UWTASP
tele-antimicrobial stewardship program

Aztreonam-Avibactam (Emblaveo)

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Project ECHO

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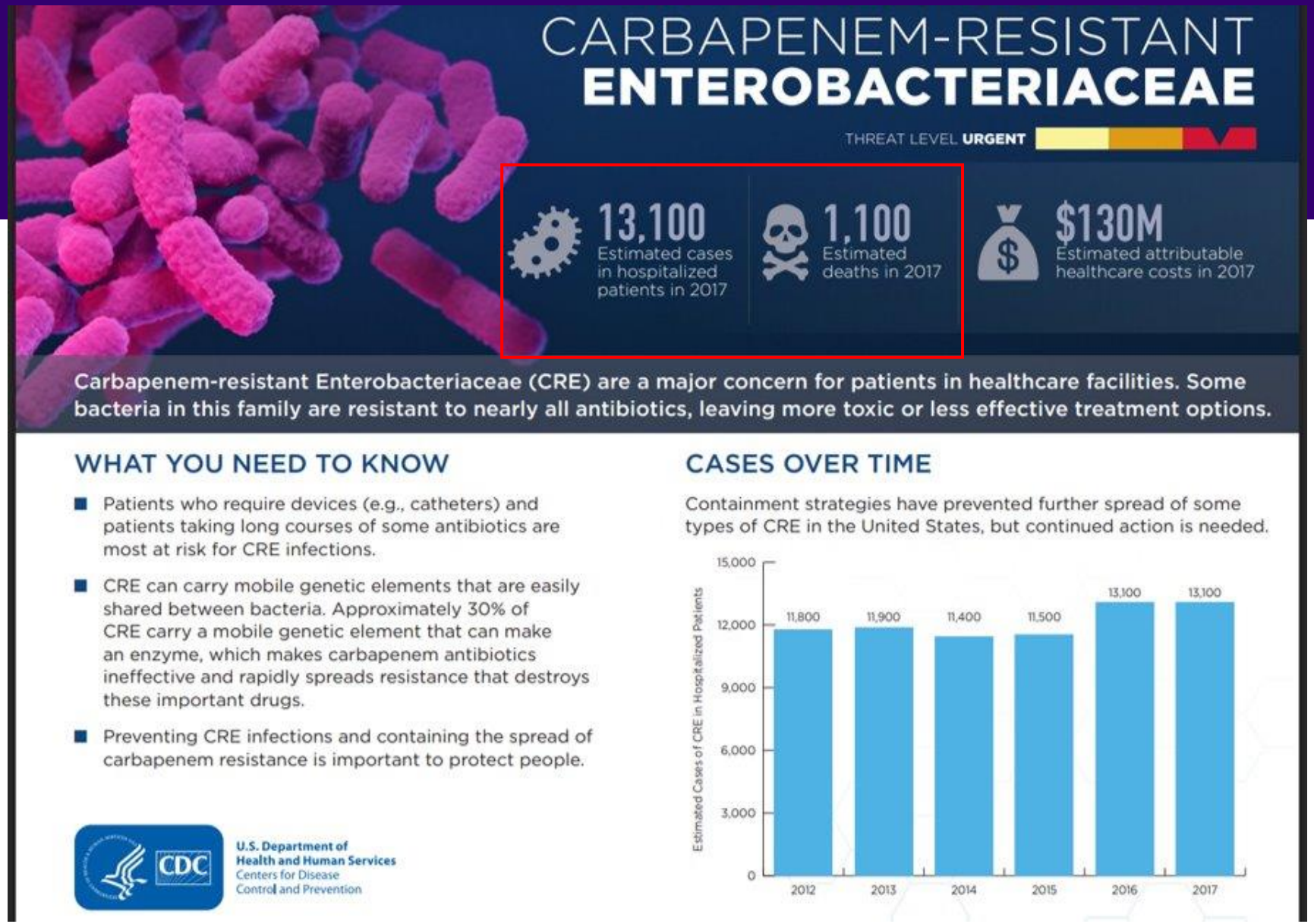
Disclosures

- I have no financial relationships or conflicts of interest to disclose.

- None of the planners for this activity have relevant financial relationships with ineligible companies to disclose.

