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Cefiderocol

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Disclosures

I am a consultant, speakers bureau member or have received research funding from:

Allergan, Bayer, Cepheid, Merck,

Melinta, Pfizer, Wockhardt, Shionogi, Tetraphase

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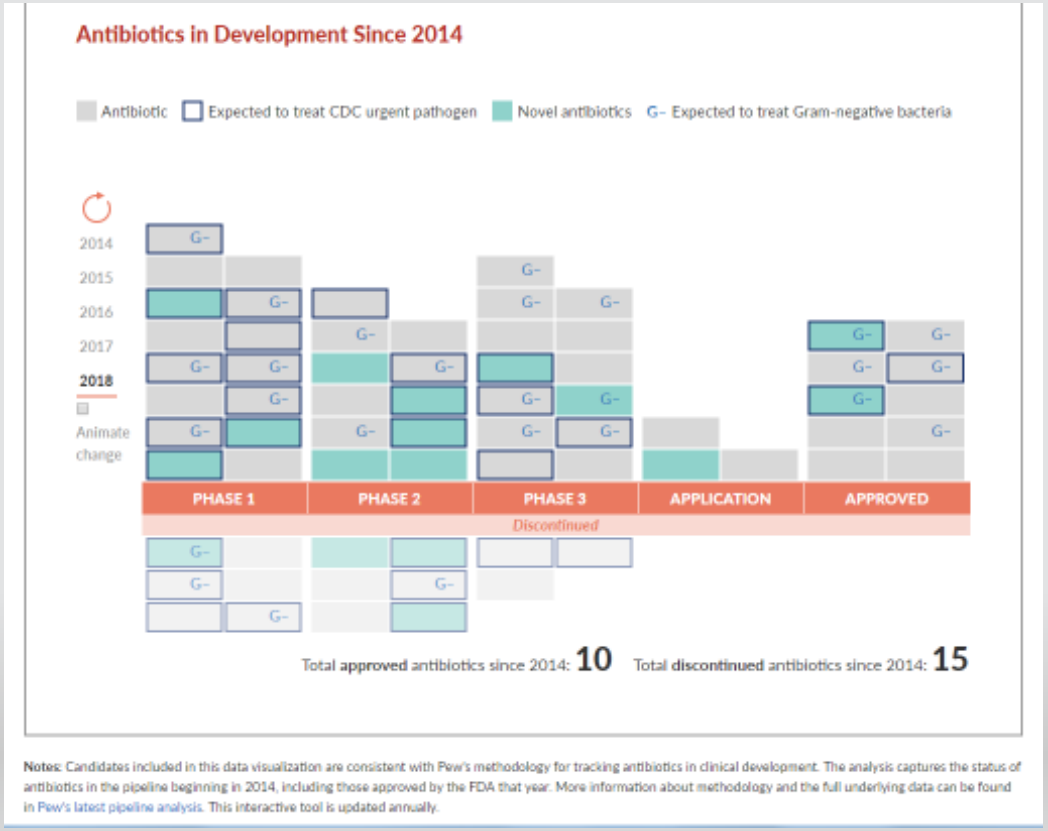
Pew Charitable Trust: Antibiotics in Development



2014-2018:

- 10 new antibiotics approved
- 6 were for Gram-negatives
  - Ceftazidime/avibactam
  - Ceftolozane/tazobactam
  - Meropenem/vaborbactam
  - Plazomicin
  - Eravacycline
  - Omadacycline

2019:

- 3 new antibiotics approved
- 2 for Gram-negatives
  - Imipenem/Relebactam
  - **Cefiderocol [Nov 14th]**

Accessed at: https://www.pewtrusts.org/en/research-and-analysis/data-visualizations/2019/five-year-analysis-shows-continued-deficiencies-in-antibiotic-development

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Siderophore - Antibiotic Conjugates

- Siderophores are small organic chelators with high affinity for iron
- Siderophores are secreted by bacteria to the extracellular environment to solubilize and import iron
- Sideromycins are natural products consisting of an antibiotic conjugated to a siderophore
  - Albomycin has been the most studied of the sideromycins
  - 1940s and 1950s used in the clinic in Soviet Union
- 1980s and 1990s renewed interest by Pharma companies
  - Link a more potent antibiotic to a microbial siderophore or siderophore mimic to overcome the bacteria cell wall permeability barrier and enhance concentration in periplasmic space
  - catechol–β-lactam antibiotic conjugates

Negash KH, et al. Molecules. 2019 Sep; 24(18): 3314. doi: 10.3390/molecules24183314

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Siderophore - Antibiotic Conjugates & Challenges

- Non-siderophores mechanisms for iron acquisition

Adaptation-based resistance to siderophore-conjugated antibacterial agents by Pseudomonas aeruginosa.
Tomaras AP, Crandon JL, McPherson CJ, Banevicius MA, Finegan SM, Irvine RL, Brown MF, O'Donnell JP, Nicolau DP. Antimicrob Agents Chemother. 2013;57(9):4197-207.

Pharmacodynamic Profiling of a Siderophore-Conjugated Monocarbam in Pseudomonas aeruginosa: Assessing the Risk for Resistance and Attenuated Efficacy.
Kim A, Kutschke A, Ehmann DE, Patey SA, Crandon JL, Gorseth E, Miller AA, McLaughlin RE, Blinn CM, Chen A, Nayar AS, Dangel B, Tsai AS, Rooney MT, Murphy-Benenato KE, Eakin AE, Nicolau DP. Antimicrob Agents Chemother. 2015;59(12):7743-52

