Recently Approved Antibiotics 2015

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Disclosures

Consultant with honorarium

- Accelerate diagnostics
- Astellas
- Cubist
- Merck
- Theravance

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Pathogens Associated With Health Care Associated Infections (HCAIs)

Pathogen	All HCAIs (N=504) Number/ (%)	Pneumonia (N=110)	Surgical Site Infections (N=110)	GI Infections (N=86)	UTIs (N=65)	Bloodstream Infections
C. difficile	61 (12.1)	0	0	61 (70.9)	0	0
S. aureus	54 (10.7)	18 (16)	17 (16)	1 (1)	2 (3)	7 (14)
K. pneumoniae or *K. oxytoca*	50 (9.9)	13 (12)	15 (14)	1 (1)	15 (23)	4 (8)
E. coli	47 (9.3)	3 (3)	14 (13)	1 (1)	18 (28)	5 (10)
Enterococcus	44 (8.7)	2 (2)	16 (15)	5 (6)	11 (17)	6 (12)
P. aeruginosa	36 (7.1)	14 (13)	7 (6)	1 (1)	7 (11)	2 (4)
Candida	32 (6.3)	4 (4)	3(3)	3 (4)	3 (5)	11 (22)

Magill SS, et al. *NEJM* 2014;370:1198

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QUALIFIED INFECTIOUS DISEASE PRODUCT—An antibiotic drug for treating, detecting, preventing, or identifying a qualifying pathogen

QUALIFYING PATHOGEN—

(A) Resistant gram-positive pathogens, MRSA, VRSA, and VRE

(B) MDR gram-negative bacteria, including Acinetobacter, Klebsiella, Pseudomonas, and *E. coli* species

(C) Multidrug-resistant tuberculosis

(D) Other infectious pathogen identified for purposes of this section by the Secretary

https://www.congress.gov/bill/112th-congress/house-bill/2182/text - Accessed 5/25/15

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QIDP Benefits

- Extension of exclusivity period – 5 years
- Priority review for any application for approval
- Fast-track review

https://www.congress.gov/bill/112th-congress/house-bill/2182/text - Accessed 5/25/15

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ORIGINAL CONTRIBUTION

Tedizolid Phosphate vs Linezolid for Treatment of Acute Bacterial Skin and Skin Structure Infections

The ESTABLISH-1 Randomized Trial

Tedizolid for 6 days versus linezolid for 10 days for acute bacterial skin and skin-structure infections (ESTABLISH-2): a randomised, double-blind, phase 3, non-inferiority trial

Gregory J Moran, Edward Fang, G Ralph Corey, Anita F Das, Carisa De Anda, Philippe Prokocimer

Summary

Background New antibiotics are needed to treat infections caused by drug-resistant bacteria. Tedizolid is a novel oxazolidinone antibacterial drug designed to provide enhanced activity against Gram-positive pathogens. We aimed to assess the efficacy and safety of intravenous to oral tedizolid for treatment of patients with acute bacterial skin and skin-structure infections.

Lancet Infect Dis 2014

Published Online
June 6, 2014
http://dx.doi.org/10.1016/S1473-3099(14)70737-6

Prokocimer P, et al. *JAMA* 2013;309:559-569
Moran GJ, et al. *Lancet Infect Dis* 2014;14:696-705

