The Ohio State University
College of Pharmacy
Journal Club

Background and Overview	
Title	**APEKS-NP - Cefiderocol vs high-dose, extended-infusion meropenem for the treatment of Gram-negative nosocomial pneumonia: a randomized, double blind, phase 3 non-inferiority trial** *The Lancet Infectious Diseases* Impact factor 25.071
Funding Source	Shionogi COI: MA, YM, AM, and TDN are employees of Shionogi. RE is a consultant for Shionogi and received a consultancy fee for his services. RGW has served as a consultant for Shionogi and Merck. MK is supported by the Barnes-Jewish Hospital Foundation and has received consultancy fees from Shionogi. J-FT has received honoraria for participating in advisory boards for Pfizer, Merck, MedImmune, Paratek, Nabriva, Bayer, and Gilead, and for lectures for Pfizer, Merck, Biomérieux, and Brahms; and has also received research grants from Merck, Pfizer, 3M, and Gilead. JMP has served as a consultant for Shionogi, Merck, and Qpex. KSK has served as a consultant for Shionogi, Melinta, Merck, and Qpex. MZ has received honoraria from Shionogi. AFS has received research grants from Merck and Tetraphase, and speaker or consultancy fees from Merck, Pfizer, Melinta, Shionogi, and Tetraphase. PC declares no competing interests.
Introduction/Background	Multi-drug resistant (MDR) pathogens are a growing concern in the hospital setting leading to higher mortality rates if treatment is delayed or ineffective. Gram negative bacteria such as *Klebsiella pneumoniae, Pseudomonas aeruginosa, Acinetobacter baumannii,* and *Escherichia coli* are among some of the more common MDR pathogens found in ICU settings. Gram negative pathogens have an arsenal of resistance mechanisms such as extended spectrum B-lactamase (ESBL) Enterobacterales, carbapenemase-producing Enterobacterales (CRE), and Klebsiella pneumonia carbapenemase (KPC) to name a few. There is a need for antimicrobials with a novel mechanism of action to combat these MDR pathogens in critically ill patients. Cefiderocol is a siderophore cephalosporin with a novel mechanism of action. Cefiderocol chelates an iron molecule and uses it to enter the iron transport channel on the outer membrane of gram-negative bacteria. Once in the periplasmic space, it can then inhibit the penicillin binding proteins stopping the synthesis of the peptidoglycan cell wall. Cefiderocol does not have any activity against gram-positive or anaerobic pathogens.

	This novel antibiotic is now the target of a multitude of studies to find the spectrum of activity amongst the MDR gram-negative pathogens. The CREDIBLE-CR study looked at cefiderocol in MDR pathogens similar to this study and found similar efficacy compared to best available therapy. However, a higher mortality in the *Acinetobacter* subgroup was found. APEKS-cUTI found that cefiderocol was non-inferior to imipenem-cilastatin in the treatment of MDR gram-negative bacteria in complicated UTI infections. This leads to the objective of this study, comparing the efficacy of cefiderocol to meropenem in patients with nosocomial pneumonia (HAP/VAP/HCAP) who are at risk for MDR gram-negative bacteria.
Methods	
Study Design	Type of study • This was a multicenter, phase 3, randomized, controlled, double-blind, parallel group, non-inferiority trial Objectives • Compare efficacy and safety of cefiderocol vs high dose extended infusion meropenem in patients with nosocomial pneumonia (HAP/VAP/HCAP) caused by gram-negative bacteria. Outcomes • **Primary:** All-cause mortality at day 14 • **Secondary:** Superiority of cefiderocol over meropenem in all-cause mortality at day 14; all-cause mortality at day 28; changes from baseline in SOFA and CPIS; test of cure 7 days plus or minus 2 days after end of treatment Interventions • 3-hour IV infusion of 2 g cefiderocol or 3-hour IV infusion 2 g of meropenem every 8 hours for 7-14 days. Could go up to 21 days based on patient assessment • If creatinine clearance >120 ml/min, cefiderocol dose adjusted to 2 g every 6 hours • All patients received IV linezolid 600 mg every 12 hours for at least 5 days for gram positive (MRSA) coverage Length of study • 7-14 day duration, up to 21 days • Between October 23, 2017 to April 14, 2019 Microbiology collection assessments • Respiratory specimens were collected by mini bronchoalveolar lavage, specimen brush, endotracheal aspirate, or expectorated sputum • Two blood samples from separate punctures obtained within 48 hours before first dose of study treatment • Assessment and susceptibility of all species done at local laboratory for identification, and a central laboratory for species confirmation
Study Population	Patients enrolled at 76 sites in 17 countries • In Asia, Europe, and USA Treatment was randomized by an interactive response technology to which treatment has already been randomly assigned by the system provider. Randomization was stratified by APACHE II scores and infection type, either HAP, VAP, or HCAP caused by gram negative bacteria. • Treatments were prepared by an unmasked pharmacist who knew the drug assignment for the antibiotic infusion bags