- Standardization of in vitro susceptibility testing

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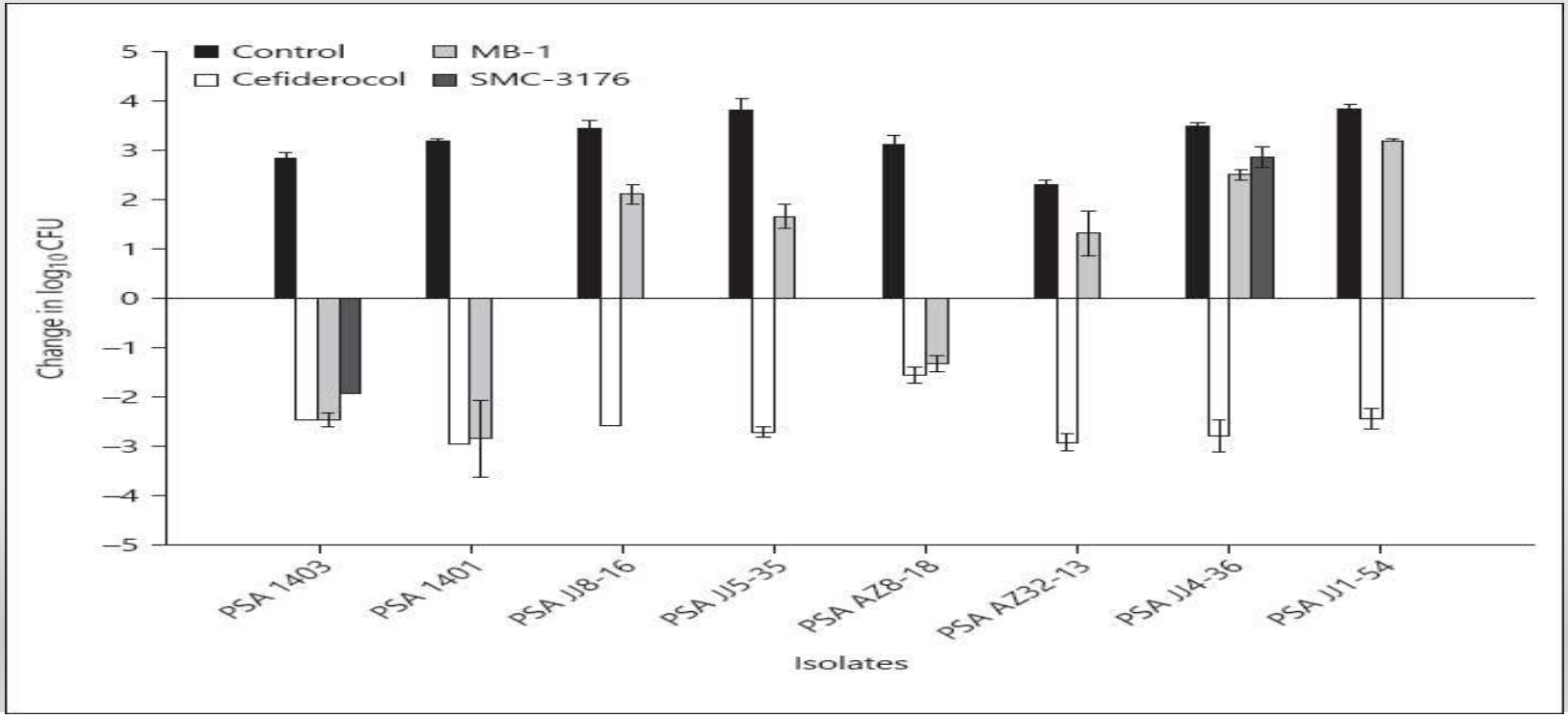
Humanized Exposures of Cefiderocol, a Siderophore Cephalosporin, Display Sustained *in vivo* Activity against Siderophore-Resistant *Pseudomonas aeruginosa*



Ghazi IM, Monogue ML, Tsuji M, Nicolau DP. Pharmacology. 2018;101(5-6):278-284

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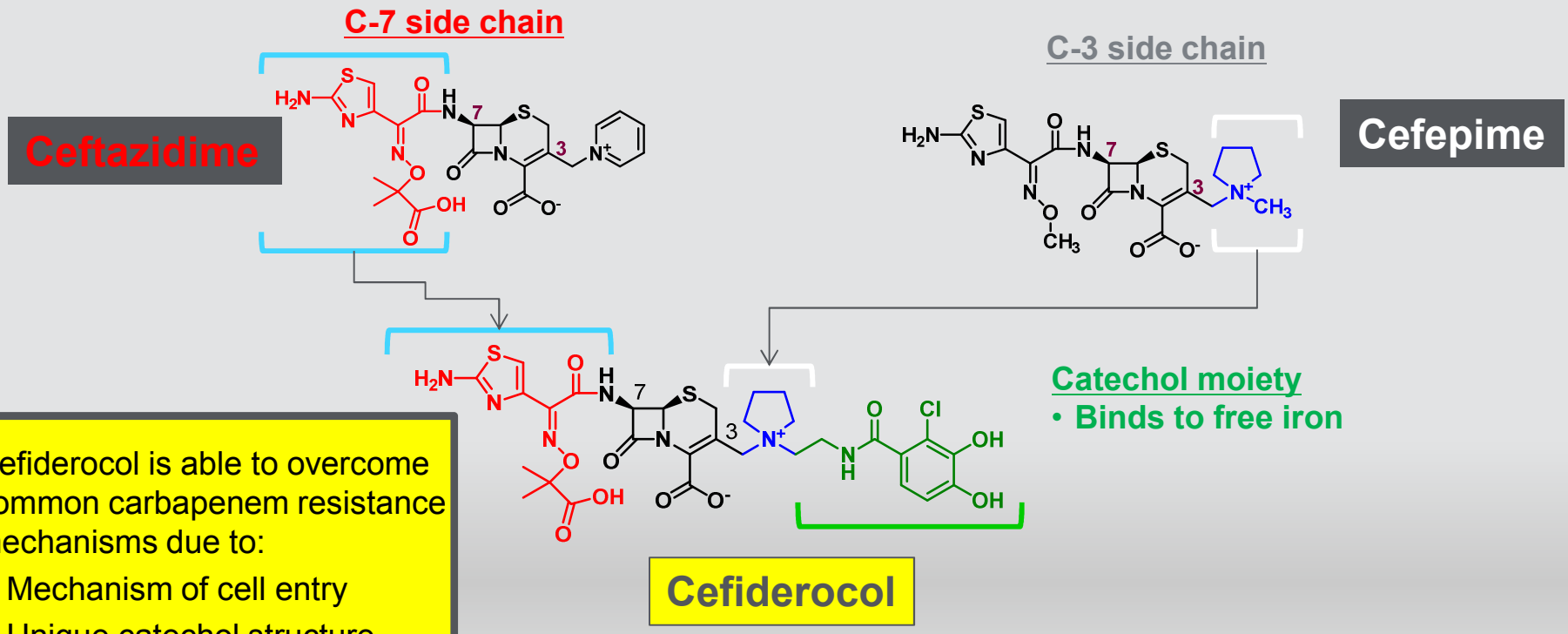
Cefiderocol Is Structurally Different From Other Recently Developed Siderophore-Conjugated Antibacterial Agents



Cefiderocol is able to overcome common carbapenem resistance mechanisms due to:

- Mechanism of cell entry
- Unique catechol structure

Ito A et al. *Antimicrob Agents Chemother*. 2016;60:7396-7401

Pubchem. https://pubchem.ncbi.nlm.nih.gov/compound/cefepime#section=Top. Accessed November 4, 2017.

