Impact of Publications on Clinical Care and Research of Antibacterial Drugs

Lindsey R. Baden, MD
Brigham and Women's Hospital, Dana-Farber Cancer Institute
Harvard Medical School
New England Journal of Medicine

FDA-IDSA-Pew-NIAID Meeting
November 18, 2019

Constituencies (6Ps)

- Practitioner
- Producer (Developer/Investigator)
  - `Purveyor (Investor)
- Permission grantor (Regulator)
- Patient

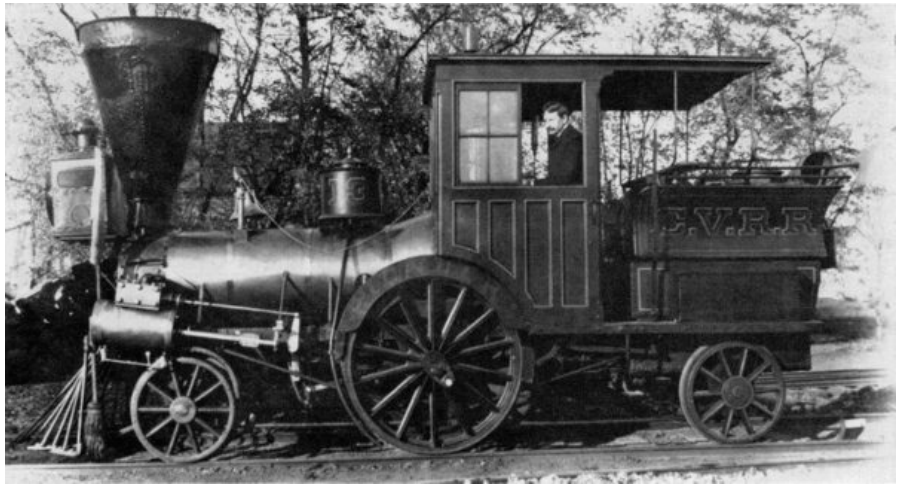
- Publisher

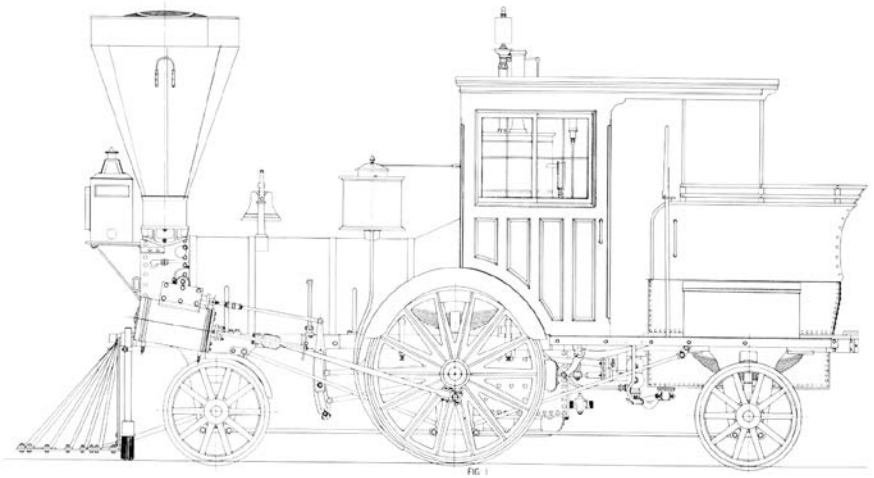
New Findings

Frame of Reference on New Therapies/Data

- Practitioner
  - My patients are all different
  - I am treating patients with more complex illnesses
  - Do these data help me take care of this patient
- Producer
  - How do we identify signals of activity and safety efficiently
  - The population under study needs to be uniform
  - Do we have the most informative endpoint(s)
    - In a relevant timeframe
- Permission giver (Regulator)
  - Do these data meet the regulatory standard
    - Is evidence of substantial efficacy demonstrated for the condition
    - Which outweighs any safety concerns
- Patient
  - Will this help me
- Publisher
  - What do the new data teach us
  - How do they advance the art

Truth





Major Challenges in Identifying ‘Truth’

- Human biology is complex
  - More complex illnesses and concomitant treatments
  - Identifying kinetically relevant endpoints that are measurable
  - Differential activity in different patient populations
- Many conditions the need is great
  - Urgency for many
- Bias
  - Financial, reputational, academic, hope, belief
- Play of chance
  - $p<0.05$ = truth!?