Gram Negative Rod Resistance
(Enterobacterales)

Epidemiology



CDC Antibiotic Resistance Threats in the United States

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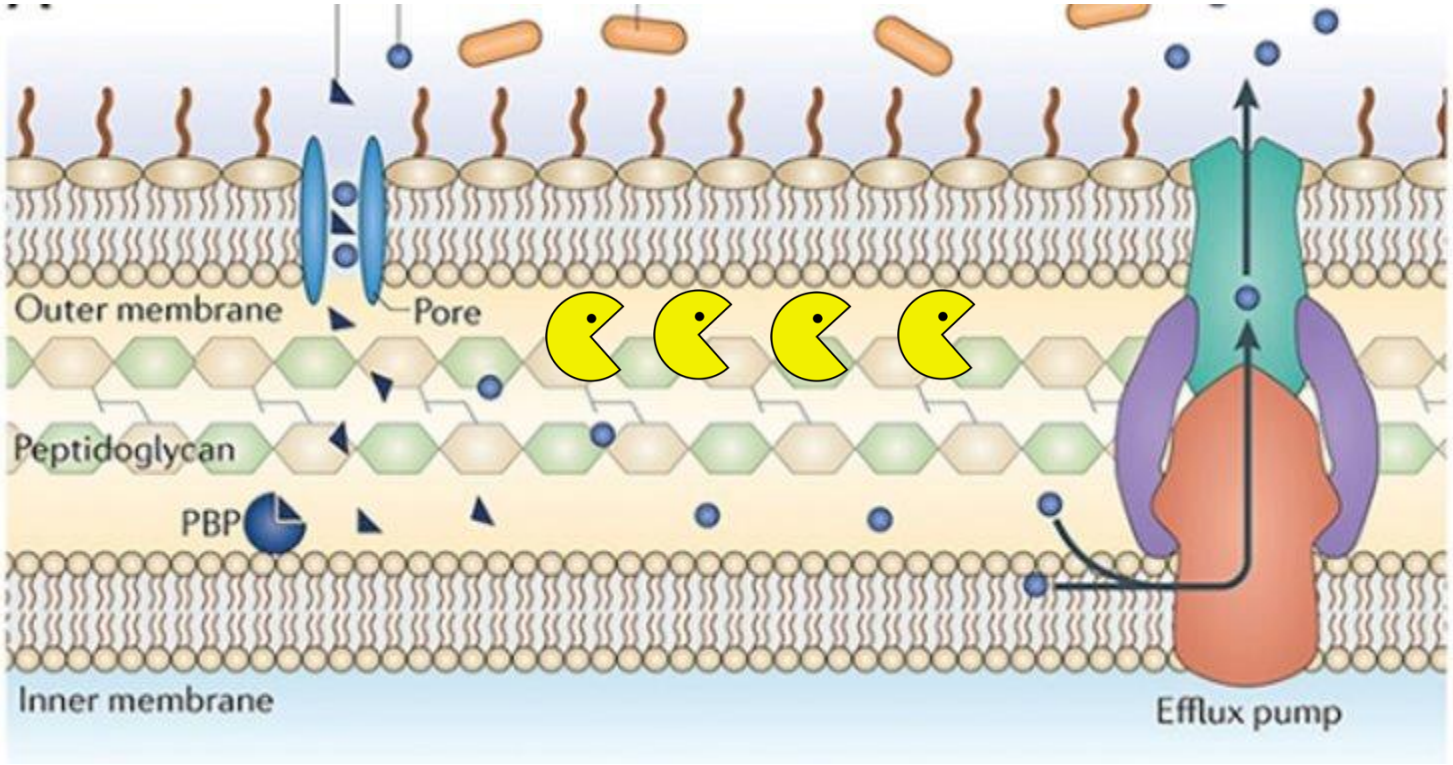
Gram Negative Rod Resistance



