New Antimicrobial Agents, Using Old Agents in New Ways and the Pipeline

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Disclosures

- Editor
  - ID Clinics of North America
  - Antimicrobial Agents and Chemotherapy
- Treasurer, Infectious Diseases Society of America
- Member, ID Board, American Board of Internal Medicine
- Voting Member, Presidential Advisory Council on Combating Antibiotic Resistant Bacteria (PACCARB)

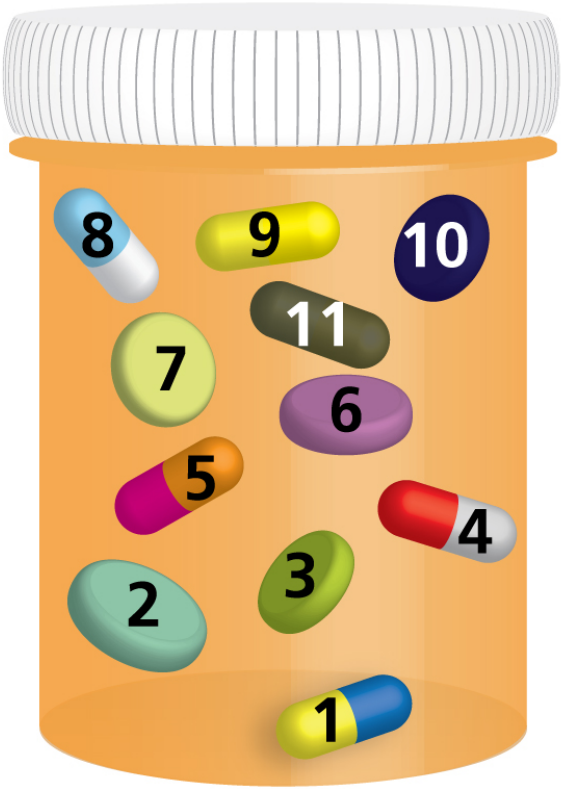
What's new?
Pew Development Pipeline June 2019

- 42 New antibiotics in development
  - > 89% small companies
  - 11 phase 1 - Not a good sign!
  - 13 phase 2
  - 13 phase 3
    - 60% likely to make it to FDA approval
- 16 + potential to treat G- ESKAPE pathogens
  - 11/16 + potential activity against carbapenem-resistant organisms
- 9 + potential to treat *N. gonorrhoeae* or *C. difficile*
- 1 in 4 = novel drug class or mechanism of action
- Initial indications: cUTI, cIAI, ABSSSI

Focus on systemically available antibiotics in phase 2 or beyond

https://www.pewtrusts.org/en/research-and-analysis/issue-briefs/2019/03/tracking-the-global-pipeline-of-antibiotics-in-development

Status of IDSA 10 x ‘20 Initiative



Bad Bugs Need Drugs

IDSA 10 x ‘20

Ten new ANTIBIOTICS by 2020

13 Lefamulin
Nabriva; Approved August 19, 2019

12 Imipenem/cilastatin+relebactam
Merck; Approved July 17, 2019

11 omadacycline
Paratek Pharmaceuticals; Approved: October 2, 2018

10 eravacycline
Tetraphase; Approved: August 28, 2018

9 plazomicin
Achaogen; Approved: June 26, 2018

8 meropenem/vaborbactam
The Medicines Company; Approved: August 30, 2017

7 delafloxacin
Melinta Therapeutics; Approved: June 17, 2017

6 ceftazidime/avibactam
Actavis plc; Approved: February 25, 2015

5 ceftolozane/tazobactam
Cubist Pharmaceuticals, Inc.; Approved: December 19, 2014

4 oritavancin
The Medicines Company; Approved: August 6, 2014

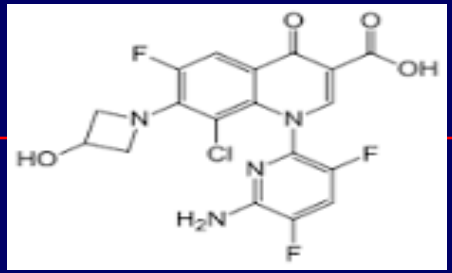
3 tedizolid phosphate
Cubist Pharmaceuticals, Inc.; Approved: June 20, 2014

2 dalbavancin
Durata Therapeutics; Approved: May 23, 2014

1 ceftaroline fosamil
Forest Laboratories, Inc.; Approved: October 29, 2010

GH Talbot, A Jezek, BE Murray, RN Jones, RH Ebright, GJ Nau, KA Rodvold, JG Newland, HW Boucher. Clin Infect Dis 2019

Delafloxacin (Baxdela®)



- Broad spectrum anionic fluoroquinolone
- Potential advantages:
  - MRSA activity
  - Gaps in Gram-negative coverage
  - Oral bioavailability
  - Accumulates in acid pH (intracellular)
  - Broad spectrum
  - Efficacy in obese patients
- Dosing
  - 300mg IV every 12 hours
    - Dose adjust for CrCl 15-29ml/min
  - 450mg orally every 12 hours

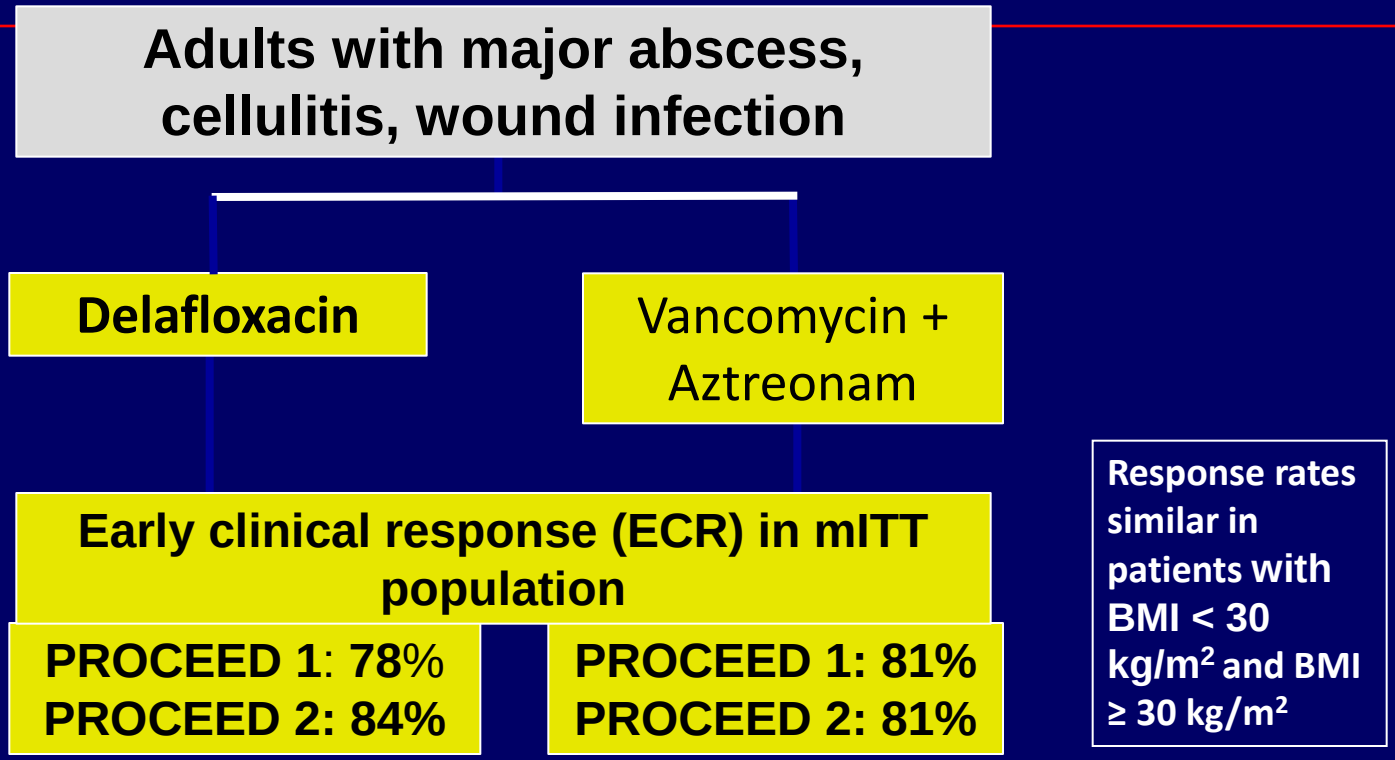
www.fda.gov

Delafloxacin

		Antibiotic MIC_{50} / MIC_{90}		
Pathogen	**N**	**Dela**	**Levo**	**Cipro**
E. coli	**4436**	**0.06/4**	**<=0.12/>4**	**<=0.03/>4**
K. pneumoniae	**2417**	**0.12/>4**	**<=0.12/>4**	**<=0.03/>4**
P. aeruginosa	**2181**	**0.5/>4**	**0.5/>4**	**0.12/>4**
K. oxytoca	**601**	**0.12/0.5**	**<=0.12/0.25**	**<=0.03/0.12**
E. cloacae	**783**	**0.06/2**	**<=0.12/0.5**	**<=0.03/0.5**
P. mirabilis	**907**	**0.06/2**	**<=0.12/>4**	**<=0.03/>4**