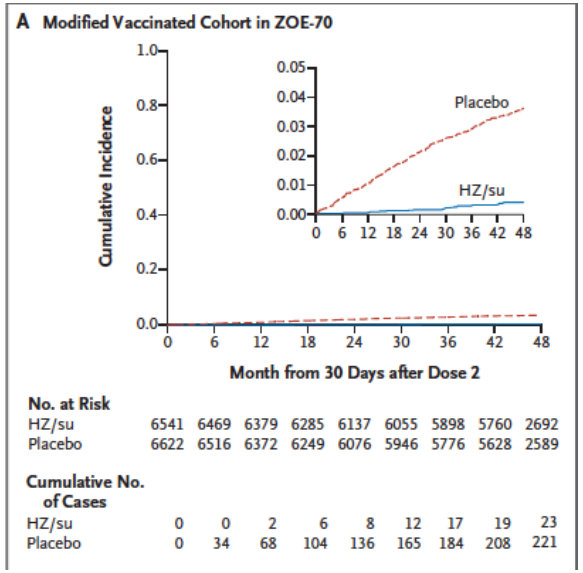
Mission of Journals

- **Find the best work**
- **Report it dispassionately**
- **Help to advance medical science**
- **Help to improve patient care**

- **Rigorous Peer Review**
  - Associate/Deputy Editors
  - Content/Methods Experts
  - Editorial Board Meeting
  - Statistical Review
  - If favorable →Revision

  - Post Acceptance (Content and Form)
    - Manuscript editing
    - Fact checking
    - Graphic arts creation
    - Proofing

- **Intrinsic Tensions**
  - Authors and sponsors want to present their data in the best possible light and have it make the maximal impact
  - We have to be sure that results are honestly presented and interpreted and adverse effects fully disclosed



We Like Work That is Likely to be Accurate

- Sound methodology
  - Participants appropriate, well defined
  - Careful data collection process with well defined exposures and outcomes
  - Adequate power
  - Analyses appropriate
  - Potential biases considered, minimized, and acknowledged

Important *Informative* *Innovative* *Accurate* *Ethical*

Issues and Implications

- Occasional issues
  - The data have not been analyzed according to the study design
  - The design favors which type of outcome…
    - ITT, MITT, micro-MITT, PP
    - Does it matter if superiority or non-inferiority
  - Only selective data are presented
  - The conclusions don’t follow from the data
- *The p-value!*

Clarity: What Publications Can and Cannot Do

- Publications are different than regulatory review and determinations
  - Independent processes which may have different findings
- Publications allow and facilitate community awareness and debate/discussion of the findings
- Provide independent expert (and statistical) review including on the totality of the data and implications for the field
- Data presentation and interpretation relevant to the readership
- Publications/publishers do not make corporate decisions

Three Recent Examples

- Plazomicin
- Cefiderocol
- Inhaled amikacin

Case 1: Plazomicin for cUTI

NDA 210303, AMDAC Meeting May 2, 2018

- Phase 3 cUTI Trial: RCT, NI – margin 15%), plazomicin 15mg/kg IV q24 compared to meropenem
- ≥4days blinded IV Rx then option to switch to open label levo for 3-6 more days
- 1ary: Composite of microbial eradication and clinical cure rate in the microbiological modified ITT population at D5 and TOC visits
- Dose adjustment based on CrCl not TDM
- MITT n=306 P and 301 M
  - mMITT: n=191 P and 197 M
    - D5: -3.4 (-10.0, 3.1), TOC 11.6 (2.7, 20.3)

Table 2. Primary and Additional Efficacy End Points (Microbiologic Modified Intention-to-Treat Population).*