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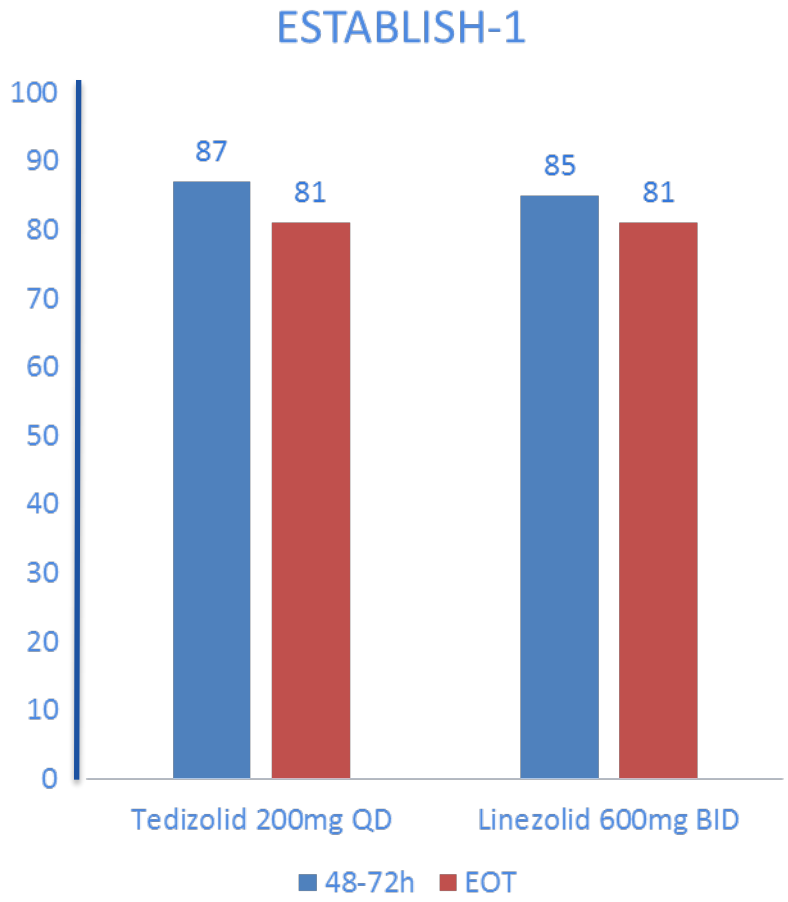
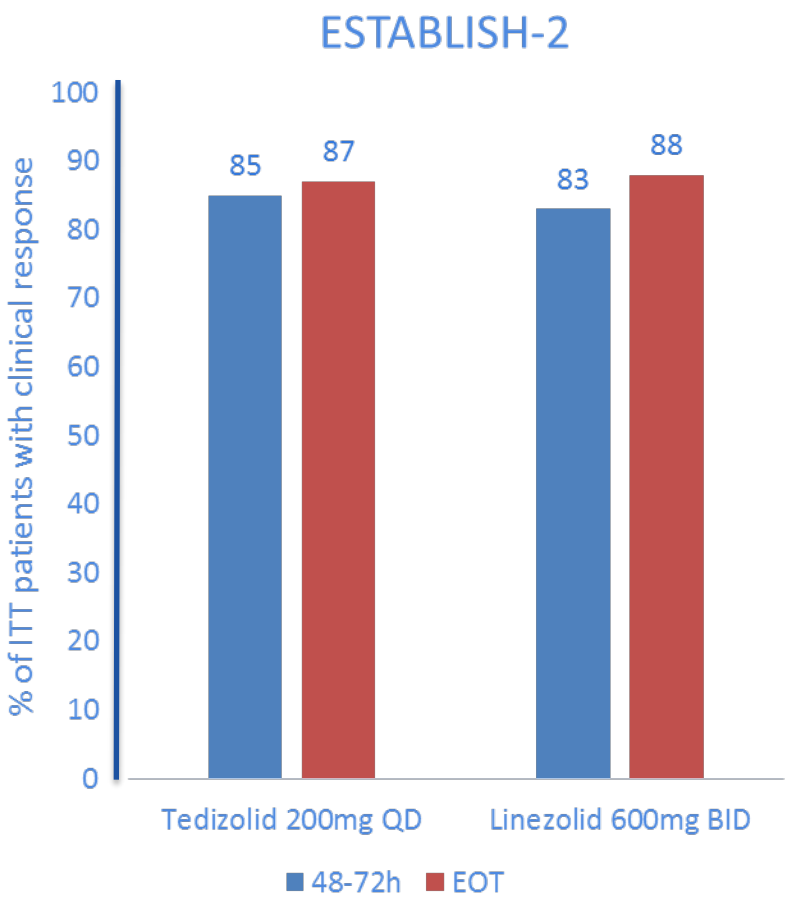
Tedizolid vs Linezolid – Response Rates





Prokocimer P, et al. *JAMA* 2013;309:559-569
Moran GJ, et al. *Lancet Infect Dis* 2014;14:696-705

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Tedizolid

- Dose: 200 mg Q24 h
- Cmax = 2.5 mcg/mL
- T1/2= 12 h
- AUC_{0-24}= 27.5 mcg·hr/mL
- Protein binding = 80%
- MIC 50/90 MRSA = 0.25/0.25
- fAUC/MIC90 = 22

