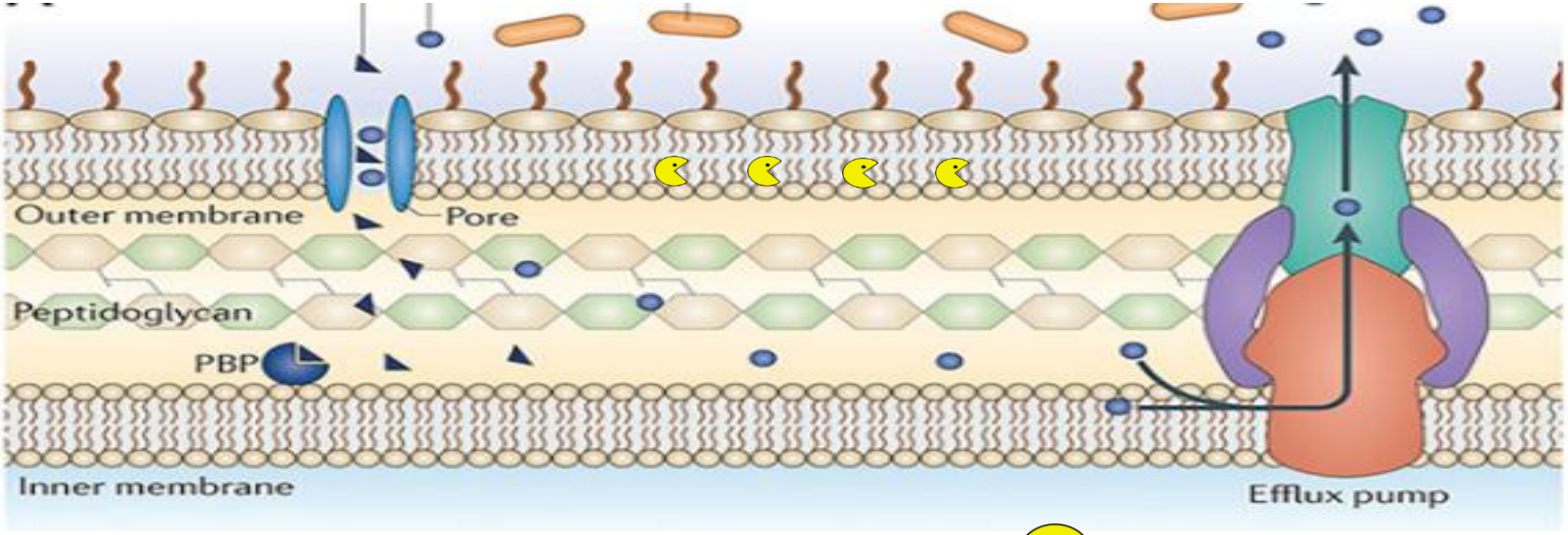
Daneman N, et al. N Engl J Med. Published November 20, 2024. doi:10.1056/NEJMoa2404991

Which of the following letters on a microbiology report would concern you the most?

- AMP-C
- ESBL
- KPC
- NDM
- Letters don’t scare me

Multiple Mechanisms of Resistance
Defense = Survival

Gram negative bacteria

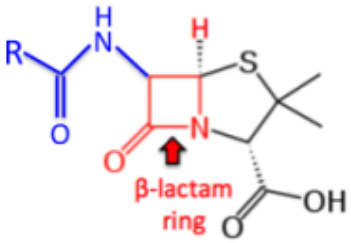


Chellat MF. 2016. Targeting antibiotic resistance. Angew Chem Int Ed Engl 55:6600–6626

Slide Credit: Frank Tverdek

Beta-Lactamases

- **MOA -** Inactivate beta-lactam antibiotics by splitting the amide bond of the beta-lactam ring.
- **Heterogeneity -** More than 600 beta-lactamases have been described!!!!
- **Genetically encoded -** by either chromosomal or transferable genes located on plasmids and transposons.
- **Expression -** Can be *suppressed*, *induced*, *derepressed* or constitutively expressed (AMP-Cs)



penicillins

Slide Credit: Frank Tverdek

New Antimicrobials

Intravenous (IV)

- Aztreonam-avibactam (2/2025)
- Cefepime/enmetazobactam (2/2024)
- Sulbactam/Durlobactam (5/2023)
- Sulopenem (10/2024)

Oral (PO)

- Gepoticidan (3/2025)

<u>These are NOT new</u>

- Cefiderocol (11/2019)
- Ceftazidime-avibactam (2/2015)
- Ceftolozane-tazobactam (12/2014)
- Meropenem-vaborbactam (8/2017)

Cefepime/enmetazobactam

2.5g IV q8h over 2-4h infusion

- FDA approved: 2024 for adults with complicated urinary tract infection including pyelonephritis
- Gap addressed: carbapenem-sparing option for ESBL, potential use in non-urinary infections
- Current option(s): Meropenem, Imipenem-cilastatin, Ertapenem

Cefepime and Enmetazobactam. 2024. Package Insert. www.accessdata.fda.gov/drugsatfda_docs/label/2024/216165s000lbl.pdf

Comparing Spectra of Activity

	Enterobacterales					Pseudmonas aeruginosa	
	ESBL	AMP-C	Carbapenemases			Garden variety Pseudomonas	Difficult to treat Pseudomonas
			Ambler class A (KPC)	Metalo-beta-lactamases (NDM, VIM, IMP)	Ambler Class D (Oxa-48)		
Meropenem or Imipenem-cilastatin							
Ertapenem							
Cefepime							
Cefepime-enmetazobactam							
Piperacillin-tazobactam							

Macesic et al. Lancet 2025;405(1044):257.