Time of Assessment and End Point	Plazomicin (N=191)	Meropenem (N=197)	Difference (95% CI)†
	number (percent)		*percentage points*
Day 5			
Primary end point: composite cure at day 5	168 (88.0)	180 (91.4)	−3.4 (−10.0 to 3.1)
Clinical cure	171 (89.5)	182 (92.4)	−2.9 (−9.1 to 3.3)
Microbiologic eradication	188 (98.4)	193 (98.0)	0.5 (−3.1 to 4.1)
End of intravenous therapy			
Composite cure	179 (93.7)	187 (94.9)	−1.2 (−6.5 to 4.0)
Clinical cure	184 (96.3)	190 (96.4)	−0.1 (−4.6 to 4.3)
Microbiologic eradication	186 (97.4)	192 (97.5)	−0.1 (−4.1 to 3.9)
Test-of-cure visit			
Primary end point: composite cure at 15 to 19 days after start of therapy	156 (81.7)	138 (70.1)	11.6 (2.7 to 20.3)
Clinical cure	170 (89.0)	178 (90.4)	−1.4 (−7.9 to 5.2)
Microbiologic eradication	171 (89.5)	147 (74.6)	14.9 (7.0 to 22.7)
Late follow-up‡			
Composite cure	147 (77.0)	119 (60.4)	16.6 (7.0 to 25.7)
Sustained clinical cure§	169 (88.5)	168 (85.3)	3.2 (−4.0 to 10.3)
Sustained eradication¶	161 (84.3)	128 (65.0)	19.3 (10.4 to 27.9)
Clinical relapse	3 (1.6)	14 (7.1)	Not calculated
Microbiologic recurrence‖	7 (3.7)	16 (8.1)	Not calculated

* Composite cure was defined as clinical cure and microbiologic eradication. Clinical cure was defined as a reduction in severity (at day 5 and at the end of intravenous therapy) or complete resolution (at the test-of-cure visit) of all core symptoms with no new symptoms or as a return to the patient's status before development of the urinary tract infection (UTI). Microbiologic eradication was defined as a reduction in the baseline uropathogen from 10^5 colony-formin units (CFU) or more per milliliter to less than 10^4 CFU per milliliter.

† Confidence intervals were calculated with the use of the Newcombe method with continuity correction and were not corrected for multiple comparisons.

Florian ME et al. *NEJM* 2019 380:729-40

Plazomicin: cUTI

- Key subgroups
  - Including 12-13% w/ bacteremia
- Baseline pathogens: ~100 ESBL, ~100 aminoglycoside nonsusceptible
- Reduced microbiologic recurrence (4 vs 8%) and clinical relapse (2 vs 7%)