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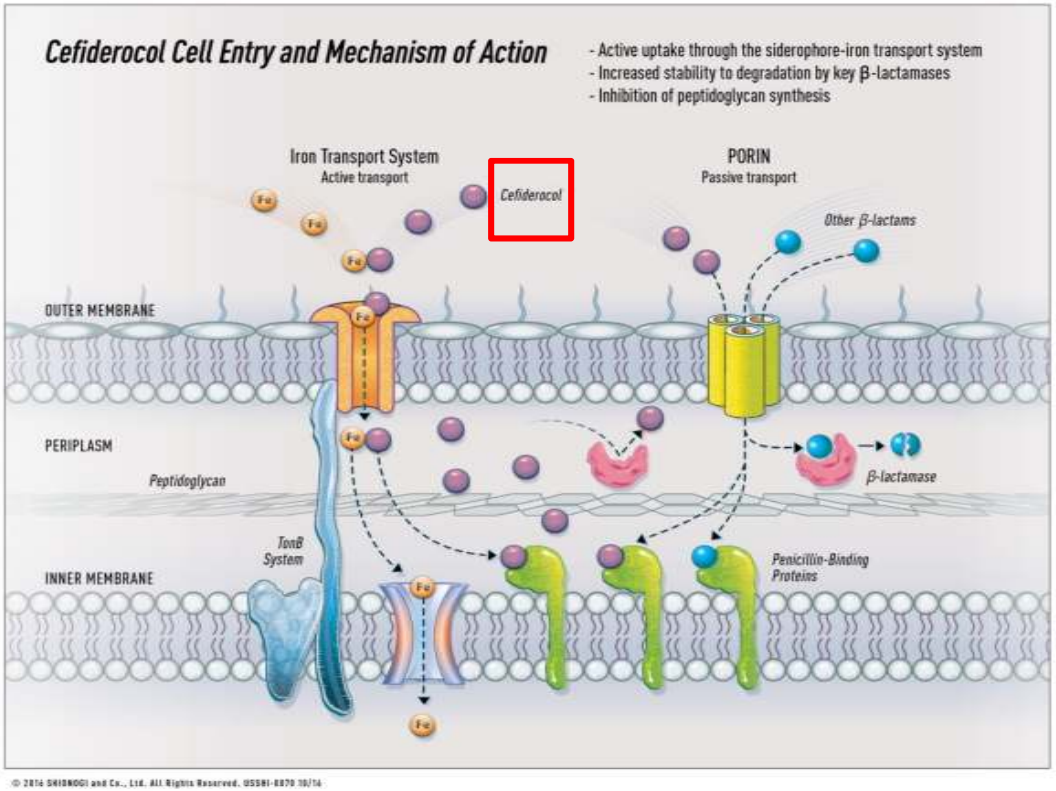
Cefiderocol – A Novel Siderophore Cephalosporin

- The entry mechanism of cefiderocol takes advantage of the native <u>active</u> iron transport system which enables the drug to penetrate the bacterial cell
  - Not dependent on porin channels for cell entry
- Inhibits peptidoglycan synthesis
  - PBP3
- Once inside the cell, cefiderocol <u>resists inactivation by all known classes of beta-lactamase enzymes</u>



Ito A et al. *Antimicrob Agents Chemother*. 2016;60:7396-7401..

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Comparative Activity of Cefiderocol to Ceftazidime-Avibactam, Ceftolozane-Tazobactam, Colistin, and Ciprofloxacin Against Gram-Negative Collected in N. America

Organism	Cefiderocol (MIC ≤4 µg/mL)	Ceftazidime-Avibactam (MIC ≤8 µg/mL)	Ceftolozane-Tazobactam (*MIC ≤4 or ≤2 µg/mL)	Colistin (MIC ≤2 µg/mL)	Ciprofloxacin %S (MIC ≤1 µg/mL)
All Gram-Negative (N=4239)	99.9	93.7	89.5	85.8	79.1
Enterobacteriaceae (N=3007)	99.96	99.9	94.2	82.4	86.2
Non-fermenters (N=1232)	99.6	79.4	77.9	94.0	61.7
Carbapenem-NS Enterobacteriaceae (N=30)	100	96.7	13.3	66.7	20
Carbapenem-NS P. aeruginosa (N=151)	100	90.7	90.1	99.3	43.7
Carbapenem-NS A. baumannii (N=173)	98.3	17.9	15.6	91.3	1.7
S. maltophilia (N=152)	100	51.3	38.2	68.4	34.9

*Ceftolozane/Tazobactam breakpoints by organism: Non-fermenters MIC ≤4 µg/mL, Enterobacteriaceae ≤2 µg/mL; Non-fermenters include: *P. aeruginosa, A. baumannii, S. maltophilia and B. cepacia.*

Hackel MA et al. *Antimicrob Agents Chemother*. 2017;61(9). pii: e00093-17.

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Bacterial-Density Study in an *in vivo* Neutropenic Thigh Infection Model

- 95 isolates (21 *P. aeruginosa*, 35 *A. baumannii*, and 39 Enterobacteriaceae) with various phenotypic profiles
  - Cefiderocol MICs ranged from 0.12 to >256 µg/mL

Bacterial stasis or ≥ 1-log-unit reduction at 24h with humanized cefiderocol exposures

	MIC ≤ 2 µg/mL	MIC ≤ 4 µg/mL
Enterobacteriaceae, % (n)	82% (17 strains)	77% (31 strains)
A. baumannii, % (n)	87% (15 strains)	88% (16 strains)
P. aeruginosa, % (n)	81% (16 strains)	85% (20 strains)

- For isolates with CFDC MIC of ≥8 µg/ml, bacterial stasis or 1-log-unit reduction was observed in 2 of 28 strains