Cefepime/enmetazobactam

JAMA

QUESTION How does the efficacy of cefepime/enmetazobactam compare with piperacillin/tazobactam for the treatment of complicated urinary tract infection (UTI) or acute pyelonephritis?

CONCLUSION This randomized clinical trial found that cefepime/enmetazobactam, compared with piperacillin/tazobactam, met criteria for noninferiority as well as superiority with respect to the primary efficacy outcome of clinical cure and microbiological eradication.

POPULATION

573 Women
468 Men

Adults >18 years with a clinical diagnosis of complicated UTI or acute pyelonephritis caused by gram-negative urinary pathogens

Mean age: 54.7 years

LOCATIONS

90
Sites worldwide

INTERVENTION

1041 Patients randomized
1034 Patients analyzed

520

Cefepime/enmetazobactam

Cefepime, 2 g/enmetazobactam, 0.5 g, given by 2-hour infusion every 8 hours for 7 days

521

Piperacillin/tazobactam

Piperacillin, 4 g/tazobactam, 0.5 g, given by 2-hour infusion every 8 hours for 7 days

PRIMARY OUTCOMES

Proportion of patients in the primary analysis set who achieved overall treatment success, defined as clinical cure combined with microbiological eradication ($<10^3$ CFU/mL in urine) of infection

FINDINGS

Rate of primary outcome occurrence among the primary analysis set

Cefepime/enmetazobactam
273 of 345 patients

Piperacillin/tazobactam
196 of 333 patients

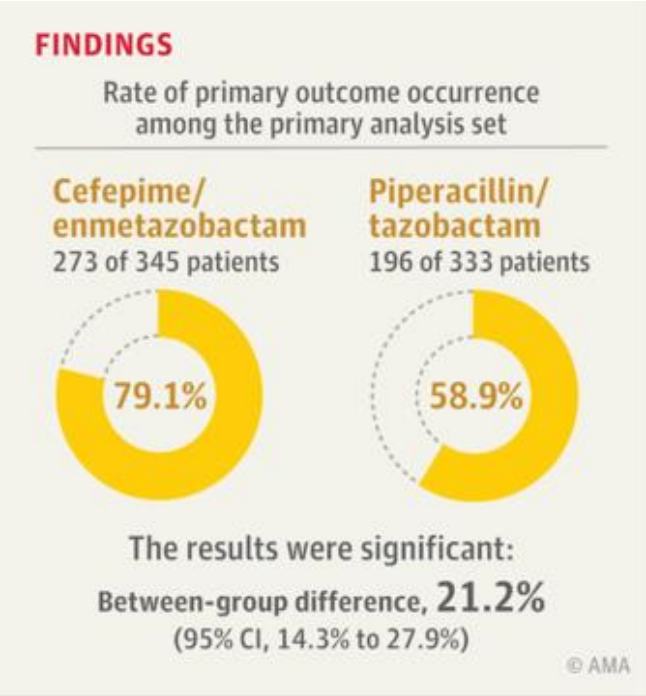
The results were significant:

Between-group difference, 21.2%
(95% CI, 14.3% to 27.9%)

Kaye KS, Belley A, Barth P, et al. Effect of cefepime/enmetazobactam vs piperacillin/tazobactam on clinical cure and microbiological eradication in patients with complicated urinary tract infection or acute pyelonephritis: a randomized clinical trial. *JAMA*. Published October 4, 2022. doi:10.1001/jama.2022.17034

Cefepime/enmetazobactam

What are we going to do with you?



- Place in therapy?
- What does it add? (no anaerobic activity)
- Why do we need to spare carbapenems?

Advani and Claeys. 2022. JAMA;328(13):1299-1301. doi:10.1001/jama.2022.15228

Sulopenem

500mg PO BID + 500mg probenecid PO BID x5 days with food

- FDA approved: 2024 for adult women with uncomplicated urinary tract infection (uUTI) caused by *E.coli, K. pneumoniae, P. mirabilis*
- Gap addressed: PO option for cystitis (uUTI) due to ESBL-producing enterobacterales
- Current option(s)[1]: Nitrofurantoin, Fosfomycin, 1x dose of IV aminoglycosides

[1]Other PO options exist (e.g. fluoroquinolones, sulfamethoxazole/trimethoprim) but are often resistant

Sulopenem. 2024. Package Insert.
https://www.accessdata.fda.gov/drugsatfda_docs/label/2024/213972s000lbl.pdf

Sulopenem, why can’t we use it for non-uUTI?