Flamm et al. IDWeek 2017

Delafloxacin Phase III ABSSSI



Pullman, et al. J Antimicrob Chemother. 2017;72:3471
O'Riordan W, et al. Clin Infect Dis. 2018;67(5):657

PROCEED 1 Delta (95% CI): -2.6 (-8.8, 3.6)
PROCEED 2 Delta (95% CI): +3.1(-2.0, 8.3)

Delafloxacin Status

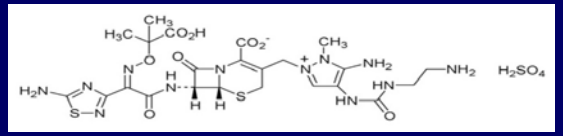
- FDA approved ABSSSI 2017
- FDA approved CABP 24 October 2019
  - Delafloxacin vs moxifloxacin

- Ongoing:
  - Phase 1 complicated UTI

https://clinicaltrials.gov/ct2/show/NCT02679573?term=delafloxacin&rank=4

Ceftolozane/Tazobactam (Zerbaxa®)

- Dose: Ceftolozane 1g/tazobactam 0.5g (total 1.5g) every 8h
  - 1 hour infusion
  - *P. aeruginosa* $MIC_{50/90}$ = 0.5/2 mg/L
  - Inhibits some carbapenem-R *P. aeruginosa*
  - Enterobacteriaceae - inhibits most class A and some class C β-lactamases (CTX-M, ESBLs)
  - No inhibition of KPC-producing Enterobacteriaceae (tazobactam is poor inhibitor)



Ceftolozane

Tazobactam

- Poor activity in *Acinetobacter* spp. (MIC_{50} = 32)
  - Not active against bacteria that produce certain serine carbapenamases (KPC), metallo-beta lactamases, stable derepressed ampC (*Enterobacter* spp.)
  - Safety similar to other β-lactams (cephalosporins)
- FDA approved
  - cUTI (1.5g vs. levofloxacin 750 QD)
  - cIAI (1.5g vs. meropenem 1g q8) - VNP (3g every 8h vs. meropenem)

Clinical cure rates in phase 3 trial of cIAI by baseline renal function (MITT population)

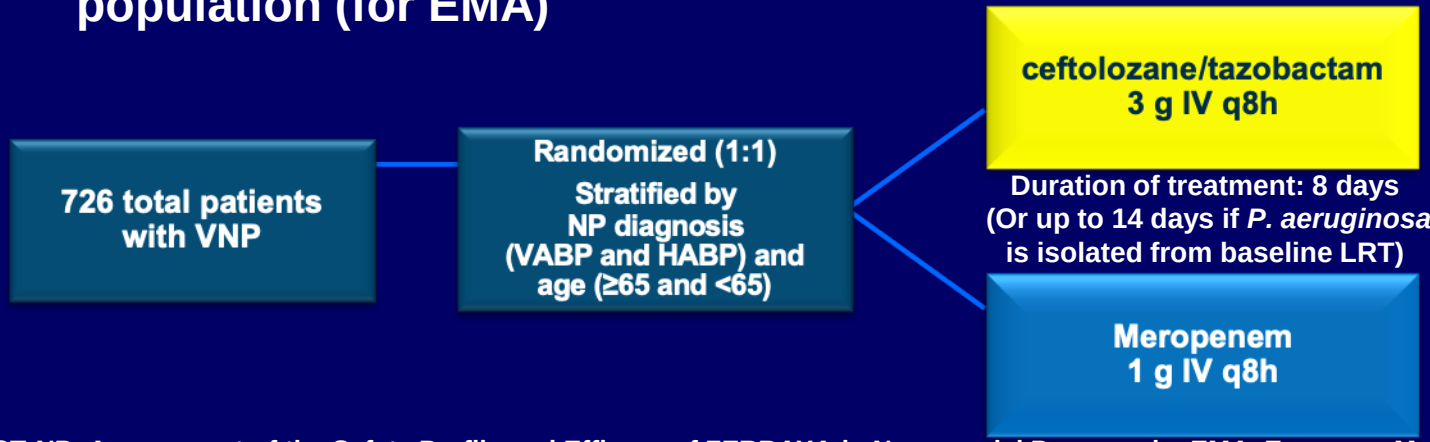
Baseline Renal Function	Ceftolozane/Tazobactam + Metronidazole n/N (%)	Meropenem n/N (%)
Normal/mild impairment (CrCL ≥50 mL/min)	312/366 (85.2)	355/404 (87.9)
Moderate impairment (CrCL 30- <50 mL/min)	11/23 (47.8)	9/13 (69.2)

- Decreased efficacy in patients with baseline creatinine clearance (CrCL) of 30 to ≤50 mL/min
- Monitor CrCL at least daily in patients with changing renal function and adjust the dose of ceftolozane/tazobactam accordingly

MITT = microbiological intent-to-treat. Zerbaxa USPI, www.fda.gov

Ceftolozane/tazobactam Phase 3 NP (ASPECT-NP) Trial Design

- Phase 3, randomized, controlled, double-blind, multicenter trial in **adult ventilated patients with nosocomial pneumonia (VNP)**
- Primary objective: demonstrate noninferiority of ceftolozane/tazobactam to meropenem, based on difference in:
  - Day 28 all-cause mortality rates in the ITT population (per FDA)
  - Clinical response rates at the TOC visit (7 days post EOT) in the CE population (for EMA)



ASPECT-NP, Assessment of the Safety Profile and Efficacy of ZERBAXA in Nosocomial Pneumonia; EMA, European Medicines Agency; FDA, Food and Drug Administration; HABP, hospital-acquired bacterial pneumonia; TOC, test-of-cure; VABP, ventilator-associated bacterial

Ceftolozane/tazobactam Phase 3 NP (ASPECT-NP)

	Cefto-tazo N = 362	Mero N = 364	Tx Diff (95% CI)
	N (%)		
VABP	263 (73)	256 (72)	
TOC Cure (CE population)	139/218 (64)	143/221 (65)	-1.3 (-10.21, 7.67)
Mortality day 28	87 (24)	92 (25)	1.1 (-2.84, 5.18)
Mortality d 28 VABP	63/263 (24)	52/256 (20)	-3.6 (-10.74, 3.52)
Mortality d 28 vHABP	24/99 (24)	40/108 (37)	12.8 (0.18, 24.75)

- DRAEs: 11% ceftol-taz vx 8% mero
- DRAE leading to discontinuation: 2% ceftol-taz vs 1% mero

Kollef et al. ECCMID 2019; P1917

Ceftazidime-Avibactam (Avycaz®)

- Dose: ceftazidime 2g / avibactam 500 mg every 8 hours
  - 2 hour infusion
- GNB potency:
  - ESBL-producing Enterobacteriaceae including class A, class C, and some class D (e.g. OXA-48); CREs – KPCs and others
  - *Pseudomonas* spp. with class A/C beta-lactamases
- QIDP
- FDA approved
  - cUTI
  - cIAI (vs. meropenem; CID 2016)
  - Pathogen focused study - CAZ-AVI comparable to other drugs (carbapenems in CAZ-R (not CRE; Lancet ID 2016)
  - nosocomial pneumonia (including VABP)
- Descriptive case series in patients with CRE from early exp published/presented

Exploratory Analyses: Clinical Outcome by Renal Function (mMITT)