Monogue M et al. Antimicrob Agents Chemother 61:e01022-17. 2017

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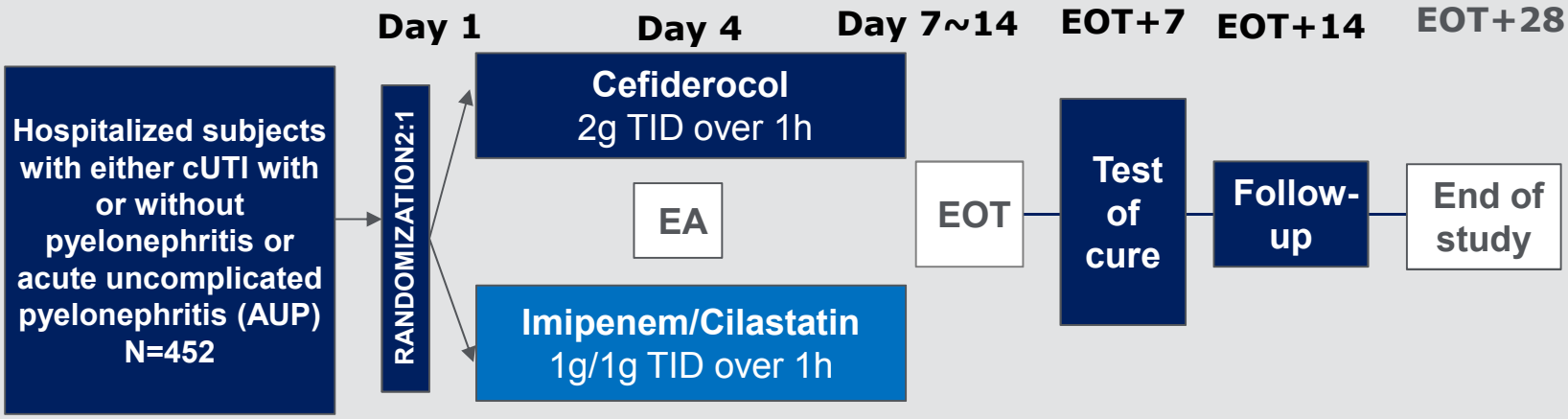
APEKS-cUTI Study Design

- Multicenter, double-blind, randomized, noninferiority trial
  - 2-sided 95% confidence interval (CI), noninferiority margin 15%



- **Primary endpoint:** Composite clinical and microbiological response at TOC in MITT population
- **Secondary endpoint**: Safety, Clinical and Microbiological response at early assessment, EOT, and follow-up in MITT population
- No oral antibiotic step-down was permitted

TID, 3 times a day; EOT, end of treatment; MITT, microbiological intent-to-treat – patients who received at least 1 dose and had a-qualifying Gram-negative uropathogen; TOC, test of cure.

Portsmouth S et al. Lancet Infect Dis 2018. Published online Oct 25 2018

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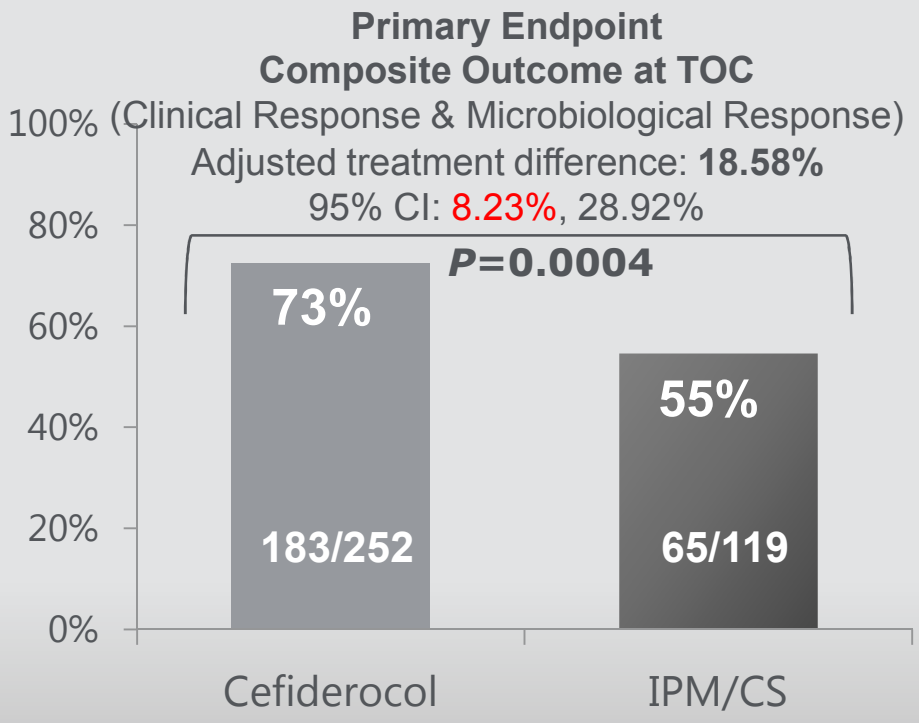
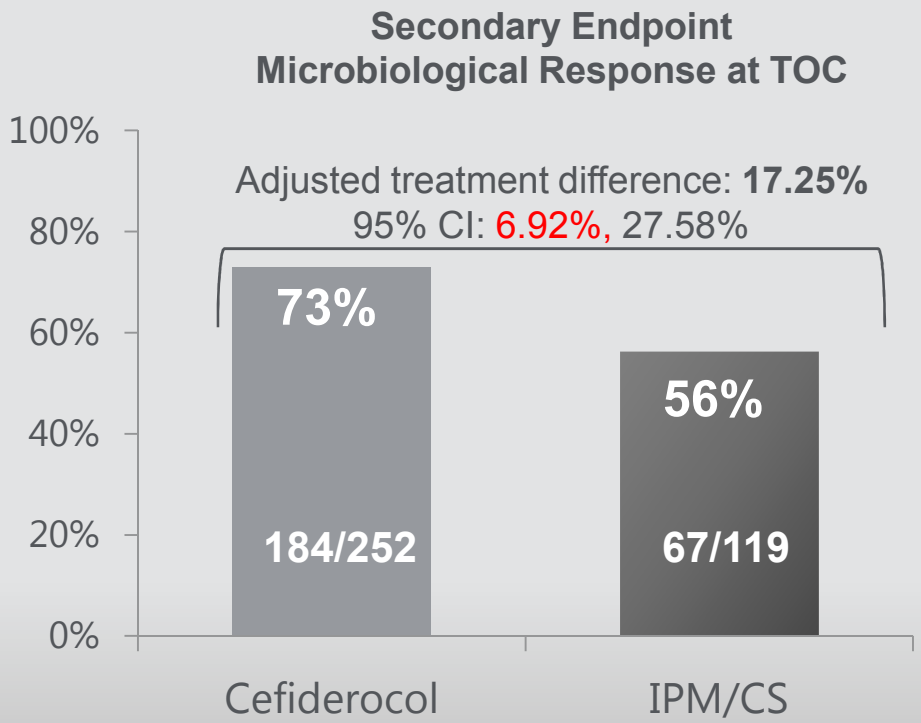
APEKS-cUTI Primary and Secondary Endpoints





Treatment difference (cefiderocol minus IPM/CS) is the adjusted estimate of the difference in the responder rate between the 2 treatment arms. The adjusted difference estimates and the 95% CIs (2-sided) are calculated using a stratified analysis with Cochran-Mantel-Haenszel weights based on the stratified factor at baseline (cUTI with or without pyelonephritis vs acute uncomplicated pyelonephritis).