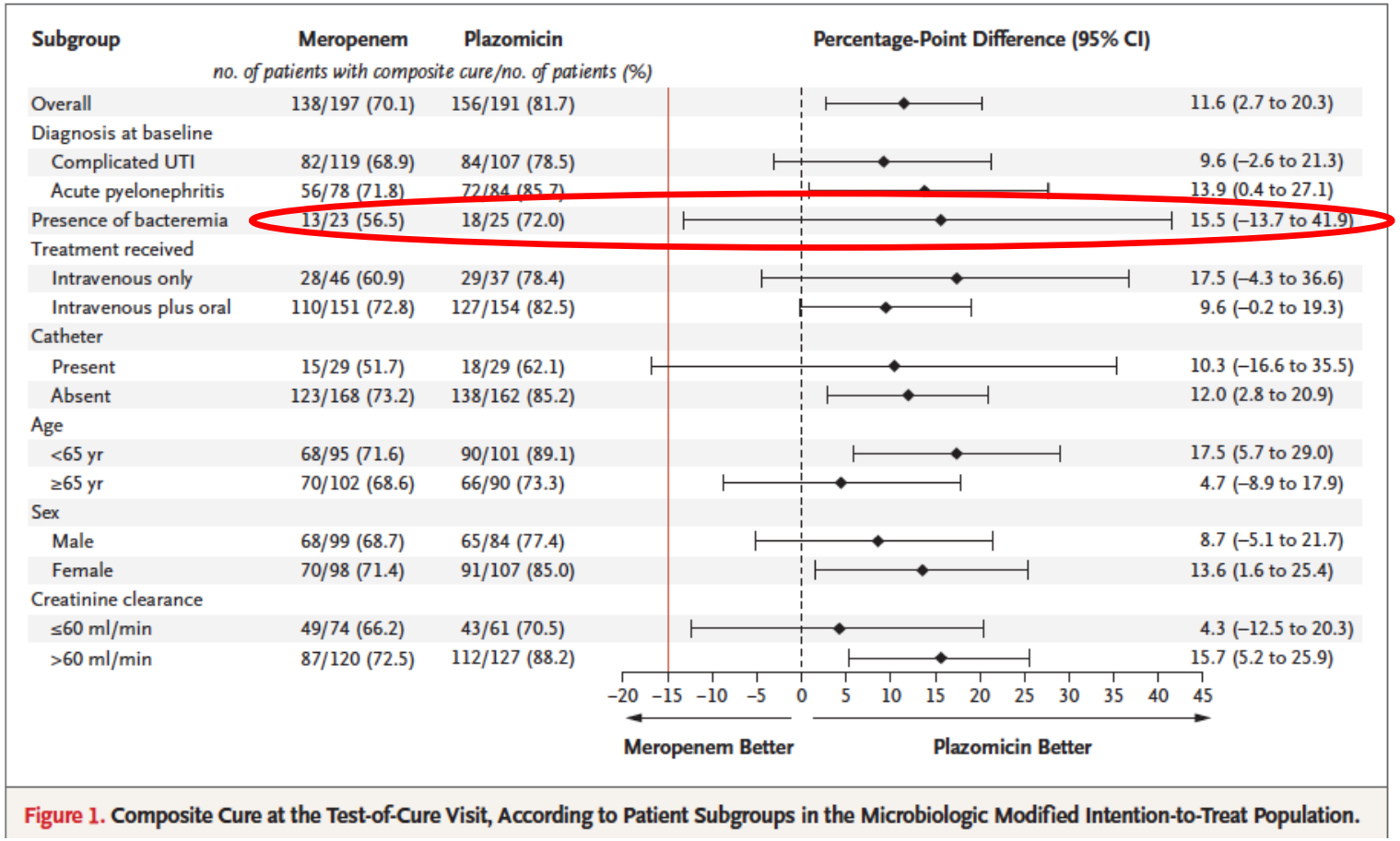


Figure 1. Composite Cure at the Test-of-Cure Visit, According to Patient Subgroups in the Microbiologic Modified Intention-to-Treat Population.

Florian ME et al. *NEJM* 2019 380:729-40

Table 3. Microbiologic Eradication at the Test-of-Cure Visit According to Pathogen (Microbiologic Modified Intention-to-Treat Population).*

Baseline Uropathogen	Plazomicin (N=191)	Meropenem (N=197)	Difference (95% CI)†
	no. of uropathogens eradicated/ total no. of uropathogens		*percentage points*
Enterobacteriaceae	177/198 (89.4)	157/208 (75.5)	13.9 (6.2 to 21.5)
Not susceptible to at least one aminoglycoside	41/52 (78.8)	35/51 (68.6)	10.2 (−8.1 to 27.8)
Not susceptible to amikacin	1/1 (100.0)	0/1	
Not susceptible to gentamicin	27/37 (73.0)	31/42 (73.8)	−0.8 (−21.8 to 19.7)
Not susceptible to tobramycin	36/44 (81.8)	32/45 (71.1)	10.7 (−8.6 to 29.0)
Not susceptible to any two aminoglycosides	22/29 (75.9)	28/36 (77.8)	−1.9 (−24.8 to 19.8)
Not susceptible to all three aminoglycosides	1/1 (100.0)	0/1	
Not susceptible to carbapenem‡	7/9 (77.8)	5/6 (83.3)	−5.6 (−46.3 to 44.7)
ESBL phenotype§	42/51 (82.4)	45/60 (75.0)	7.4 (−9.6 to 23.1)
Multidrug resistant¶	44/57 (77.2)	45/64 (70.3)	6.9 (−10.1 to 23.0)
Escherichia coli	120/128 (93.8)	106/142 (74.6)	19.1 (10.0 to 27.9)
Not susceptible to at least one aminoglycoside	20/23 (87.0)	16/26 (61.5)	25.4 (−2.4 to 48.3)
Not susceptible to amikacin	0/0	0/0	
Not susceptible to gentamicin	10/12 (83.3)	14/19 (73.7)	9.6 (−26.6 to 38.3)
Not susceptible to tobramycin	16/18 (88.9)	15/24 (62.5)	26.4 (−4.4 to 50.0)
Not susceptible to any two aminoglycosides	6/7 (85.7)	13/17 (76.5)	9.2 (−37.2 to 39.2)
Not susceptible to all three aminoglycosides	0/0	0/0	
Not susceptible to carbapenem‡	0/0	0/0	
ESBL phenotype§	18/20 (90.0)	19/28 (67.9)	22.1 (−5.7 to 44.0)
Multidrug resistant¶	19/23 (82.6)	21/33 (63.6)	19.0 (−8.0 to 40.8)
Klebsiella pneumoniae	27/33 (81.8)	32/43 (74.4)	7.4 (−13.9 to 26.5)
Not susceptible to at least one aminoglycoside	14/18 (77.8)	15/20 (75.0)	2.8 (−27.3 to 31.4)
Not susceptible to amikacin	1/1 (100.0)	0/1	
Not susceptible to gentamicin	12/16 (75.0)	13/18 (72.2)	2.8 (−29.7 to 33.5)
Not susceptible to tobramycin	14/18 (77.8)	14/18 (77.8)	0.0 (−29.8 to 29.8)
Not susceptible to any two aminoglycosides	12/16 (75.0)	12/16 (75.0)	0.0 (−32.2 to 32.2)
Not susceptible to all three aminoglycosides	1/1 (100.0)	0/1	
Not susceptible to carbapenem‡	0/0	1/1 (100.0)	
ESBL phenotype§	15/20 (75.0)	20/26 (76.9)	−1.9 (−29.7 to 24.1)
Multidrug resistant¶	15/20 (75.0)	18/24 (75.0)	0 (−28.3 to 26.9)
Proteus mirabilis	9/11 (81.8)	4/7 (57.1)	24.7 (−21.4 to 64.5)
Enterobacter cloacae	13/16 (81.3)	3/3 (100.0)	−18.8 (−46.3 to 51.6)