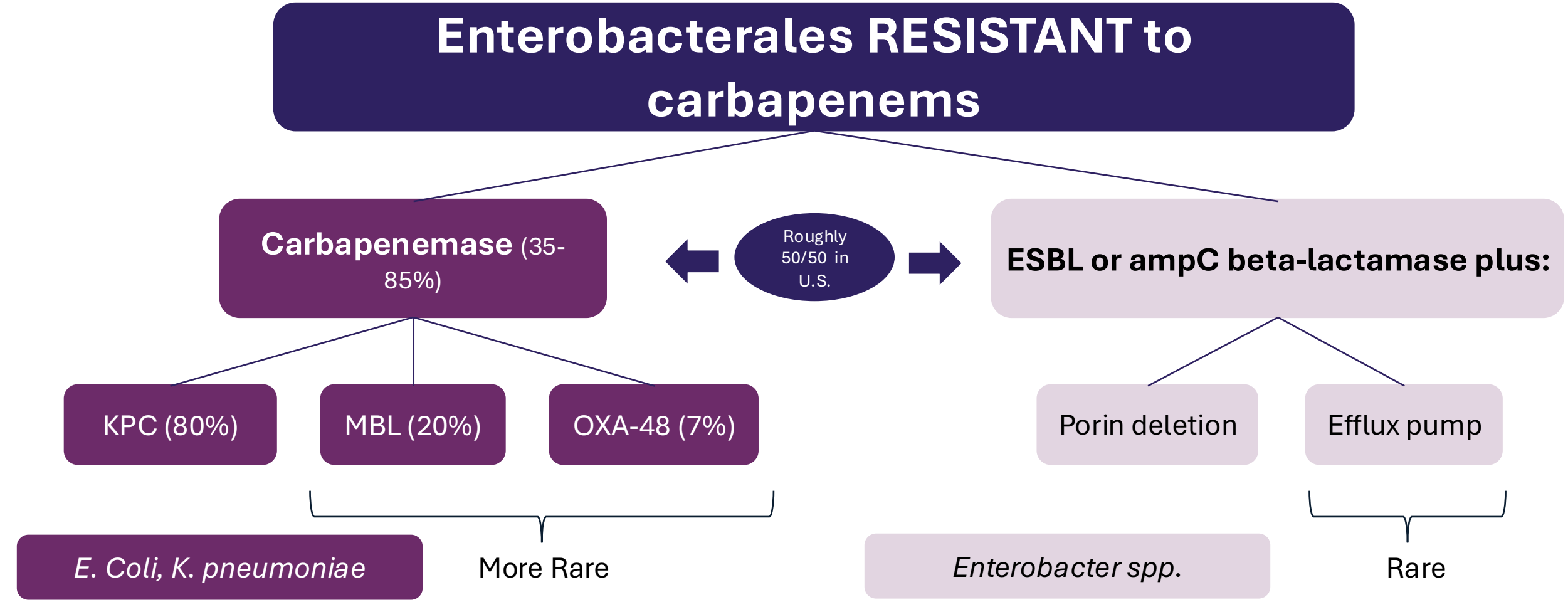
= beta-lactamase

Targeting Antibiotic Resistance

Slide credit: Frank Tverdek, PharmD

ESBL – Extended spectrum beta-lactamase
KPC – Klebsiella pneumoniae carbapenemase
MBL – metallo-beta-lactamase

Mechanism of Resistance



Detection and Characterization of Targeted Carbapenem-Resistant Health Care-Associated Threats; Changing Epidemiology of Carbapenemases Among Carbapenem-Resistant Enterobacterales From United States Hospitals and the Activity of Aztreonam-Avibactam Against Contemporary Enterobacterales (2019-2021)

Slide credit: Frank Tverdek, PharmD

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HOW do I know if my patient's isolate has a carbapenemase?

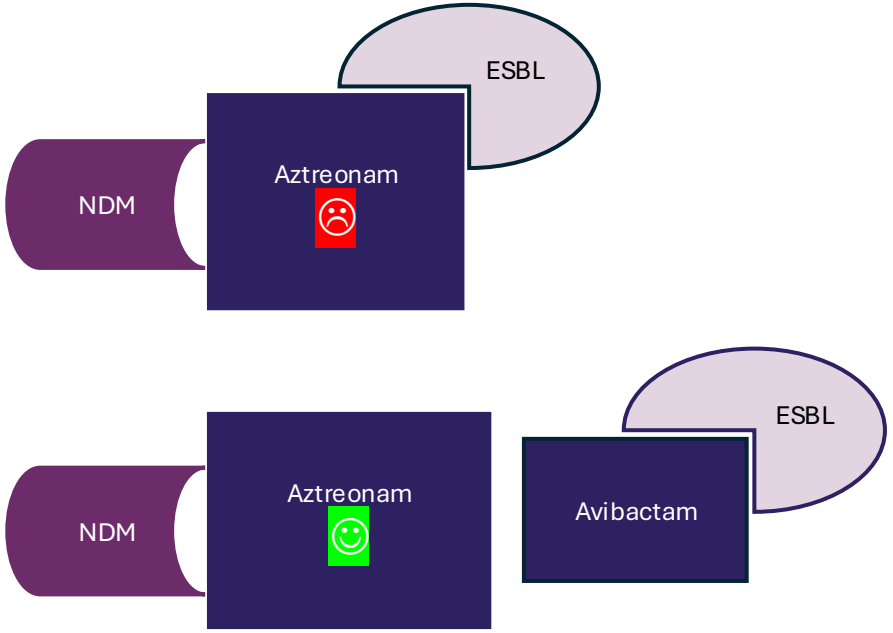
Organism	Susceptibility testing
Enterobacterales (except for PPM* group)	Non-susceptible to any carbapenem (ertapenem, imipenem, meropenem)
Proteus, Providencia, and Morganella* bacteria intrinsically less susceptible to imipenem	Ertapenem and/or meropenem non-susceptible