Portsmouth S et al. Lancet Infect Dis 2018. Published online Oct 25 2018

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cUTI Study: AEs With an Incidence >2% in Each Group

AE Incidence >2.0% in Safety Population	Cefiderocol (N=300)	Imipenem/Cilastatin (N=148)	Total (N=448)
Diarrhea	13 (4%)	9 (6%)	22 (5%)
Hypertension	13 (4%)	8 (5%)	21 (5%)
Constipation	10 (3%)	6 (4%)	16 (4%)
Infusion site pain	9 (3%)	5 (3%)	14 (3%)
Headache	7 (2%)	8 (5%)	15 (3%)
Nausea	7 (2%)	6 (4%)	13 (3%)
Cough	7 (2%)	1 (1%)	8 (2%)
Vomiting	6 (2%)	2 (1%)	8 (2%)
Hypokalemia	5 (2%)	4 (3%)	9 (2%)
Insomnia	4 (1%)	3 (2%)	7 (2%)
Renal cyst	4 (1%)	5 (3%)	9 (2%)
Infusion site erythema	3 (1%)	3 (2%)	6 (1%)
Abdominal pain upper	2 (1%)	5 (3%)	7 (2%)
Cardiac failure	2 (1%)	3 (2%)	5 (1%)
Clostridium difficile colitis*	1 (<1%)	4 (3%)	5 (1%)
Vaginal infection	1 (<1%)	3 (2%)	4 (1%)

*An additional adverse event with the preferred term of *C.difficile* infection was reported in the imipenem-cilastatin group.

Portsmouth S et al. Lancet Infect Dis 2018. Published online Oct 25 2018

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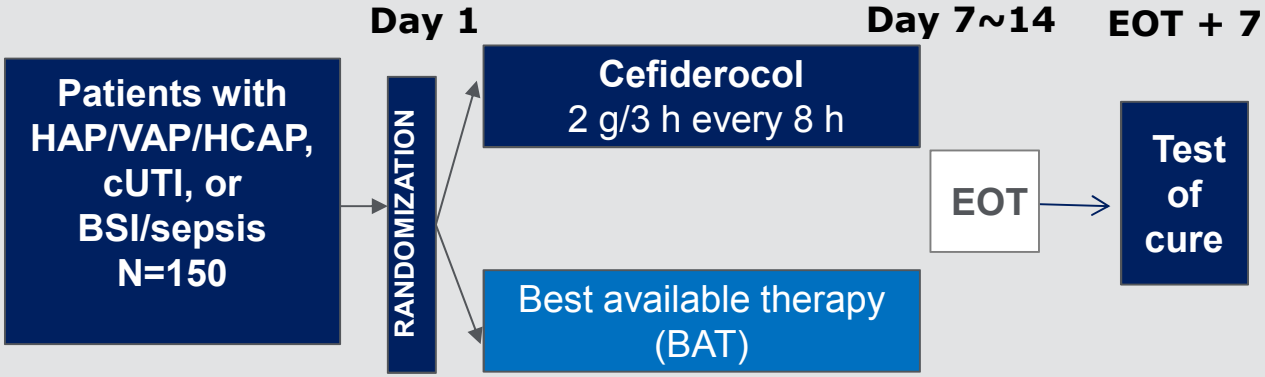
CREDIBLE-CR: Cefiderocol Treatment of Severe Infections Caused by Carbapenem-Resistant Gram-Negative Pathogens

- Multicenter, randomized, open-label, parallel-group phase 3 efficacy trial in adult patients with carbapenem-resistant Gram-negative pathogens



Key Inclusion: Documented infection caused by GN pathogen with evidence of CR; Prior treatment with antibiotics and failure (clinical and microbiological)

Key Exclusion:
Need for >3 systemic antibiotics for BAT; Co-infection with invasive fungal infection; CNS infection; Need for >3 weeks antibiotic therapy; Neutropenia; Refractory Septic Shock, APACHE II>30

Primary Endpoints

- Clinical outcome per patient at test of cure (TOC) in patients with HAP/VAP/HCAP or BSI/sepsis
- Microbiological outcome (for Gram-negative pathogen) per patient at TOC in patients with cUTI

BAT, best available therapy; BSI, bloodstream infection; cUTI, complicated urinary tract infection; EOT, end of treatment; HAP, hospital-acquired pneumonia; HCAP, health care-associated pneumonia; TOC, test of cure; VAP, ventilator-associated pneumonia.

ClinicalTrials.gov. https://clinicaltrials.gov/ct2/show/NCT02714595. Updated August 10, 2017. Accessed March 20, 2018.