	• The investigator, site personnel, sponsor, and other designees involved in monitoring, data management, and the patients were masked to the treatment assignment **Inclusion criteria:** Patients ≥18 years old with acute bacterial pneumonia determined to be HAP, VAP, or HCAP. Criteria for those diagnoses were in accordance with the FDA guidelines. Gram negative bacterial infections eligible were of the lower respiratory tract within 72 hours of admission. Risk factors that had enrolled patients were previous antibiotic use or logical epidemiological evidence of gram-negative outbreak, or those that did not respond to antibiotics within 2 calendar days **Exclusion criteria:** Community acquired, atypical, or viral pneumonia; chemical pneumonitis; known carbapenem resistant pathogen at time of randomization; an APACHE II score of more than 35; refractory septic shock; concomitant mold infection, cystic fibrosis, bronchiectasis, and concomitant CNS infection
Statistical Analysis	**Power:** A sample of at least 244 randomized patients (122 in each group) was estimated to provide 90% power with a one-sided significance level of 0.025. With an estimated non-evaluable rate of 20%, 300 patients were randomized • In agreement with the FDA, a 12.5% non-inferiority margin was set for all-cause mortality for the upper boundary of the two-sided 95% CI • If the upper limit of the 95% CI for the difference between Cefiderocol mortality – Meropenem Mortality was less than 12.5%, non-inferiority could be concluded • Cochran-Mantel-Haenszel (CMH) method was used to adjust the difference in mortality between cefiderocol and meropenem groups based on infection diagnosis (HAP/VAP/HCAP) and APACHE II score • The CMH method tests for an association between an exposure and an outcome and adjusting for cofounding variables ○ Exposure to antibiotic and mortality, while adjusting for type of pneumonia and disease severity (APACHE II score)
Results	
Results of Study	**298 patients** randomized in ITT population>>**292** in modified ITT (mITT) population met inclusion criteria and received at least one dose of study drug, excluding gram positive infections>>**206** in microbiological evaluable per-protocol (ME-PP) population included mITT without a major protocol violation and with culture-confirmed diagnosis of gram-negative bacteria.