Slide credit: Frank Tverdek, PharmD

Aztreonam-Avibactam

Mechanism of Action

- Aztreonam
  - Binds to penicillin binding proteins
  - Inhibits bacterial peptidoglycan cell wall synthesis → cell lysis
  - Stable against MBL-producing pathogens
- Avibactam
  - Beta-lactamase inhibitor
  - Inhibits Ambler class A, C, and D beta-lactamases (ESBL, KPC, OXA-48 carbapenemases, and AmpC enzymes)



Emblaveo Prescribing Information

Slide credit: Frank Tverdek, PharmD

Guideline Recommendations

- FDA Indication: complicated intra-abdominal infection
- Limited treatment options for MBL (Ambler Class B) infections
  - First-line treatment options
    - Ceftazidime-avibactam in combination with aztreonam
    - Cefiderocol monotherapy

IDSA 2024 Guidance on the Treatment of Antimicrobial Resistant Gram-Negative Infections

Spectrum of Activity

Antimicrobial Combination Agent*	Ambler Class A (ESBL)	Ambler Class A (KPC)	Ambler Class B (IMP, NDM, VIM)	Ambler Class C (AmpC)	Ambler Class D (OXA-48)	Carbapenem resistant *pseudomonas*	*S. Maltophilia*	CRAB
ATM/AVI						‡		
CTZ/AVI			£					
Cefiderocol								¶
C/T								
Imi/Rel			£					
M/V			£					
SUL/DUR								
Not stable	Stable	Limited Action						

*ATM/AVI (Aztreonam-avibactam), CTZ/AVI (Ceftazidime-avibactam), C/T (Ceftolozane-tazobactam), Imi/Rel (Imipenem-cilastatin-relebactam), M/V (Meropenem-vaborbactam), SUL/DUR (Sulbactam-durlobactam).

‡In vitro data only.

£May be used in combination with aztreonam. Meropenem-vaborbactam and imipenem-cilastatin-relebactam cannot be considered if OXA-type carbapenemases are present.

¶Higher all-cause mortality when compared to best-available therapy in infections caused by carbapenem-resistant Acinetobacter and Enterobacteriaceae.

Emblaveo Prescribing Information; Evaluation of Aztreonam-Avibactam In Vitro Activity Against VIM and GES β-lactamase Producing Carbapenem-Resistant Pseudomonas aeruginosa; IDSA 2024 Guidance on the Treatment of Antimicrobial Resistant Gram-Negative Infections; Aztreonam and avibactam combination therapy for metallo-β-lactamase-producing gram-negative bacteria: A Narrative Review; Sanford Guide; CREDIBLE-CR Trial

REVISIT Trial

Aztreonam–avibactam versus meropenem for the treatment of serious infections caused by Gram-negative bacteria (REVISIT): a descriptive, open-label, phase 3, randomized trial

THE LANCET Infectious Diseases

Purpose:
To assess the efficacy and safety of aztreonam-avibactam

Population:
- cIAI, HAP/VAP caused by gram negative rods
- 19 (24%) of 80 isolates were serine/MBL carbapenemase-positive

Limitations:
- Optional co-administration of other antibiotics
- Lower clinical cure rate in HAP/VAP vs. cIAI
- Less patients with HAP/VAP
- Descriptive study, no power analysis

GROUP 1: AZM-AVI ± metronidazole
(cIAI = 208, HAP/VAP = 74)

GROUP 2: Meropenem ± colistin
(cIAI = 104, HAP/VAP = 36)

Duration: cIAI 5–14 days, HAP/VAP 7–14 days

	Clinical Cure		28-Day Mortality
	cIAI	HAP/VAP	
GROUP 1	76.4%	45.9%	4%
GROUP 2	74.0%	41.7%	7%

- CONCLUSION: There was no significant difference in clinical cure rates and were overall low 28-day all-cause mortality rates. Aztreonam-avibactam appears as effective as meropenem. Aztreonam-avibactam is a potential option for treatment of cIAI and HAP/VAP.