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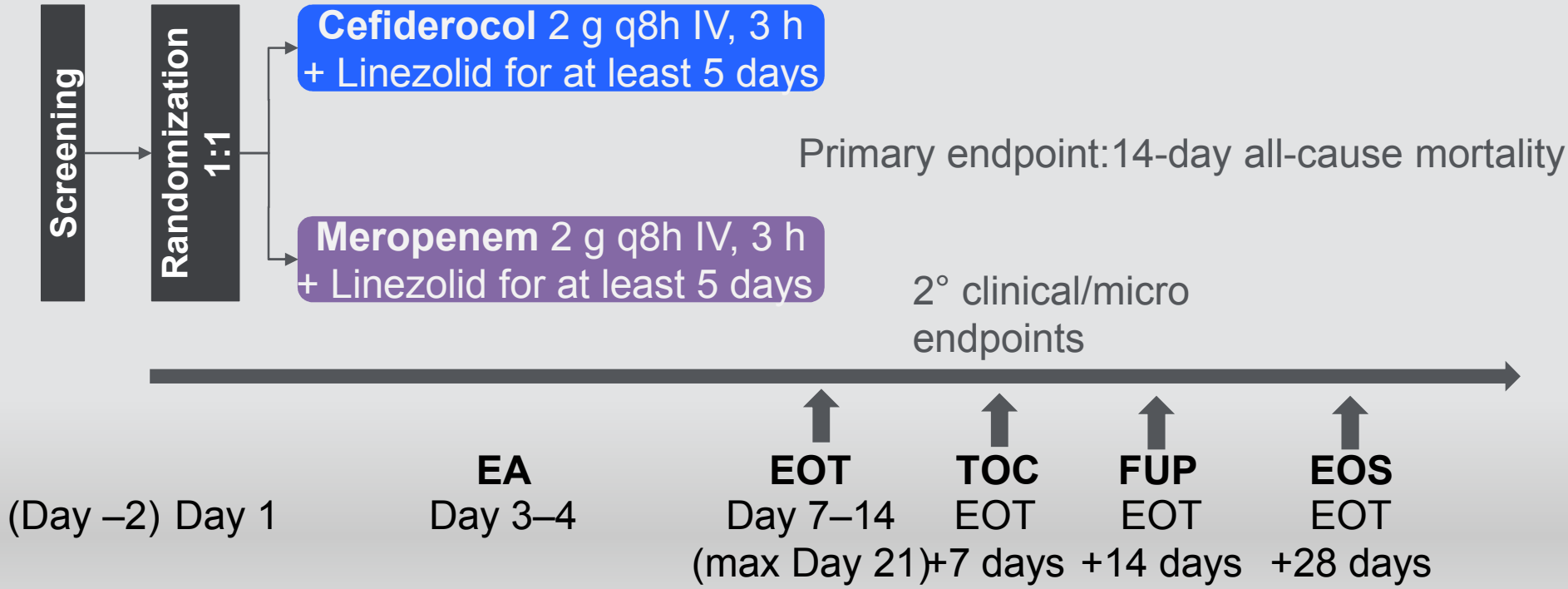
APEKS-NP: Schematic Randomization and Treatment Arms



EA, early assessment; EOS, end of study; EOT, end of therapy; FUP, follow-up; IV, intravenous; LZD, linezolid; TOC, test of cure.

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APEKS-NP: Baseline Characteristics and Demographics in the ITT Population

Characteristics	Cefiderocol N=148	Meropenem N=150
Age, years		
• Mean (SD)	64.7 (14.5)	65.6 (15.1)
Region, %		
• North America	4.1	4.0
• Europe	66.9	66.7
• Asia Pacific	29.1	29.3
Male sex, %	68.2	69.3
Clinical diagnosis, %		
• VAP	40.5	45.3
• HAP	40.5	40.7
• HCAP	18.9	16.0
Ventilation status at randomization, %	61.5	58.0
Creatinine clearance, mL/min		
• Mean (SD)	77.8 (55.1)	82.1 (56.2)
• >120 mL/min	14.9	17.3
• <30 mL/min	13.5	13.3
APACHE-II score		
• Mean (SD)	16.1 (6.1)	16.3 (6.9)

APACHE, Acute Physiology, Age, Chronic Health Evaluation; HAP, hospital-acquired pneumonia; HCAP, healthcare-associated pneumonia; SD, standard deviation; VAP, ventilator-associated pneumonia.

APEKS-NP Primary Endpoint: Day 14 ACM
Secondary endpoints Day 28 and EOS ACM

	Cefiderocol 2 g, q8h N=145	Meropenem 2 g, q8h N=146	Treatment difference 95% CI
Primary Endpoint			
Day 14	12.4%	11.6%	0.8 (–6.6; 8.2)
Secondary Endpoints			
Day 28	21.0%	20.5%	0.5 (–8.7; 9.8)
End of Study	26.8%	23.3%	3.6 (–6.3; 13.4)

ACM, all-cause mortality; CI, confidence interval; EOS, end of study.

ID Week 2019; Oct 2-6, 2019; Washington, DC

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Summary: Cefiderocol Role in Clinical Practice

- Indication: Adults with limited or no alternative treatment options for cUTIs including pyelonephritis caused by susceptible Gram-negative organisms
- *Mortality Imbalance → Acinetobacter* in the Credible-CR study
  - Warnings & Precautions
    - Increase in All-Cause Mortality in Patients with Carbapenem-Resistant Gram-negative Bacterial Infections: An increase in all-cause mortality was observed in FETROJA-treated patients compared to those treated with best available therapy. Reserve FETROJA for use in patients who have limited or no alternative treatment options for the treatment of cUTI
- Use as monotherapy:
  - cUTI and HAP/VAP: good clinical & micro outcomes with monotherapy
  - Credible-CR: 80+% monotherapy = good outcomes; *Acinetobacter combo??*
- Provisional susceptibility breakpoint ≤ 4 mg/L for Enterics, PSA, ACBN & Steno → Approval breakpoints not yet provided by FDA?
- sNDA for HABP/VABP indication

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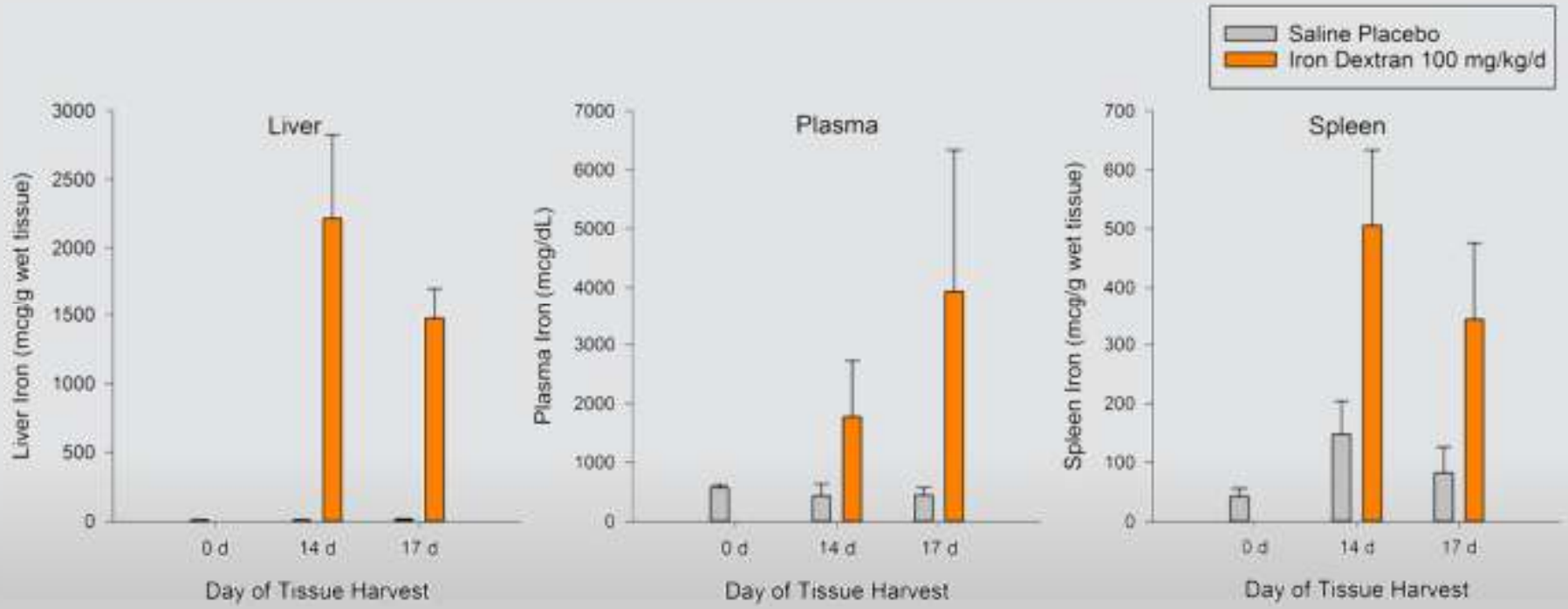
14 Days of Iron Dextran Vastly Increases Tissue Iron