	Cefiderocol (n=145)	Meropenem (n=147)
Sex		
Male	99 (68%)	101 (69%)
Female	46 (32%)	46 (31%)
Age (years)		
Mean (SD)	64·6 (14·6)	65·4 (15·1)
≥65	80 (55%)	89 (61%)
≥75	40 (28%)	44 (30%)
Body-mass index (kg/m²)	26·4 (6·1)	26·7 (6·9)
Region		
Europe	99 (68%)	98 (67%)
Asia-Pacific	40 (28%)	43 (29%)
North America	6 (4%)	6 (4%)
Race		
White	102 (70%)	98 (67%)
Asian	41 (28%)	43 (29%)
Other or missing	2 (1%)	6 (4%)
Clinical diagnosis		
VAP	59 (41%)	64 (44%)
HAP	59 (41%)	60 (41%)
HCAP	27 (19%)	23 (16%)
Ventilated at randomisation		
VAP*	58/59 (98%)	63/64 (98%)
HAP	22/59 (37%)	21/60 (35%)
HCAP	9/27 (33%)	2/23 (9%)
Creatinine clearance (mL/min)		
Mean (SD)	78·5 (55·4)	82·7 (56·6)
>120	22 (15%)	26 (18%)
>80 to 120	33 (23%)	35 (24%)
>50 to 80	43 (30%)	35 (24%)
30–50	27 (19%)	31 (21%)
<30	20 (14%)	20 (14%)
Empirical treatment failure	48 (33%)	47 (32%)
Previous therapy		
Antibiotics†	105 (72%)	101 (69%)
Carbapenems	11 (8%)	10 (7%)
Systemic corticosteroids	61 (42%)	39 (27%)
Medical history by preferred term, ≥15% in either treatment group‡		
Diabetes	46 (32%)	36 (24%)
Chronic obstructive pulmonary disease	39 (27%)	31 (21%)
Hypertension	94 (65%)	102 (69%)
Atrial fibrillation	33 (23%)	38 (26%)
Cardiac failure	32 (22%)	41 (28%)
Coronary artery disease	24 (17%)	18 (12%)
Myocardial ischaemia	18 (12%)	26 (18%)
Hypokalaemia	26 (18%)	24 (16%)
Anaemia	28 (19%)	27 (18%)

	Cefiderocol (n=145)	Meropenem (n=147)
(Continued from previous column)		
In ICU at randomisation	102 (70%)	97 (66%)
APACHE II score		
Mean (SD)	16·0 (6·1)	16·4 (6·9)
≤15	74 (51%)	76 (52%)
16–19	31 (21%)	25 (17%)
≥20	40 (28%)	46 (31%)
CPIS score		
Overall	5·4 (1·7)	5·2 (1·9)§
Ventilated patients¶	5·9 (1·6)	5·8 (1·9)
Non-ventilated patients¶	4·7 (1·7)	4·2 (1·4)
SOFA score		
Overall	4·7 (3·0)	4·9 (3·4)§
Ventilated patients‖	6·1 (2·8)	6·3 (3·1)
Non-ventilated patients‖	2·6 (2·0)	2·8 (2·6)
Severity of disease**		
Mild	4 (3%)	7 (5%)
Moderate	70 (48%)	91 (62%)
Severe	71 (49%)	49 (33%)

Table 1: Baseline characteristics of the modified ITT population (from APEKS-NP)

Klebsiella pneumoniae – 32% (92/292)

Pseudomonas aeruginosa – 16% (48/292)

Acinetobacter baumannii – 16% (47/292)

Escherichia coli – 14% (41/292)

Baseline characteristics: cefiderocol mITT = 145, meropenem mITT = 147

Results:

- **Primary outcome:** All-cause mortality at day 14 in mITT population was 12.4% for cefiderocol (18/145) and 11.6% for meropenem (17/146) **(adjusted difference 0.8%, 95% CI -6.6 to 8.2; p=0.002)**
- **Secondary Outcomes:**
  - All-cause mortality at day 28 was 21.0% for cefiderocol (30/143) and 20.5% for meropenem (30/146) **(adjusted difference 0.5%, 95% CI -8.7 to 9.8)**
  - Superiority of cefiderocol to meropenem could not evaluated in the protocol-specified multiplicity strategy that was used
  - Changes from baseline in CPIS and SOFA score were similar in the mITT population in the cefiderocol and meropenem groups
  - Treatment emergent adverse events (TEAEs) such as UTI, hypokalemia, and diarrhea were similar in both groups
  - Clinical test of cure for cefiderocol was 65% (94/145), and 67% (98/147) for meropenem **(adjusted difference -2.0, 95% CI -12.5 to 8.5)**
  - Serious adverse events occurred in 36% (54/148) of cefiderocol patients and 30% (45/150) of meropenem patients.
  - Subgroup analysis: 19% (56/292) of patients with isolates of meropenem MIC>8 ug/mL, test of cure was 57% (17/30) in cefiderocol group compared with 58% (15/26) in meropenem group at the end of therapy