Renal Function (CrCl at Baseline)	CAZ-AVI + MTZ n / N	CAZ-AVI + MTZ Cure Rate (%)	Meropenem n / N	Meropenem Cure Rate (%)	Difference (95% CI)	
Normal (>80 mL/min)	232 / 271	85.6	248 / 283	87.6	-2.0	(-7.81, 3.68)
Mild (>50 to 80)	90 / 108	83.3	73 / 90	81.1	2.2	(-8.46, 13.35)
Moderate (MRIB) (>30 to 50)	14 / 31	45.2	26 / 35	74.3	-29.1	(-50.05, -5.36)

- Magnitude of MRIB dose adjustment differed between groups
  - 66% reduction in CAZ-AVI (7.5 to 2.5 g/day)
  - 33% reduction in meropenem (3 to 2 g/day)

FDA briefing document. Ceftazidime-avibactam.
http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/Anti-InfectiveDrugsAdvisoryCommittee/UCM425459.pdf

Ceftazidime-Avibactam Revised Renal Dosing

Estimated Creatinine Clearance (mL/minute)	Ceftazidime-avibactam Dose
31-50	1.25g every 8 hrs
16-30	0.94g every 12 hrs
6-15	0.94g every 24 hrs
<= 5	0.94g every 48 hrs

Ceftazidime-avibactam for CRE - Outcomes Toxicity and Emergence of Resistance

	Caz-avi N = 37
Success	22 (59%)
30-day survival	28 (76%)
90-day survival	23 (62%)
Microbiologic failure	10 (27%)
Caz-avi resistance	3/10 (30%)

- Series of patients over 10 months at UPMC
  - — 1/3 transplant
  - — Infection type: 12 pneumonia, 10 bacteremia
  - — 30% caz-avi + another abx
- Recurrent CRE: 5/22 successful pts (23%) , med 74 days (34-84)
- Outcomes not better with combination therapy
- "We're Gonna Need a Bigger Boat!"

Shields et al. Clin Infect Dis 2016; 63(12): 1615
Spellberg & Bonomo Clin Infect Dis 2016; 63(12): 1619

REPRISE - Ceftazidime-avibactam vs BAT
CRE & *P. aeruginosa* Infections – cUTI/cIAI

	Caz-avi N = 154	BAT N =148
	n (%)	
cUTI (10 + bacteremia)	144 (94%)	137 (93%)
cIAI	10 (6%)	11 (7%)
Baseline pathogen		
E. Coli	63 (41)	63 (43)
K. Pneumoniae	60 (39)	68 (46)
Outcome		
Cure at TOC	140 (91%)	135 (91%)

- Open-label, Eastern Europe, 2013-14
- Ceftazidime resistant at baseline
- 163/168 (97%) BAT rec'd carbapenem tx, 161 (96%) as monotx
- AEs:
  - — 51/164 caz-avi (31%) vs 66/168 (39%) BAT

Carmeli et al. Lancet ID 2016 (16): 661

Ceftazidime-Avibactam
REPROVE Study Nosocomial Pneumonia

	Caz-avi N = 356	Mero N = 370	Tx Diff (95% CI)
	N (%)		
VABP	118 (33)	128 (35)	
No prior abx	122 (34)	117 (32)	
Cure MITT	245 (69)	270 (73)	-4.2 (-10.76, 2.46)
Mortality day 28	30 (8.4)	27 (7.3)	1.1 (-2.84, 5.18)
Mortality d 28 caz NS*	8.2%	8.5%	

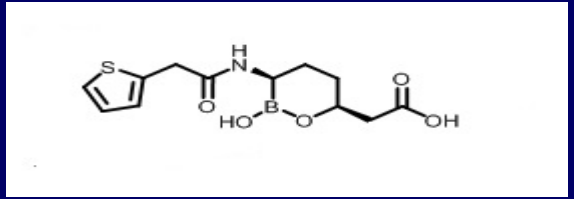
- NO US patients (China 33%, Eastern Europe 26%), Prior abx <= 48 hrs
- 355 (44%) micro MITT pop – K. pneumo, *P. aeruginosa* most freq GNB
- 100 (28%) + ceftaz NS GNB
- Overall mortality LOWER than expected
- SAEs: 19% caz-avi (N=4 drug-related) vs 13% meropenem

Torres et al. Lancet ID 2017. *www.FDA.gov

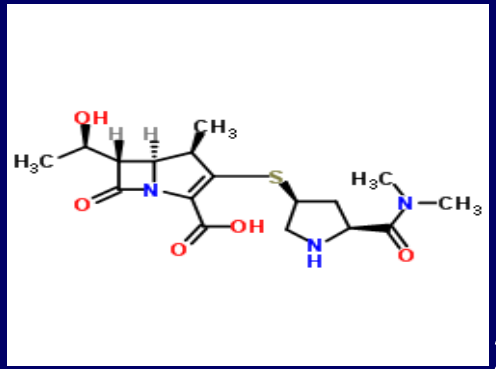
Ceftazidime-avibactam for MDR Gram-negative Bacteremia

- Data
  - case series
  - compassionate use
  - Subsets of registrational and strategy trials
- Superiority to colistin?
  - Efficacy and toxicity
- Gaps
  - Prospective trials, RCTs
  - Cost effectiveness

Meropenem-Vaborbactam (Vabomere®, formerly RPX7009)



- Vaborbactam pK matched with meropenem
- Inhibits class A & C serine B-lactamases (including KPC)
  - Distinct binding site from avibactam and tazobactam
- BARDA funding
- QIDP
- Dose: meropenem 2g /vaborbactam 2g as 3 h infusion every 8 h
  - Dose adjust for renal dysfunction
- FDA approved cUTI
- NDA submitted
  - Pathogen focused
  - HABP/VABP



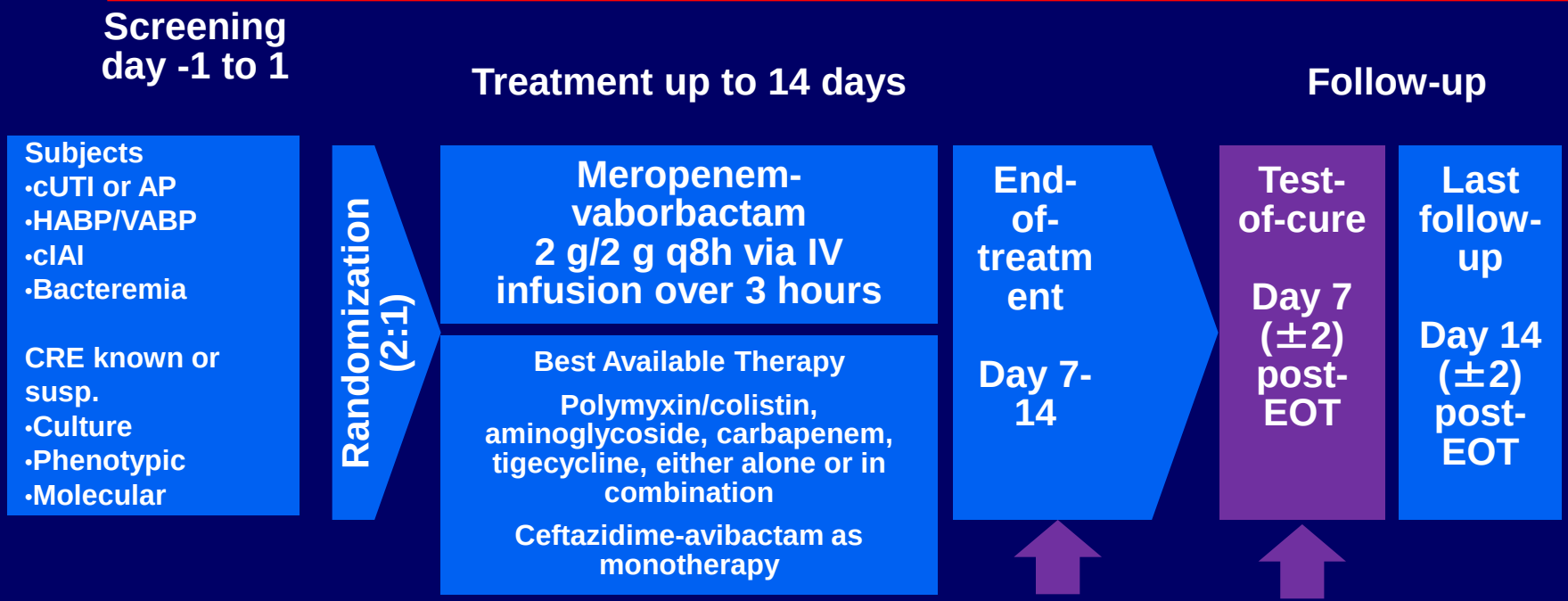
TANGO I - Meropenem-vaborbactam vs Piperacillin-tazobactam for cUTI/AP