Table 4. Safety Analysis (Safety Population).*

Variable	Plazomicin (N=303)	Meropenem (N=301)
Patients with any adverse event — no. (%)	59 (19.5)	65 (21.6)
Adverse events reported in ≥1% of patients in the plazomicin group — no. (%)		
Diarrhea	7 (2.3)	5 (1.7)
Hypertension	7 (2.3)	7 (2.3)
Headache	4 (1.3)	9 (3.0)
Nausea	4 (1.3)	4 (1.3)
Vomiting	4 (1.3)	3 (1.0)
Hypotension	3 (1.0)	2 (0.7)
Adverse events related to renal function — no. (%)†	11 (3.6)	4 (1.3)
Adverse events related to cochlear or vestibular function — no. (%)‡	1 (0.3)	1 (0.3)
Patients with any serious adverse event — no. (%)§	5 (1.7)	5 (1.7)
Increase of ≥0.5 mg/dl in serum creatinine level — no./total no. (%)		
Any time during the trial¶	21/300 (7.0)	12/297 (4.0)
Onset during intravenous therapy‖	11/300 (3.7)	9/297 (3.0)
Full recovery at end of intravenous therapy**	6/11 (54.5)	4/9 (44.4)
Full recovery at last follow-up visit**	9/11 (81.8)	9/9 (100.0)
Onset after end of intravenous therapy	10/300 (3.3)	3/297 (1.0)

Florian ME et al. *NEJM* 2019 380:729-40

Plazomicin: Phase 3 BSI, HABP/VABP

- RCT, open-label, superiority of plazomicin (15mg/kg) vs colistin (5mg/kg) w/ CRE for 7-14 days
- Prior Abx up to 72 hours, concomitant tigecycline or meropenem OK
- 1ary – 28day mortality in mMITT
- Target n=286 patients w/ confirmed CRE
- Difficulty conducting trial
  - 1ary changed to include significant disease related complications
  - Stopped after 2 years due to difficulty enrolling (N=37 or 12.9% of planned)
  - 29 BSI, 8 HABP/VABP
  - Majority confirmed CRE, KPC
- Actual n=37 (12.9% target w/ 20 C , 17 P)
  - 28 day mortality: 10 (50%) C, 4 (24%) Plazo (−26% points; 95%CI, −55 to 6)
  - Time to clearance (days) of CRE 1.5 P, 6 C