Linezolid

- Dose 600 mg Q12h
- Cmax = 15.1 mcg/mL
- T1/2= 5 h
- AUC_{0-24}=180 mcg·hr/mL
- Protein binding = 31%
- MIC 50/90 MRSA = 1/2
- fAUC/MIC90 = 62

Linezolid Prescribing Information updated 1/2014
Tedizolid Prescribing Information updated 6/2014
Prokocimer P, et al. *Antimicrob Agents Chemother* 2012;56:4608

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Hematological Effects: Tedizolid vs Linezolid

	Maximum % Decrease Over 21 Days (Mean | Individual)			
Dose	**Platelets (%)**	**Neutrophils (%)**	**Reticulocytes (%)**	**RBCs (%)**
Placebo	*−5 | −23*	*−2 | −57*	*−8 | −38*	*−3 | −11*
Tedizolid 200 mg	−15 | −38	−18 | −51	−14 | −42	−2 | −9
Tedizolid 300 mg	−23 | −43	−4 | −44	−5 | −57	−3 | −7
Tedizolid 400 mg	−38 | −50	−37 | −66	−39 | −91	−11 | −27
Linezolid 600 mg bid	−22 | −54	−38 | −66	−21 | −95	−7 | −13

Prokocimer P, et al. *ICAAC* 2008 Abstract F1 2069a

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The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 JUNE 5, 2014 VOL. 370 NO. 23

Once-Weekly Dalbavancin versus Daily Conventional Therapy for Skin Infection

Helen W. Boucher, M.D., Mark Wilcox, M.D., George H. Talbot, M.D., Sailaja Puttagunta, M.D., Anita F. Das, Ph.D., and Michael W. Dunne, M.D.

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Single-Dose Oritavancin in the Treatment of Acute Bacterial Skin Infections

G. Ralph Corey, M.D., Heidi Kabler, M.D., Purvi Mehra, M.D., Sandeep Gupta, M.D., J. Scott Overcash, M.D., Ashwin Porwal, M.D., Philip Giordano, M.D., Christopher Lucasti, M.D., Antonio Perez, M.D., Samantha Good, Ph.D., Hai Jiang, Ph.D., Greg Moeck, Ph.D., and William O'Riordan, M.D., for the SOLO I Investigators*

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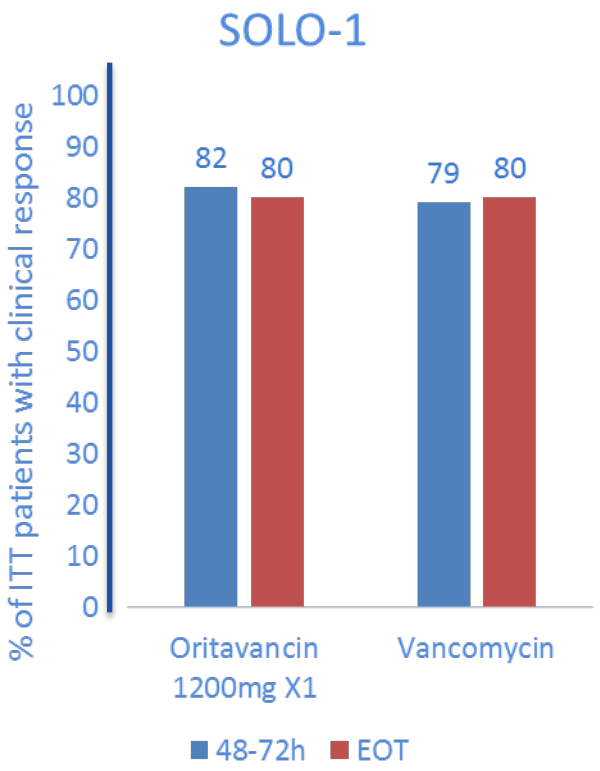
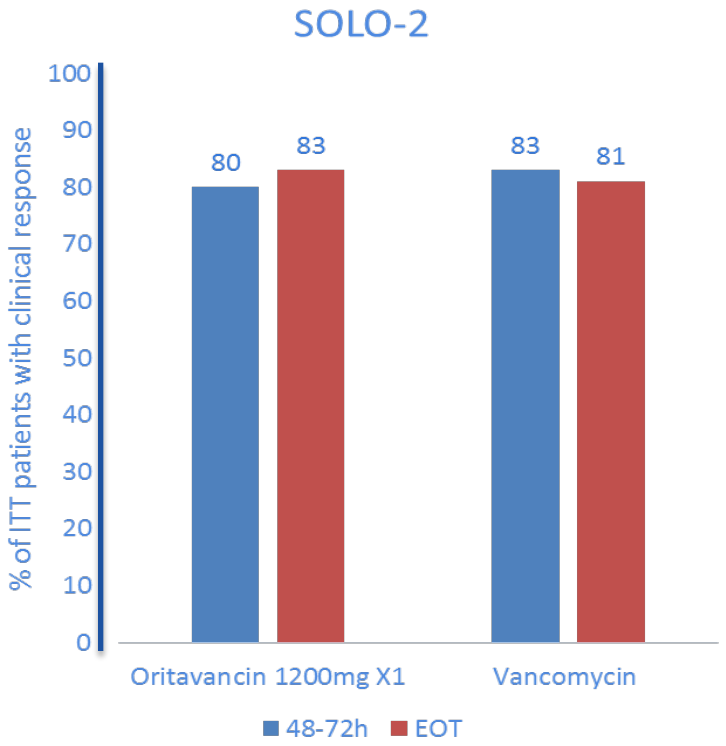
Oritavancin vs Vancomycin – Response Rates