	Mero-vabor	Pip-Tazo	Tx Diff (95% CI)
	n/N (%)		
End of IV therapy (FDA)	189/192 (98.4)	171/182 (94.0)	4.5 (0.7, 9.1)
Micro erad TOC (EMA)			
Micro MITT	128/192 (66.7)	105/182 (57.7)	9.0 (-0.9, 18.7)
Micro Eval	118/178 (66.3)	102/169 (60.4)	5.9 (-4.2, 16.0)

- Mero-vabor 2g/2g over 3 hrs vs Pip-tazo 4.5/0.5 over 30 mins every 8h; both with option to switch to oral levofloxacin p 5 days; total 10 d therapy
- 59% acute pyelonephritis/40-41% + complicated UTI
- FDA endpoint: clin cure/improved + micro erad at end of IV tx in mMITT population

Kaye et al. JAMA. 2018;319(8):788-799. doi:10.1001

TANGO-II : meropenem-vaborbactam vs. Best Available Therapy in suspected or documented CRE infection



Randomized study stopped upon recommendation of DSMB after interim analysis of 72 patients showed efficacy and safety advantage for meropenem-vaborbactam

TANGO II - Meropenem-vaborbactam vs BAT CRE Infections

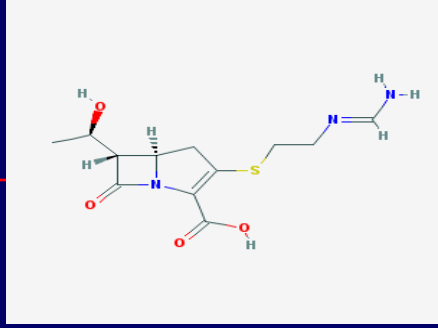
	Mero-vabor N = 32	BAT N = 15	Tx Diff (95% CI)
	n/N (%)		
Cure at EOT	21 (65.6)	5 (33.3)	32.3 (3.3, 61.3)
Cure at TOC	19 (59.4)	4 (26.7)	32.7 (4.6, 60.8)
Micro Cure at EOT	21 (65.6)	6 (40.0)	25.6 (-4.1, 55.4)
Micro Cure at TOC	17 (53.1)	5 (33.3)	19.8 (-9.7, 49.3)
Day 28 Mortality	5 (15.6)	5 (33.3)	-17.7 (-44.7, 9.3)

Wunderink et al. Infect Dis Ther 2018

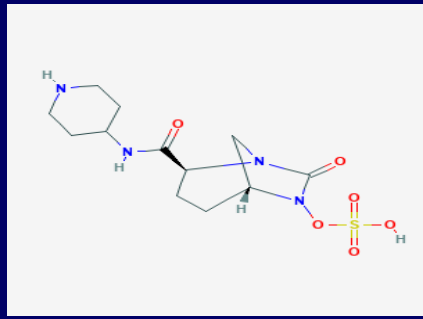
Meropenem-Vaborbactam

- Meropenem-vaborbactam better than “best available therapy” against CRE (not OXA-48 or MBLs)
- Active against most KPC-producing CRE resistant to ceftazidime-avibactam
- Potent and “optimized” PK/KD
- High barrier for resistance? Uptake affected by porin changes
- No advantage over meropenem against *P. aeruginosa* or *Acinetobacter*
- Complexities of MDROs require all therapeutic options
- “Real world” evidence will be crucial to define the niche of each B-lactam/ B-lactamase inhibitor combination

Imipenem/relebactam (formerly MK-7655)



- Imipenem/cilastatin + relebactam
- Inhibits class A & C serine β-lactamases, ESBLs, some CREs (no MBLs), *P. aeruginosa*
- Dose: imipenem 500mg /relebactam 250mg every 6 h over 30 minutes
- FDA approved cUTI and cIAI (significant # R GNB)
- Resistant pathogen study vs colistin (N = 54) complete
  - Imi-resistant but IMI/rel and colisitin-susceptible
- Phase 3 complete
  - HABP/VABP vs pip-tazo 4.5g every 6 hrs
    - Linezolid allowed for MRSA
    - Primary endpoint
      - All cause mortality day 28



Paschke IDWeek 2017, www.clinicaltrials.gov

Imipenem-relebactam vs Colistin + Imipenem

	IMI-REL N = 21	CST + IMI N = 10	Tx Diff (90% CI)
	n/N (%)		
Success	15/21 (71.4)	7/10	1.4 (-27.5, 21.4)
HABP/VABP	7/8	2/3	
cIAI	0/2	0/2	
cUTI	8/11 (72.7)	5/5	-27.3 (-52.8, 12.8)
Success at day 28	15/21 (71.4)	4/10	31.4 (1.3, 51.5)
Day 28 mortality	2/21 (9.5)	3/10	-20.5 (-46.4, 6.7)

- 31/47 randomized in mMITT
- Pathogens: 77% *P. aeruginosa*, 16% *K. pneumoniae*, 6% other Enterobacteriaceae
- BLA: 85% Amp C, 39% ESBL, 16% KPC , 3% OXA-48
- Tx-emerg nephrotox: 3/29 (10%) Imi-rel vs 9/16 (56%) CST+IMI

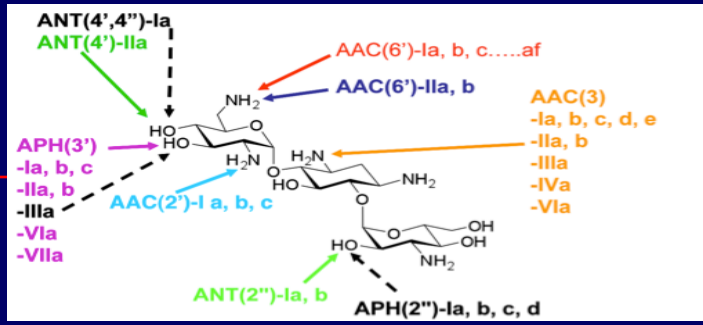
Motsch, et al. CID 2019

Aztreonam/Avibactam

- Potent vs
  - Enterobacteriaceae
    - Including ESBLs and KPCs
    - Active vs metallo-β-lactamase producers
  - *A. baumannii*
  - NOT *P. aeruginosa*
- Dose: Aztreonam 6500mg /2167mg avibactam loading dose, extended infusion day one, then 6000mg aztreonam/2000mg avibactam daily via extended infusion; adjust for renal dysfunction
- Phase 3 studies ongoing
  - Pathogen specific vs meropenem/colisitn
  - cIAI – Aztreonam/avibactam + metronidazole
  - HABP/VABP

Sader et al. AAC 2017; Karlowsky et al. AAC 2017; www.clinicaltrials.gov

Plazomicin



- Aminoglycoside designed to not be affected by major AG modifying enzymes
- Active vs. Enterobacteriaceae including CRE (but not in methylase co-producing strains, e.g. NDM) and ESBLs, MBLs, fluoroquinolone-R and aminoglycoside-R GNB
- Organisms with antibiotic modifying enzymes or efflux pumps (*Acinetobacter/Providencia/Proteus* spp.) and ribosomal methylase are resistant
- 15 mg/kg IV daily over 30 minutes
- Dose based on AUIC
- FDA approved –25 June 18
  - cUTI (vs. levofloxacin)
- Not approved: pathogen focused study CRE (combo Rx)

EPIC
Plazomicin vs Meropenem cUTI/AP

	Plazomycin N = 191	Meropenem N = 197	Tx Diff (95% CI)
	N (%)		
Day 5	168 (88.0)	180 (91.4)	-3.4 (-10.0, 3.1)
End of IV	179 (93.7)	187 (94.9)	-1.2 (-6.5, 4.0)
TOC	156 (81.7)	138 (70.1)	11.6 (2.7, 20.3)

- Similar results: IV only, IV + oral levofloxacin
- Bacteremia composite cure: 18/25 (72%) plazo vs 13/23 (56.5%) mero
- Adverse events similar
- Creat increase: 7%plazo vs 4% mero