Kidd JM, Abdelraouf K, Nicolau DP. Antimicrobial Agents Chemotherapy, In press

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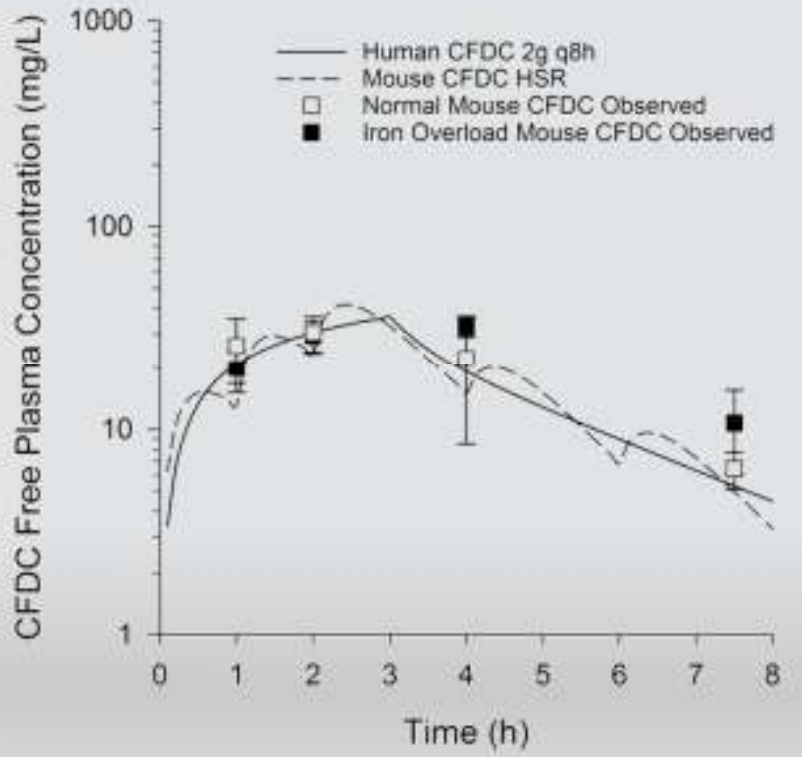
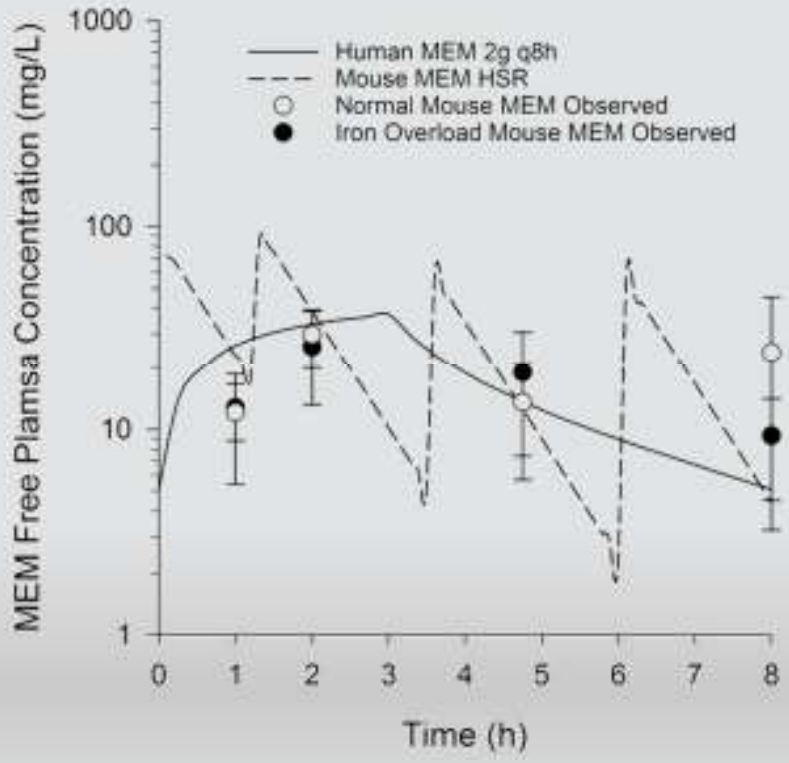
Iron Overload Does Not Alter PK of CFDC or MEM