Corey RG, et al. *NEJM* 2014;370:1280-90
Corey RG, et al. ICAAC 2013 Poster L-206c

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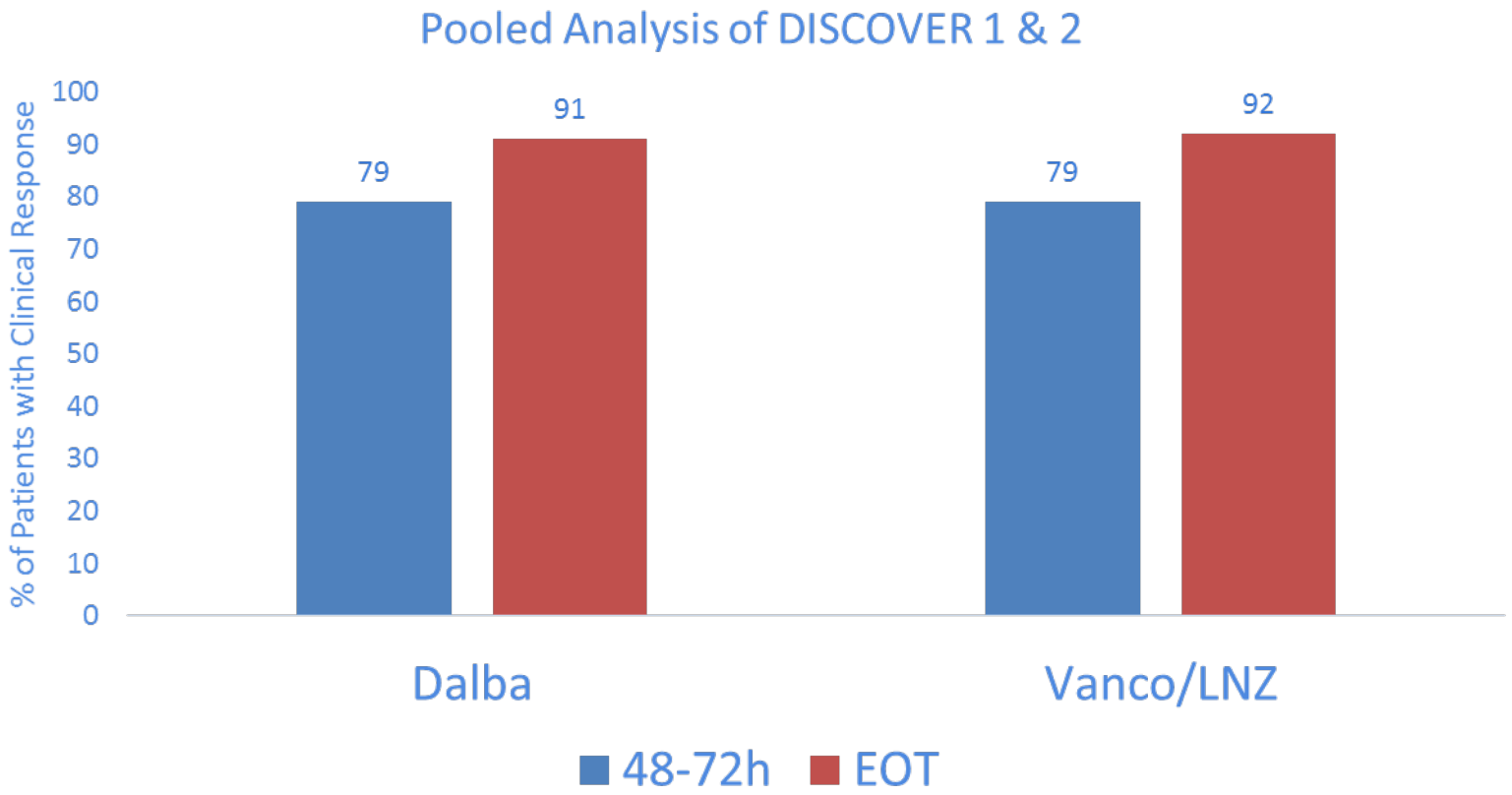
Dalbavancin 1000 mg Followed by 500 mg vs 3d of Vancomycin Followed by Linezolid