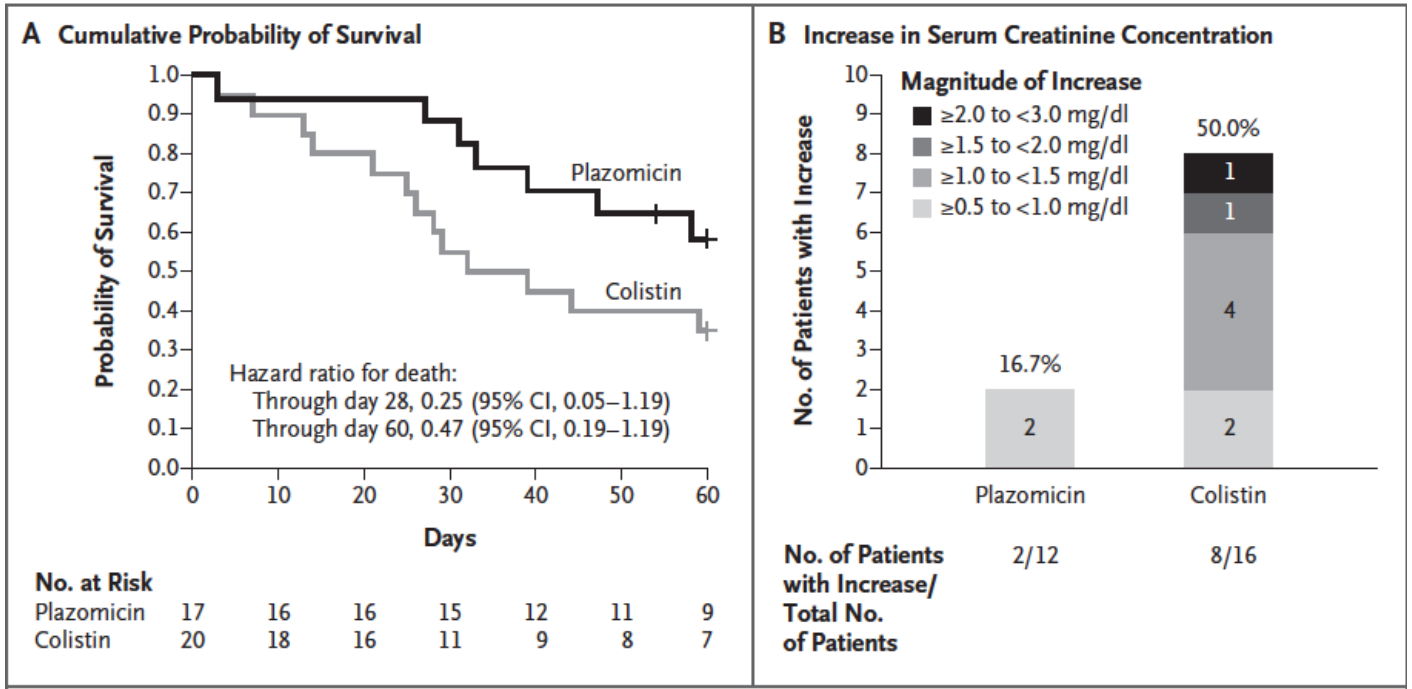


Figure 1. Results of a Definitive Combination-Therapy Regimen with Plazomicin or Colistin for Serious Infections Caused by Carbapenem-Resistant Enterobacteriaceae.

McKinnell JA et al. *NEJM* 2019 380:8

When Data are Published

- Published the research
  - Raising the potential risks and benefits with measures of certainty of the data
- Commentary
  - Raising discussion about these data and the antimicrobial field
- Letters to the Editor
  - Community discussion about the data

Case 2: Cefiderocol

NDA 209445, AMDAC October 16, 2019, Shionogi Inc.

- cUTI trial comparing cefiderocol to imipenem/cilastatin in patients with carbapenem-susceptible Gram-negative pathogens
- CREDIBLE-CR trial comparing cefiderocol to best available therapy (BAT) in patients infected with carbapenem-resistant pathogens across body sites
- Phase 3 trial in adults with nosocomial pneumonia due to carbapenem–susceptible Gram-negative pathogens (APEKS-NP)

Cefiderocol – cUTI

Micro-ITT Population

Study Endpoint	Cefiderocol (N/n (%))	Imipenem (N/n (%))	Treatment Difference (95% CI)
Composite Response	183/252 (72.6%)	65/119 (54.6%)	**18.6 (8.2, 28.9)**
Microbiologic Response	184/252 (73.0%)	67/119 (56.3%)	**17.3 (6.9. 27.6)**
Clinical Response	226/252 (89.7%)	104/119 (87.4%)	**2.4 (-4.7, 9.4)**