N Engl J Med 2019; 380:729-740

CARE
Plazomicin vs Colistin for CRE Infections

	Plazomicin N = 17	Colisitin N = 20	Tx Diff (95% CI)
		N (%)	
BSI, HABP/VABP			
Mortality d 28	2 (11.8)	8 (40.0)	28.2 (0.7, 52.5)
Mortality d 28/cx	4 (23.5)	10 (50.0)	26.5 (-0.7, 51.2)

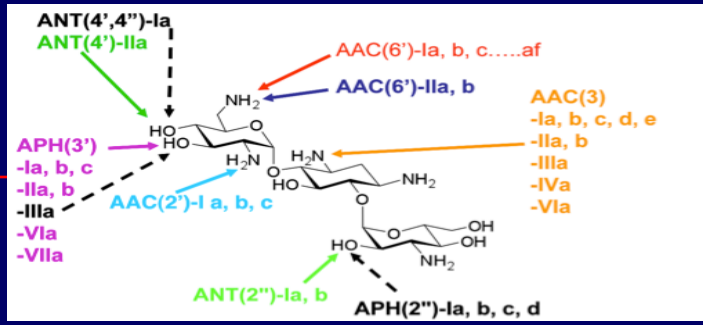
- Plazo vs Colisitin BOTH + meropenem or tigecycline

- Significant benefit in 60-day survival in BSI pts, HR 0.37 (0.15, 0.91)
- Fewer AEs, less renal dysfunction in plazomicin-treated patients

* 2100+ patients screened

N Engl J Med 2019; 380:791-793

Plazomicin



Regulatory Status

- FDA approved: cUTI (vs. levofloxacin)
- Not approved: pathogen focused study CRE (combo Rx)

- FDA Advisory Committee 2 May 18
  - 15 vs 0 vote in favor of effectiveness/safety in cUTI
  - 4 vs 11 vote against effectiveness/safety in BSI
    - Issues:
      - Small numbers
      - Risk vs benefit/LPAD

Should We Use Polymyxin or Aminoglycoside-based Therapy?

- CRE
  - Small studies
  - Less toxicity
  - ? Improved outcomes, mortality

Pseudomonas aeruginosa	Ceftolozane-tazobactam	Polymyxin/ Aminoglycoside
	N = 100	N = 100
Clinical cure	81%	61%
Acute kidney injury	6%	34%
In hospital mortality	20%	25%

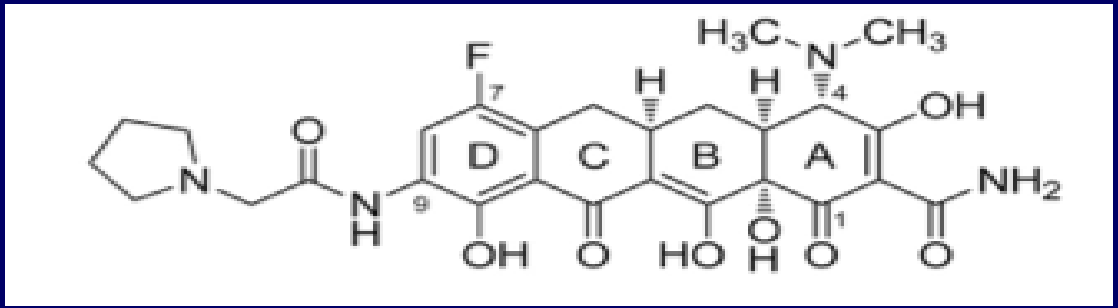
Retrospective, observational study
NNT with ceft/tazo for cure = 5

Pogue et al. CID 2019

NEW Tetracyclines
Aminomethylcycline and Fluorotetracycline

PTK 0796-
Omadacycline

TP 434-
Eravacycline

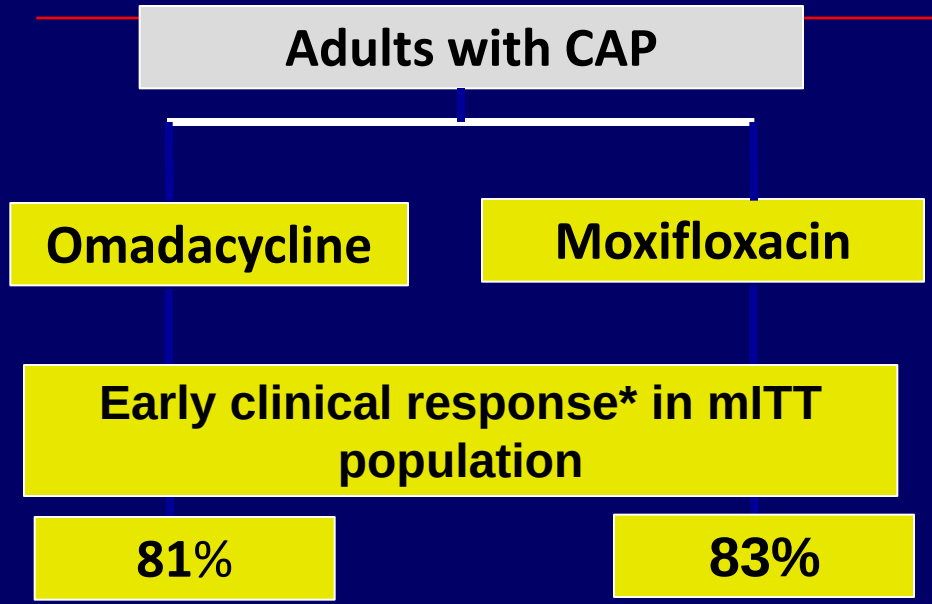


Omadacycline (IV/Oral)

- Minocycline derivative, active against tetracycline resistant pathogens – IV/oral
- Gram+: VRE, MRSA, VRSA, MDR *S. pneumoniae*, GAS, GBS
- GNB coverage:
  - Carbapenem-resistant *E. coli*
    - Limited activity vs carbapenem-resistant *K. pneumoniae*
  - ESBL, drug-resistant *Salmonella* spp.
- Anaerobes: *C. difficile* (not being developed for this indication)
- Potential advantages:
  - MRSA activity, Oral bioavailability
- FDA Approved CABP and ABSSSI
- Safety issues – class effects:
  - GI, skin rash, Heart rate ?

www.clinicaltrials.gov; www.paratekpharm.com

Omadacycline Phase III CABP (OPTIC)



ECR: survival with improvement of at least one level compared to baseline (e.g., severe to moderate) of at least 2 CABP symptoms (cough, sputum, CP, SOB) at 72-120 hours

OPTIC Delta (95% CI): -0=1.6 (-7.1, 3.8)

Non-inferiority study (NI margin 10%)

100 mg IV Q12 day one then 100 mg daily with option to switch to oral after 3 days, Treatment 7-14 days

Patient characteristics
- 60% >65 years
- 60% PORT risk class III, 25% PORT risk class IV
- 21% with COPD/structural lung ds

Bacterial pathogen identified in ~50% of patients; more *H flu* on omadacycline arm

N/V in 2.5%; 8 patient with CDI in moxi group

Stets et al. NEJM 2019; 380 (6): 517

Omadacycline

- FDA approved CABP and ABSSSI
  - ABSSSI IV/ORAL OASIS study
    - Omadacycline not inferior to linezolid
  - ABSSSI ORAL only OASIS-2 study
    - Omadacycline 300mg daily vs linezolid 600mg twice daily
  - CABP OPTIC
- Phase 2 uUTI oral omada vs nitrofurantoin and cUTI (AP) oral-IV omada vs oral-IVlevoflox
  - Comparable efficacy but lower micro success with omada
  - Analysis pending