Boucher HW, et al. *NEJM* 2014;370:2169-79.

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Oritavancin: *In Vitro* Activity and FDA Breakpoints

Organism	N	Range	MIC50	MIC90
MRSA	169	0.12–0.25	.0125	0.25
VISA	24	0.5–1	0.5	1
VRSA	5	0.125–1	–	–

Pathogen	MIC (mcg/mL)			Zone Diameter		
	S	I	R	S	I	R
S. aureus	≤0.12	–	–	–	–	–
Beta-streps and *S. anginosus*	≤0.25	–	–	–	–	–
E. faecalis	≤0.12	–	–	–	–	–

Lin G, et al. *Antimicrob Agents Chemother* 2014;58:6251
Ortitavancin Prescribing Information – Updated 8/2014

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Dalbavancin: *In Vitro* Activity and FDA Breakpoints

Organism	N	Range	MIC50	MIC90
MSSA	22	0.06–0.12	0.06	0.12
MRSA	15	<0.03–0.12	0.06	0.06
VISA	8	0.5–2	0.5	–
hVISA	10	0.125–0.5	0.25	0.5

Pathogen	MIC (mcg/mL)			Zone Diameter		
	S	I	R	S	I	R
S. aureus	≤0.12	–	–	–	–	–
Beta-streps	≤0.12	–	–	–	–	–
S. anginosus	≤0.12	–	–	–	–	–

Citron DM, et al. *Diagn Microbiol Infect Dis* 2014;79:438-440.
Dalbavancin prescribing information: revised 5/14

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Head-to-Head Comparison

Oritavancin 1200 mg

Parameter	Mean (%CV)
Cmax (mcg/mL)	138 (23%)
AUC_{0-24} (mcg*hr/mL)	1100 (34%)
$AUC_{0-\infty}$ (mcg*hr/mL)	2800 (29%)
Protein Binding	85%
fCmax	20.7
$fAUC_{0-24}$ (mcg*hr/mL)	165

Dalbavancin 1000 mg

Parameter	Mean (%CV)
Cmax (mcg/mL)	287 (14%)
AUC_{0-24} (mcg*hr/mL)	3185 (13%)
AUC_{0-d7} (mcg*hr/mL)	11 160 (41%)
Protein Binding	93%
fCmax	20.1
$fAUC_{0-24}$ (mcg*hr/mL)	223

Oritavancin Prescribing Information – Revised 8/2014
Dalbavancin Prescribing Information – Revised 5/2014

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So What's New About These?

Oritavancin 1200 mg

Parameter	Mean (%CV)
$T_{1/2\alpha}$	2.3h (50%)
$T_{1/2\beta}$	13.4h (10%)
$T_{1/2\gamma}$	**245h (15%)**

Dalbavancin 1000 mg

Parameter	Mean (%CV)
$T_{1/2\alpha}$	–
$T_{1/2\beta}$	–
$T_{1/2\gamma}$	**346h (17%)**

That is 10.2 and 14.4 **DAYS,** respectively.