In a multicenter, randomized, comparative, double-blind, phase 3 trials including 131 sites in 13 countries and 1392 patients. Sulopenem did NOT meet non-inferiority criteria vs. IV ertapenem followed by PO ciprofloxacin for treatment of pyelonephritis or complicated urinary tract infection

Dunne M et al. Clin Infect Dis. 2023; 76(1):78–88, https://doi.org/10.1093/cid/ciac704

The UTI Trial, Sulopenem

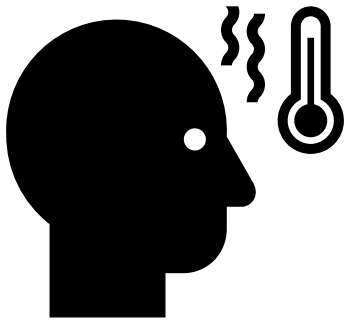
Trial Criteria = clinical cure AND microbiological cure

Design	Double-blind phase 3 trial in 131 sites in 13 countries
Treatments	Sulopenem IV followed by Sulopenem/probenecid PO vs. Ertapenem IV followed by Ciprofloxacin or Amox/Clav PO
Duration	Total: 7-10 days, could be extended to 14 days if bacteremia At least 5 days of IV therapy then can switch to PO if tolerable
Patients	41.4% with complicated UTI 58.6% with acute pyelonephritis

Dunne M et al. Clin Infect Dis. 2023; 76(1):78–88, https://doi.org/10.1093/cid/ciac704

Trial Criteria = clinical cure AND microbiological cure

Noninferiority of sulopenem to ertapenem was to be concluded if the lower bound of the 95% CI was greater than −10%.



Clinical cure: s/sx resolved and no new symptoms

Microbiological cure: bacterial pathogen found at $\geq 10^5$ CFU/mL in the baseline urine culture was reduced to $<10^3$ CFU/mL in the test of cure urine culture
And clearance of blood cultures (if positive)8

Dunne M et al. Clin Infect Dis. 2023; 76(1):78–88, https://doi.org/10.1093/cid/ciac704

Not Non-Inferior driven by Microbiological response

Trial Criteria = clinical cure AND microbiological cure

Clinical cure: s/sx resolved and no new symptoms

Microbiological cure: <10^3 CFU/mL in the test of cure urine culture
And clearance of blood cultures (if positive)

Outcome at Test of Cure Day 21	Sulopenem IV then PO sulopenem N = 444	Ertapenem IV then PO ciprofloxacin or amox/clavulanate N = 440	Difference, 95% Confidence Interval
Overall response (clinical + microbiological)	301 (67.8)	325 (73.9)	−6.1 (−12.0 to −.1)
Clinical response	397 (89.4)	389 (88.4)	1.0 (−3.1 to 5.1)
Microbiological response Success Failure	 316 (71.2) 111 (25.0)	 343 (78.0) 74 (16.8)	−6.8 (−12.5 to −1.1)

Dunne M et al. Clin Infect Dis. 2023; 76(1):78–88, https://doi.org/10.1093/cid/ciac704

But before we feel too confident about the data….we should talk about cIAI

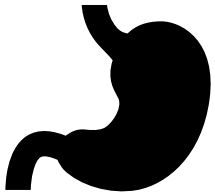
- Phase 3, randomized, double-blind, double-dummy trial: 91 sites in 10 countries
- Sulopenem IV then PO vs. Ertapenem IV then ciprofloxacin[1] + metronidazole PO

Outcome at Test of Cure Clinical success -alive -baseline s/sx resolved -no new symptoms -no new abx or surgery	Sulopenem IV then PO sulopenem N = 249	Ertapenem IV then PO ciprofloxacin + metronidazole or amox/clavulanate N = 266	Difference, 95% Confidence Interval
FDA endpoint, Day 28	213 (85.5)	240/266 (90.2)	-4.7 (-10.3, 1.0)
EMA endpoint, Day 21	216 (86.7)	240/266 (90.2)	-3.5 (-9.0, 2.0)

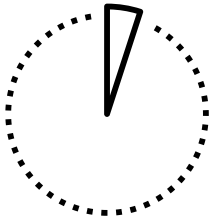
Dunne MW et al. Clin Microbiol Infect 2025. 31(3):396-401. doi: 10.1016/j.cmi.2024.10.025.

Sulopenem, PO carbapenem with niche use

Not non-inferior to ertapenem for pyelonephritis



Not non-inferior to ertapenem for complicated intraabdominal infection



Niche use: women with cystitis due to resistant enterobacterales and age/renal function precluding use of other options

Dunne MW, Aronin SI, Das AF, et al. Clin Infec Dis 2022;76(1):78-88. doi: 10.1093/cid/ciac704
Dunne MW, Aronin SI, Das AF, et al. Clin Microbiol Infect. 2025;31(3):396-401.

10 years: From approval to place in therapy

2014/15

Ceftazidime-avibactam and Ceftolozane-tazobactam FDA-approved

2016-2023

Enrollment in multicenter, retrospective observational study CACTUS

2025

Ceftolozane-tazobactam > Ceftazidime-avibactam for MDR *P. aeruginosa* infection

When are we going to figure out what to do with cefepime/enmetazobactam?

My best guess:

In the year 2025