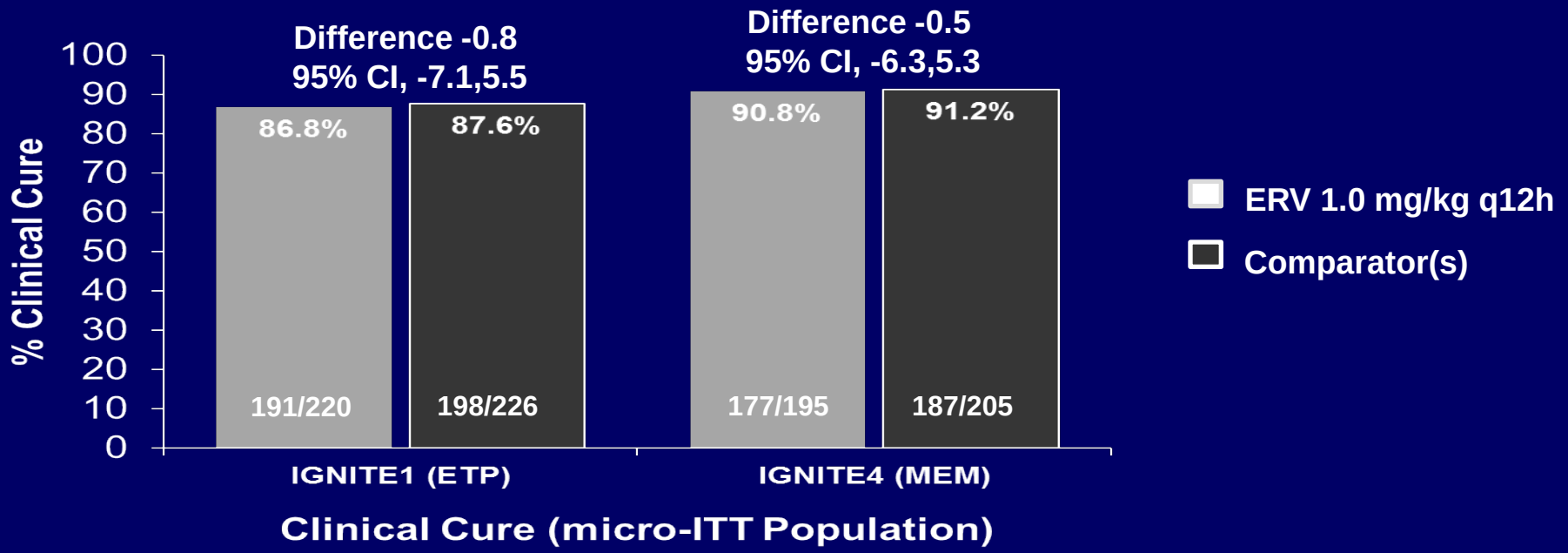
www.clinicaltrials.gov; www.paratekpharm.com; https://investor.paratekpharma.com/news-releases/news-release-details/paratek-announces-top-line-results-phase-2-clinical-studies

Eravacycline (IV/Oral)

- Overall ~ 2-fold more potent than tigecycline
- Active vs gram- (ESBL, CRE, *A. baumannii*, colistin-resistant GNB), gram+ (MRSA, VRE), anaerobes
- Not active vs. *Pseudomonas* spp or *Acinetobacter* spp.
- Orally bioavailable (but new formulation in development)
- Dose: Eravacycline 1mg/kg IV q 12h
- Issues:
  - High MIC *Pseudomonas*, *Burkholderia* spp.
  - Nausea, vomiting (< tigecycline)
    - FDA apporved for cIAI (vs. ertapenem, meropenem)
- Phase 3 trials - cUTI
  - IV/po erava vs. IV/PO levofloxacin failed
  - IV erava vs IV ertapenem failed

Horn IDWeek 2017, http://ir.tphase.com/news-releases/news-release-details/tetraphase-announces-top-line-results-ignite3-phase-3-clinical

IGNITE1 and 4: Primary Efficacy Endpoint Clinical Response in micro-ITT at TOC



- Eravacycline demonstrated non-inferiority to ertapenem (IGNITE 1) and meropenem (IGNITE 2) in the FDA primary analyses

ERV: Eravacycline, ETP: Ertapenem, MEM: meropenem;
Solomkin J et al. CID 2019; 69: 921. Solomkin J, et al. JAMA Surg. 2017;152(3):224-232

Lefamulin CABP – LEAP 1
FDA Analysis/Early Endpt (ITT)

	Lefamulin N = 276	Moxifloxacin+/- LZD N = 275	Tx Diff (95% CI)
Day 4 Response	87.3%	90.2%	-2.9 (-8.5, 2.8)
S. Pneumo	82/93 (88.2%)	91/97 (93.8%)	ND
S. aureus	10/10	4/4	ND

IV therapy with oral step down allowed
PORT > III; 25% PORT IV or V

File et al. CID 2019

Oral Lefamulin vs Moxifloxacin for CABP LEAP 2

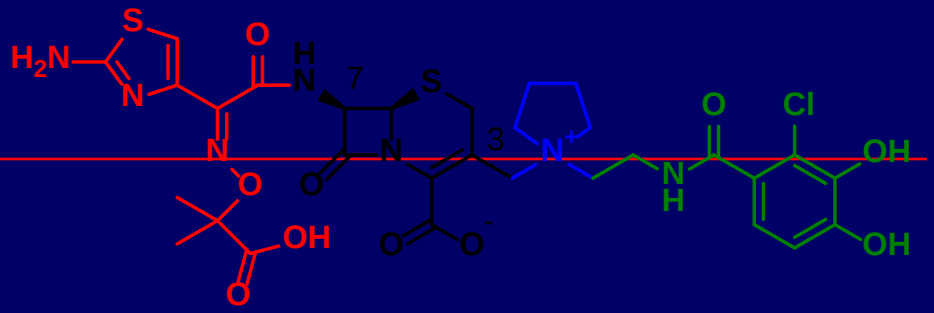
	Lefamulin N = 370	Moxifloxacin N = 368	Tx Diff (95% CI)
	N (%)		
Day 4 (FDA)	336 (90.8)	334 (90.8)	0.1 (-4.4, ∞)
TOC (EMA)	322 (87.5)	328 (89.1)	-1.6 (-6.3, ∞)
S pneumo day 4	110/123 (89.4)	115/126 (91.3)	

Oral therapy: 5 days lefamulin vs 7 days moxifloxacin (PORT II, III, IV)

- GI AEs: 17.9% lefamulin vs 7.6% moxi
  - Diarrhea 12.2% lefamulin vs 1.1% moxi; not tx-limiting
  - Nausea 5.2% lefamulin vs 1.9% moxi

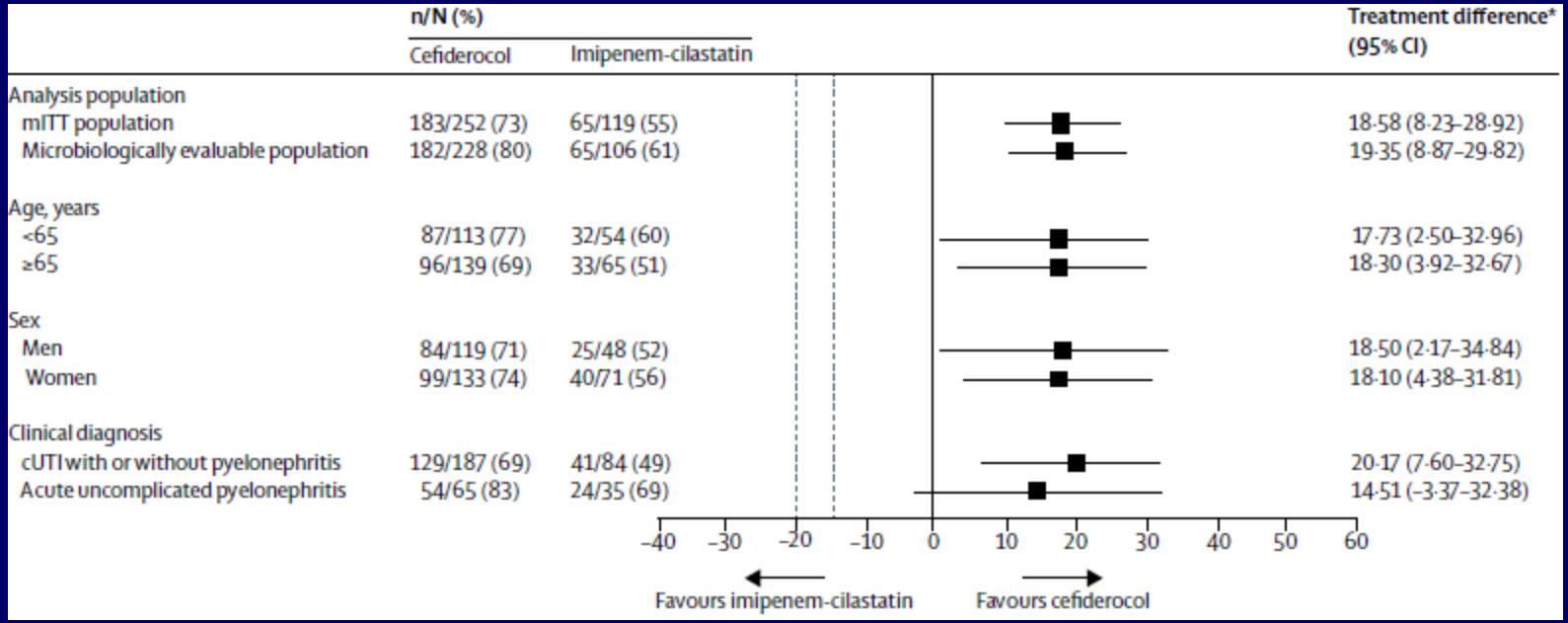
Alexander et al. JAMA 2019

Cefiderocol



- Cephalosporin + siderophore
  - Catechol moiety
    - additional stability against β-lactamases
    - binds to free iron to enhance uptake by GNB
- Broad gram-negative spectrum
- Dose: 2g IV every 8 hours
- Completed studies
  - cUTI vs imipenem
  - HABP/VABP/HCAP vs meropenem
  - CRE vs best available therapy