Authors' Conclusion	• Cefiderocol monotherapy was non-inferior to high dose, extended infusion time meropenem monotherapy in 14-day all-cause mortality in critically ill patients with nosocomial pneumonia • Cefiderocol was well tolerated, and its safety profile was similar to meropenem in this study • Cefiderocol might be an option for nosocomial pneumonia in patients who are at high risk of MDR gram negative bacteria
Student's Discussion and Conclusion	

Strengths/Limitations	• Study met power: 292 patients included in final modified ITT population; 244 evaluable patients required to have 90% power
	• Study design was a good snapshot of a clinically relevant population with different types of nosocomial pneumonia due to gram negative pathogens
	• Publishing bias: the manufacturer of cefiderocol funded the trial, study authors received financial support from the manufacturer for their work
	• Internal and external validity
	  o Internal: randomized, double-blind, multicenter trial; confirmation of species, susceptibility pattern and characterization for B-lactam antibiotic resistance were confirmed as a central laboratory along with the local laboratory
	  o External: excluding critically ill patients (APACHE II > 35), excluding carbapenem resistant infections, cystic fibrosis, and non-gram-negative infections
	• Limitations:
	  o Bronchoalveolar lavage not required for diagnosis of pneumonia, which may have improved identification of pathogens
	  o Subgroup analyses and secondary outcomes were not adequately powered to draw conclusive treatment comparisons
	  o Linezolid use for gram-positive and MRSA coverage not applicable to all practice sites, vancomycin being the usual DOC empiric coverage
	  o Difficult to define a role for cefiderocol, regardless of meropenem susceptible or resistant, mortality was similar between them
	  o Exclusion of known carbapenem resistance pathogens while good for the non-inferiority design, skews what clinicians would see in clinical practice

Conclusion/ Recommendations for practice site	• Cefiderocol was found non-inferior to extended infusion meropenem as empiric monotherapy over 14 days in nosocomial pneumonia • Patients who are critically ill and have risk factors for MDR nosocomial pneumonia may benefit from using empiric cefiderocol for a 14 to 21-day course • Depending on the site specific antibiogram, if there is a high prevalence of MDR bacteria, the addition of cefiderocol may be beneficial as an alternative option, or last line, along with the others in the carbapenem class • Additional studies looking at cefiderocol in meropenem resistant gram-negative (MIC>8 ug/mL) bacteria, and further elucidating mechanisms

	of resistance to cefiderocol, would be beneficial to determine place in therapy
Glossary	HAP = hospital acquired pneumonia VAP = ventilator acquired pneumonia HCAP = health care associated pneumonia APACHE II = acute physiology and chronic health evaluation II SOFA = sequential organ failure assessment score CPIS = clinical pulmonary infection score ITT = intention to treat mITT = modified intention to treat ME-PP = microbiologically evaluable per protocol TEAE = treatment emergent adverse events
References	1. Wunderink RG, Matsunaga Y, Ariyasu M, et al. Cefiderocol versus high-dose, extended-infusion meropenem for the treatment of Gram-negative nosocomial pneumonia (APEKS-NP): a randomised, double-blind, phase 3, non-inferiority trial. *Lancet Infect Dis*. 2021;21(2):213-225. doi:10.1016/S1473-3099(20)30731-3 2. Bassetti M, Echols R, Matsunaga Y, et al. Efficacy and safety of cefiderocol or best available therapy for the treatment of serious infections caused by carbapenem-resistant Gram-negative bacteria (CREDIBLE-CR): a randomised, open-label, multicentre, pathogen-focused, descriptive, phase 3 trial. *Lancet Infect Dis*. 2021;21(2):226-240. doi:10.1016/S1473-3099(20)30796-9 3. El-Lababidi RM, Rizk JG. Cefiderocol: A Siderophore Cephalosporin. *Ann Pharmacother*. 2020;54(12):1215-1231. doi:10.1177/1060028020929988 4. Portsmouth S, van Veenhuyzen D, Echols R, et al. Cefiderocol versus imipenem-cilastatin for the treatment of complicated urinary tract infections caused by Gram-negative uropathogens: a phase 2, randomised, double-blind, non-inferiority trial. *Lancet Infect Dis*. 2018;18(12):1319-1328. doi:10.1016/S1473-3099(18)30554-1