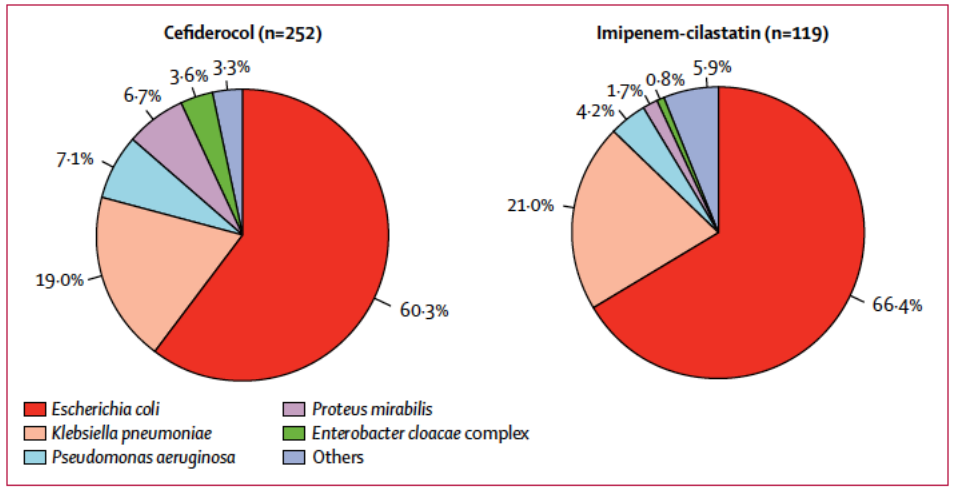


Figure 2: **Distribution of pathogens isolated at baseline**

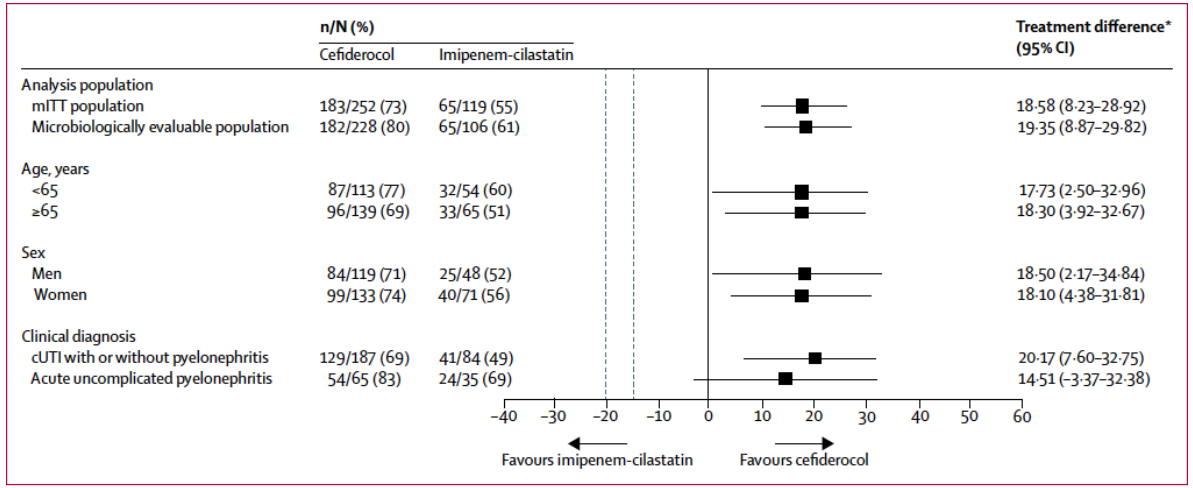


Figure 3: **Composite outcome at test of cure by predefined subgroups**
cUTI=complicated urinary tract infection. mITT=modified intention-to-treat. Dotted lines represent prespecified non-inferiority margins at –20% and –15%.
*Treatment difference was adjusted for stratification factors at baseline (cUTI with or without pyelonephritis vs acute uncomplicated pyelonephritis and region).