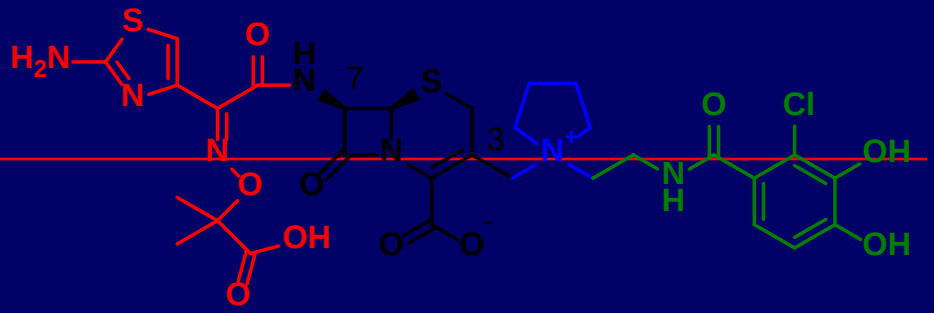
Cefiderocol vs Imipenem cUTI Phase 2



- **GI AEs: 4% cefiderocol vs 6% imipenem**

Portsmouth et al. Lancet ID 2018; 18: 1319

Cefiderocol

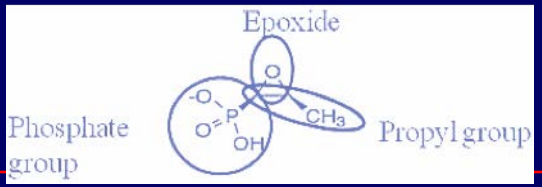


Regulatory Status

- **NDA under review:**
  - **cUTI (vs. imipenem)**
- **FDA Advisory Committee 16 October 19**
  - **14 vs 2 vote in favor of effectiveness/safety in cUT**
  - **Death imbalance in CREDIBLE-CR study**
    - **? warning**

www.FDA.gov

Fosfomycin (ZTI-01)



- Cell wall synthesis inhibitor
- Broad spectrum
  - Active vs. MRSA, MSSA, enteric GNB (some ESBL and serine carbapenemase producers), some P. aeruginosa
  - Not active vs. *Morganella*, *Acinetobacter*, *Stenotrophomonas*, *Burkholderia*, or *Bacteroides* spp.
- Available in EU x 45 years IV
- Fosfomycin 3g oral (Monurol) available in US

- Dose: 6 g every 8 hours IV over 1 hour
- Phase 3
  - cUTI vs. Piperacillin-tazobactam IV only
- NDA submitted 2 November 2018

Fosfomycin
ZEUS Study cUTI/AP

- Fosfo 6g every 8 hrs vs Piperacillin-tazobactam 4.5g every 8 hrs x 7 days
- Success: 64.7% Fosfo vs 54.5% pip-tazo; diff 10.2% (95% CI: -0.4, 20.8)
- M-MITT:
  - 32% (115/362) Extended Spectrum B-lactamase (ESBL)
  - 17% (62/362) Aminoglycoside resistance (AGR)
  - 6% (22/362) Carbapenem Resistant (CR)
  - 19% (70/362) Multi-Drug Resistant (MDR)
- AEs similar; fosfo diarrhea, LFT increase, low K+

	ESBL		AGR		CR		MDR	
	Cure (n)	Erad. (n)	Cure (n)	Erad. (n)	Cure (n)	Erad. (n)	Cure (n)	Erad. (n)
Fosfo	93% (52/56)	55% (32/58)	97% (29/30)	67% (20/30)	100% (9/9)	56% (5/9)	92% (34/37)	54% (20/37)
Pip-Tazo	93% (51/55)	47% (27/57)	94% (29/31)	38% (12/32)	85% (11/13)	31% (4/13)	90% (28/31)	36% (12/33)

Kaye et al. CID 2019

Using Old Antibiotics in New Ways…

Shorter is better

- Gram-negative (Enterobacteriaecae) bloodstream infection
  - 7 days not inferior to 14 days after clinical stability and source control
- ABSSI – more failure with >= 8 days
- Male UTI: no increased recurrence with < = 7days

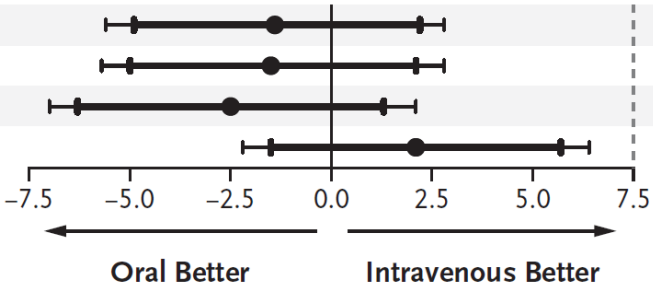
Yahav et al. CID 2019; Ihm et al. OFID 2019; Germanos et al. OFID 2019

Stewardship: Shorter = Better
B Spellberg

Diagnosis	Short (d)	Long (d)	Result
CABP	3 or 5	7-14	Equal
VABP	8	15	Equal
Pyelonephritis	7 or 5	14 or 10	Equal
Intra-abdominal infection	4	10	Equal
Gram-neg bloodstream inf	7	14	Equal
AECB	≤5	≥7	Equal
Cellulitis	5-6	10	Equal
Osteomyelitis	42	84	Equal
Septic Arthritis	14	28	Equal
Neutropenic Fever	AF x 72 h	+ANC > 500	Equal
P. vivax Malaria	7	14	Equal

Oral Step-down Therapy for Osteomyelitis OVIVA

Subgroup	Oral Group	Intravenous Group	Risk Difference (90% CI; 95% CI)
	patients with treatment failure/ total no. of participants		
Intention-to-treat population	70.0/527	77.3/527	−1.4 (−4.9 to 2.2; −5.6 to 2.9)
Modified intention-to-treat population	67/509	74/506	−1.5 (−5.0 to 2.1; −5.7 to 2.8)
Per-protocol population	61/466	69/443	−2.5 (−6.3 to 1.3; −7.0 to 2.1)
Worst-case sensitivity analysis	85/527	74/527	2.1 (−1.5 to 5.7; −2.2 to 6.4)



Pragmatic Randomized control trial, UK **13% vs 14% FAILURE**

- **Standard IV therapy vs early oral switch**
- **Included both PJI and hardware-assoc infections**
- **Tx tailored individually by ID experts**
  - **Rifampin and follow-on tx allowed**

Li et al. N Engl J Med 2019; 380:425-436

Oral Step-down Therapy for Osteomyelitis OVIVA

Strengths

- **Pragmatic**
- **Diverse bone infections**
- **Long follow-up, low attrition rate**

Limitations

- **No set treatment strategy**
- **Diverse bone infections/tx (heterogenity), mild disease**
- **Open label, selection bias**
- **Few MRSA, MDRs**
- **Patients with “poor adherence” excluded**

Boucher H. N Engl J Med 2019; 380(5)