REVISIT Trial

ASSEMBLE Trial

Aztreonam–avibactam for the treatment of serious infections caused by MBL-producing Gram-negative pathogens (ASSEMBLE): a Phase 3 randomized trial

JAC - Antimicrobial Resistance
Education and research in antimicrobial stewardship and resistance

Purpose:
To assess the efficacy and safety of aztreonam-avibactam

Population:
cIAI, complicated UTI, bloodstream infection, or HAP/VAP with confirmed MBL-positive gram-negative bacteria

Limitations:

- Optional co-administration of other antibiotics
- Caution is warranted in drawing interpretations from the findings due to small sample size

	Clinical Cure	28-Day Mortality
GROUP 1: AZM-AVI ± metronidazole (n = 12)	42%	8%
GROUP 2: Best available therapy (amikacin/polymyxin/meropenem or amikacin/colistin) (n = 3)	0%	33%

- CONCLUSION: A greater percentage of patients receiving aztreonam-avibactam achieved clinical cure vs. best available therapy. There was no treatment-related 28-day all-cause mortality. Aztreonam-avibactam appears as effective as best available therapy. Aztreonam–avibactam is a potential option for management of difficult to treat MBL-positive gram-negative infections.

ASSEMBLE Trial

Adverse Effects – Prescribing Information

	Aztreonam-avibactam ± metronidazole (N=275) N (%)	Meropenem ± colistin (N=137) N (%)
Hepatic adverse reactions	40 (14.5)	16 (11.7)
Anemia	22 (8.0)	7 (5.1)
Diarrhea	16 (5.8)	5 (3.6)
Hypokalemia	16 (5.8)	4 (2.9)
Pyrexia	16 (5.8)	7 (5.1)

Emblaveo Prescribing Information

Adverse Effects – REVISIT

	cIAI		HAP/VAP	
Adverse Effect, n (%)	Aztreonam-avibactam + metronidazole (n = 203)	Meropenem ± colistin (n = 103)	Aztreonam-avibactam (n = 72)	Meropenem ± colisitin (n = 34)
Adverse event	120 (59.1)	58 (56.3)	57 (79.2)	29 (85.3)
Treatment-related adverse event	34 (16.7)	11 (10.7)	7 (9.7)	4 (12.5)
Elevated liver enzymes	25 (12.3)	5 (4.9)	4 (5.6)	2 (5.9)
Diarrhea	6 (3)	1 (1)	1 (1.4)	0 (0)
Nausea	3 (1.5)	0 (0)	0 (0)	0 (0)
Injection site reaction	1 (0.5)	4 (3.9)	0 (0)	0 (0)

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Dosing Regimen

Loading Dose

2.67 g (Aztreonam 2 g + Avibactam 0.67 g) IV x1*

Maintenance Dose

2 g (Aztreonam 1.5 g + Avibactam 0.5 g) Q6h IV Q6H administered over 3 hours*

*renal adjustments as needed

- Safety of Ceftazidime-Avibactam in Combination with Aztreonam (COMBINE) in a Phase I, Open-Label Study in Healthy Adult Volunteers
  - Looked at various dosing and infusion strategies
    - Dose related – Aztreonam 8 g/day as continuous infusion associated with more severe liver injury
    - 2-hour intermittent infusions generally safe
- Aztreonam-avibactam dosing chosen to minimize adverse effects
- Synergy
  - Aztreonam-avibactam (Q6H) may optimize synergy vs. Ceftazidime-avibactam (Q8H) + Aztreonam (Q6H)

Emblaveo Prescribing Information; COMBINE Trial; Synergistic activity of ceftazidime-avibactam and aztreonam against serine and metallo-β-lactamase-producing gram-negative pathogens

Cost Analysis

Carbapenemase producing isolates 7/2023 - 7/2025 at UWML and HMC

Carbapenemase	UWMCML	HMC	Total
NDM	16	5	21
VIM	1	0	1
OXA-48/NDM	2	2	4
			26

- Total annual inpatient cost
  - Ceftazidime-avibactam + Aztreonam: $114,600
  - Cefiderocol: $156,500
- Total annual savings with Aztreonam-avibactam compared to:
  - Ceftazidime-avibactam + Aztreonam: $9, 100
  - Cefiderocol: $60, 000

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Place in Therapy

- Limited treatment options for MBL (Ambler Class B) infections
  - First-line treatment options
    - Ceftazidime-avibactam in combination with aztreonam
    - Cefiderocol monotherapy
- Aztreonam-avibactam place in therapy
  - Demonstrated clinical and cost effectiveness for difficult to treat gram-negative infections, particularly MBL producing infections when compared to other guideline directed therapy

Takeaways

- Nursing: maintenance dose is administered over 3 hours which may complicate line access for other medications

- Pharmacy & Physician: consider use for MBL producing infections if cost effective compared to other guideline directed therapy

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