FDA AMDAC Meeting October 16, 2019 and Portsmouth S et al. *Lancet Inf Dis* 2018;18:1319-28

Cefiderocol – CREDIBLE-CR Trial

- 2:1 randomized trial cefiderocol vs BAT for CRE
  - For nosocomial cUTI, pneumonia, BSI
  - Colistin based regimen in most BAT

Mortality Data	Cefiderocol	BAT	Difference	95% CI
Overall				
Day 14	19/101 (18.8%)	6/49 (12.2%)	**6.6%**	-5.4% to 18.5%
Day 28	25/101 (24.8%)	9/49 (18.4%)	**6.4%**	-7.3% to 20.1%
Day 49	34/101 (33.7%)	10/49 (20.4%)	**13.3%**	-1.3% to 27.8%

FDA NEWS RELEASE

FDA approves new antibacterial drug to treat complicated urinary tract infections as part of ongoing efforts to address antimicrobial resistance

For Immediate Release: November 14, 2019

The U.S. Food and Drug Administration today approved Fetroja (cefiderocol), an antibacterial drug for treatment of patients 18 years of age or older with complicated urinary tract infections (cUTI), including kidney infections caused by susceptible Gram-negative microorganisms, who have limited or no alternative treatment options.

"Today's approval provides an additional treatment option for patients with cUTIs who have limited or no alternative treatment options," said John Farley, M.D., M.P.H., acting director of the Office of Infectious Diseases in the FDA's Center for Drug Evaluation and Research. "A key global challenge the FDA faces as a public health agency is addressing the threat of antimicrobial-resistant infections, like cUTIs. This approval represents another step forward in the FDA's overall efforts to ensure safe and effective antimicrobial drugs are available to patients for treating infections."

Case 3: Phase 3 Study of amikacin liposome inhalation suspension

Arikayce, NDA 207356, AMDAC August 7, 2018, Insmed

- Primary Finding
  - Culture conversion by month 6
    - ALIS+OBR n=65 (29.0%), OBR n=10 (8.9%); p<0.0001 (aOR 4.22 (95%CI 2.08, 8.57)
- Key Secondary Endpoint 6MWT in Meters
  - Month 6 mean (sd): ALIS+OBR 426 (135); OBR 423 (132)
    - Change from baseline to M6 (se): ALIS+OBR -10.4 (12.8); OBR -5.6 (13.9)
      - Difference (95%CI): -4.8 (-23.0, 13.5), p=0.61
    - In MAC culture
      - Converters vs non-converters: 16.8 vs -7.9
        - Converters: ALIS+OBR (n=63) 13.6 (60.5); OBR (n=9) 27.7 (42.7)
        - Non-converters: ALIS+OBR (n=104) -13.4 (68.0); OBR (n=94) 0.5 (74.9)
  - More hospitalizations (19 vs 13%) in ALIS+OBR group
    - Pneumonias, COPD exacerbations

Balancing Perspectives Over Time

- Data needed for regulatory approval
  - Ongoing data generation to inform practice
- Optimizing patient benefit
  - Continual reassessment as new data emerge
- Protecting community benefit
  - Unique aspect of antimicrobials (stewardship)
- Incentivizing the marketplace
  - Availability of agents
  - New development

Managing Information Flow

- Maintain the trust of the community

- New agents vs not so new agents
- New data
  - In progress, study complete
- Strength and completeness of the data
- Safety more complex than efficacy

- Information Dissemination
  - What do we know
  - When do we know it
  - Who curates it
  - Why share now
  - How do we share it and update it

Conclusion: Role of Publishers

Facilitate, Air, and Provoke Discussion from All Perspectives

- Provide factual (trust), interpretable (communicate) and relevant (complete/balanced) information
- Data mean different things depending on your point of view
  - Enable constructive, factual debate and discussion across perspectives
- Publish data which informs the understanding of risk-benefit
  - Pre- and post-registration studies which expand our understanding of activity for key conditions
  - Different role than the FDA (Regulatory approval, periodic update of the label, marketing)
  - Publish data as fully as possible
- Deal with the data we have
  - Not the data we wish we had (push the community to generate this)
- Inform all relevant stake holders
  - 6Ps
- Discuss issues impacting improving health
  - Economics, policy
  - Antimicrobials are different than other therapies

OUR GOAL

Find the best work
Report it dispassionately
Help to advance medical science
Help to improve patient care