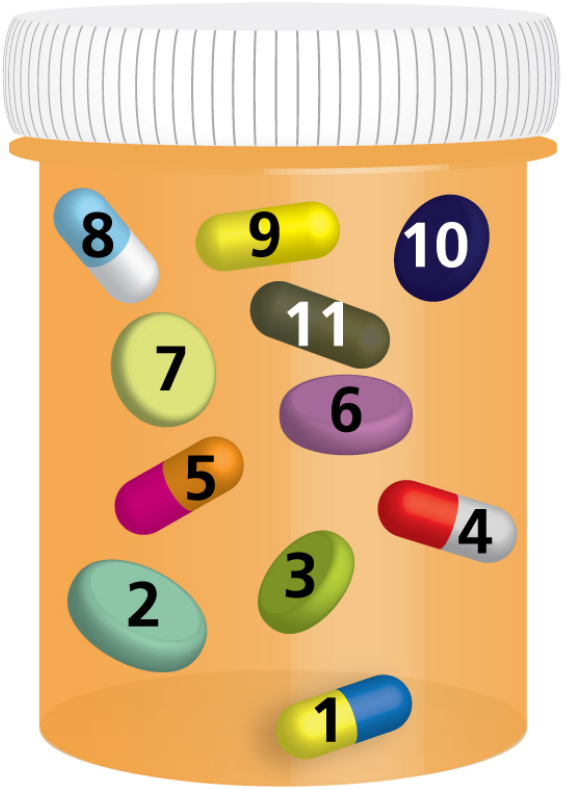
Oral therapy is better

- **Early oral switch in left-sided endocarditis**
  - **POET 3.5 year follow-up**
  - **Mortality, unplanned surgery, embolic event, relapsed BSI: 38% IV vs 26% oral, HR 0.64**
  - **No difference: relapse and infection-related death**
  - **Limitations: no MRSA, few IVDU, comorbidity imbalance**

- **Linezolid to complete *S. aureus* bloodstream infection therapy ?**

NEJM 2019; 380: 415; Boucher NEJM 2019 *380;5* ; Jorgensen et al. JAC 2019

10 x ‘20 but Nobody’s Buying



Bad Bugs Need Drugs

10 x ‘20 Ten new ANTIBIOTICS by 2020

13 **Lefamulin**
Nabriva; Approved August 19, 2019

12 **Imipenem/cilastatin+relebactam**
Merck; Approved July 17, 2019

11 omadacycline
Paratek Pharmaceuticals; Approved: October 2, 2018

10 eravacycline
Tetraphase; Approved: August 28, 2018

9 plazomicin
Achaogen; Approved: June 26, 2018

8 meropenem/vaborbactam
The Medicines Company; Approved: August 30, 2017

7 delafloxacin
Melinta Therapeutics; Approved: June 17, 2017

6 ceftazidime/avibactam
Actavis plc; Approved: February 25, 2015

5 ceftolozane/tazobactam
Cubist Pharmaceuticals, Inc.; Approved: December 19, 2014

4 oritavancin
The Medicines Company; Approved: August 6, 2014

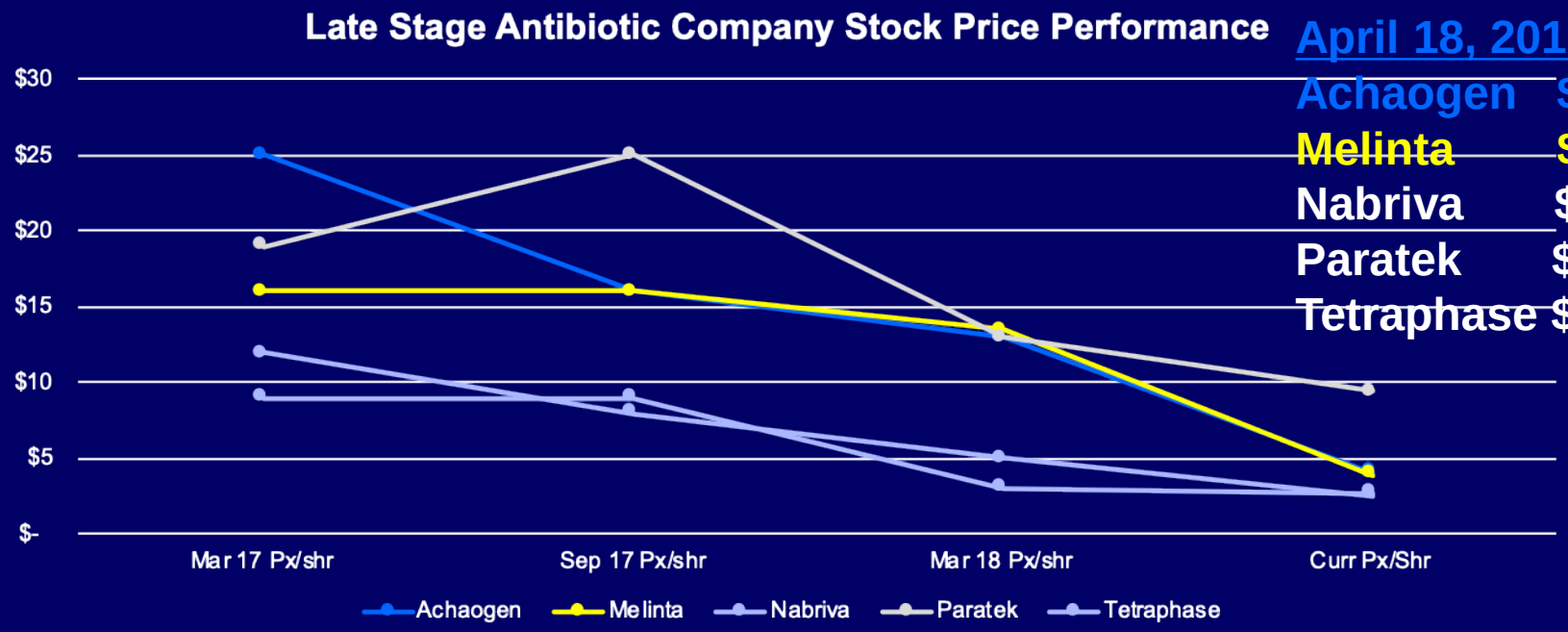
3 tedizolid phosphate
Cubist Pharmaceuticals, Inc.; Approved: June 20, 2014

2 dalbavancin
Durata Therapeutics; Approved: May 23, 2014

1 ceftaroline fosamil
Forest Laboratories, Inc.; Approved: October 29, 2010

GH Talbot, A Jezek, BE Murray, RN Jones, RH Ebright, GJ Nau, KA Rodvold, JG Newland, HW Boucher. Clin Infect Dis 2019

Over the last 18 months, stock prices for all late stage antibiotic companies have fallen precipitously

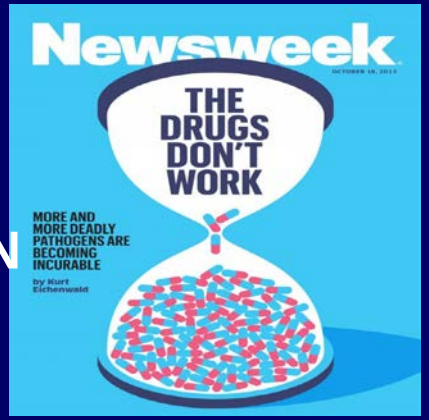


April 18, 2019:

Achaogen	$0.17
Melinta	$4.33
Nabriva	$2.72
Paratek	$5.57
Tetraphase	$1.06

Broad Agreement: Fix the Antibiotic Pipeline

STAT NEWS FIRST OPINION
Medicare payment rules hinder the fight against superbugs
By KEVIN OUTTERSON and HELEN W. BOUCHER
APRIL 17, 2019



THE HILL

The antibiotic market is broken and won't fix itself

New Agents for Gram-negative Pathogens Progress, Challenges, Incentives

- Progress
  - New agents in existing classes, activity vs MBLs
  - Stewardship – inpatient, outpatient, long-term care
  - Study design/development
    - HABP/VABP
    - Single pathogen studies (MDR)
- Challenges
  - New classes, mechanisms
  - Alternative types of therapeutics (antibodies, vaccines, phage)
  - Lack of Big Pharma engagement, poor return on investment
  - Poor uptake, delayed publication, guidelines
- Incentives
  - Push – grants, R&D tax credits, CARB-X, BARDA, GAIN, 21st Century Cures (LPAD)
  - Pull – market entry rewards, de-linkage

Thank You!

- Sue Cammarata
- G. Ralph Corey
- Sara Cosgrove
- Mike Dunne
- Roger Echols
- EJ Ellis-Grosse
- Amanda Jezek
- Kenneth Lawrence
- Evan Loh
- Brad Spellberg
- George H. Talbot
- Our patients and their families