CFDC: Cefiderocol
MEM: Meropenem
HSR: Human-Simulated Regimen

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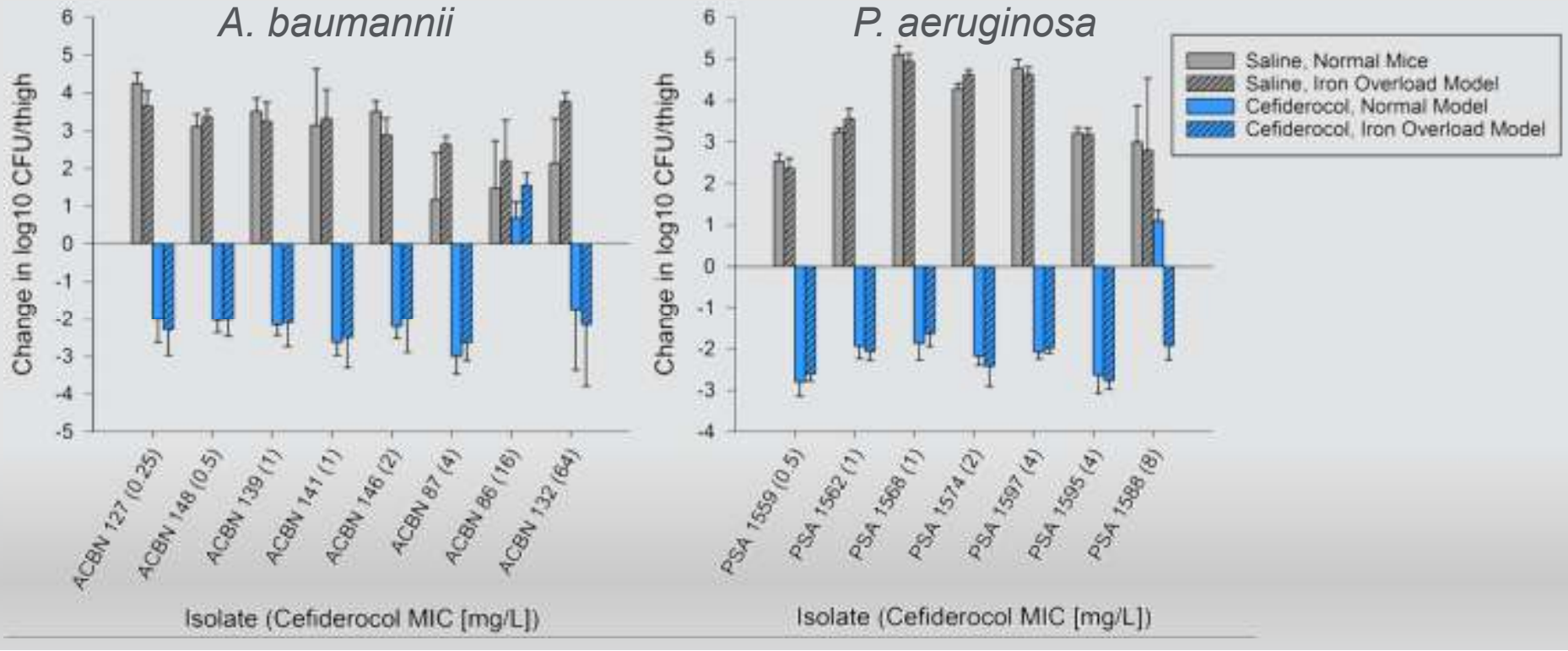
Cefiderocol Efficacy is Similar in Iron Overload and Normal Thigh Infection Models



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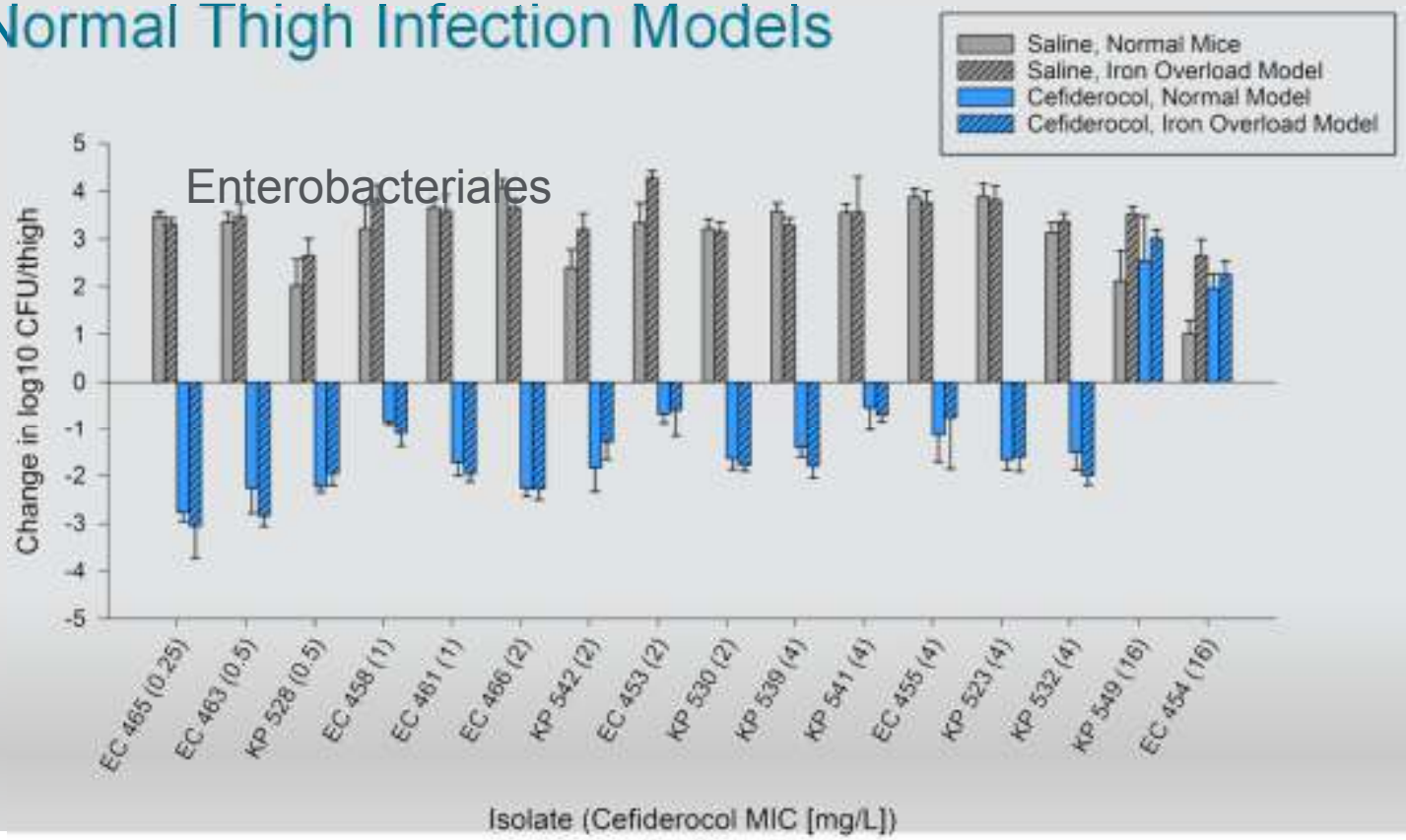

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