Oritavancin Prescribing Information – Revised 8/2014
Dalbavancin Prescribing Information – Revised 5/2014

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Dalbavancin and Oritavancin vs Enterococci

Dalbavancin	N	MIC50	MIC90	MIC Range
VSE	30	≤0.03	0.06	≤0.03–0.12
VRE – VanA	24	>4	>4	0.25–>4
VRE – VanB	2	≤0.03	≤0.03	–

Oritavancin	N	MIC50	MIC90	MIC Range
E. faecalis	1275	0.015	0.03	≤0.008–0.5
Vanco S *E. faecium*	383	≤0.008	≤0.008	≤0.008–0.03
VRE – VanA	470	0.03	0.06	≤0.008–0.25
VRE – VanB	16	≤0.008	≤0.008	≤0.008

Jones RN, et al. *Diagn Microbiol Infect Dis* 2013;75:304-307
Mendes RE, et al. *Antimicrob Agents Chemother* 2012;56:1639-1642

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Prices as of May 2015

Agent	Inpatient Price
Daptomycin 500 mg vial	$380
Dalbavancin 500 mg vial	$1400
Oritavancin 400 mg vial	$920

- Daptomycin is 6–8 mg/kg daily
- Dalbavancin is 1000 mg X1, then 500 mg 7d later
- Oritavancin is 1200 mg X1
- So for 10 days of therapy
  - Daptomycin = $3800–$7600
  - Dalbavancin = $4200
  - Oritavancin = $2760
  - Tedizolid = $2350

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The Role of the New Gram-Positive Agents

- Potential to revolutionize OPAT?
- Super long half life…
- Oritavancin: VRE activity vs PI challenges
- Dalbavancin: No VRE, 2 doses, LFTs, cleaner PI
- ADRs? Nephrotoxicity
- Tedizolid vs linezolid?
- Generic linezolid in 2015

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Resistance Among Gram Negatives in US Hospitals 2009–2012

Gram-negative	% Resistance (n) in nonurinary isolates			
	ICU		Non-ICU	
	Ceftazidime R	Imipenem R	Ceftazidime R	Imipenem R
E. coli	11.0 (3084)	0.3 (3287)	6.9 (43 445)	0.1 (47 559)
K. pneumoniae	26.8 (1780)	11.5 (1907)	14.5 (16 475)	5.8 (17 228)
A. baumanii	60.1 (550)	52 (535)	35.4 (5532)	28.0 (4370)
P. aeruginosa	18.6 (2615)	23.2 (2689)	7.3 (35 210)	8.4 (35 810)

Shlaes DM, et al. *Antimicrob Agents Chemother* 2013;57:4605

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Ceftolozane/Tazobactam

- FDA-approved (December 2014) indications
  - Urinary tract infections
  - Intra-abdominal infections
- Susceptibility testing is still key!
- This is not the package insert you are looking for.
- Dosing issues 1.5 gm vs…
- How do you use this in your patients?

Zerbaxa Prescribing Information – 12/14

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More Ceftolozane/Tazobactam

- *P. aeruginosa* including ceftazidime, carbapenem, and piperacillin/tazobactam resistant
- AmpC questions… ie, *Enterobacter* spp.
- Gram-positive challenges
- More tazobactam than you are accustomed to
- And again… *Bacteroides* spp. issues

http://www.cubist.com/products/cxa_201: Accessed 12/18/2014
Sader HS, et al. *J Antimicrob Chemother* 2014;69:2713.
Zhanel GG, et al. *Drugs* 2014;74:31.

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Ceftazidime/Avibactam

- NDA filed September 5, 2014 – with phase 2 data
- Phase 3 cIAI studies just completed = meropenem
- Dose 2 gm/500 mg Q8h as a 2-hr infusion
- Active vs many imipenem-resistant *Enterobacteriaceae*
- MIC90 vs *P. aeruginosa* = 4 mcg/mL
- MIC90 vs ceftazidime or meropenem R *P. aeruginosa* = 16 mcg/mL
- Active against KPCs, ESBLs, and AmpC, but…

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Ceftazidime/Avibactam

- FDA-approved February 14, 2015 – with phase 2 data
- Indications – Intra-abdominal infections and complicated UTIs
- Phase 3 cIAI studies just completed = meropenem
- Dose 2 gm/500 mg Q8 h as a 2-hr infusion
- Price…

Ceftazidime/Avibactam Prescribing Information 2/15
Lagace-Wiens P, et al. *Core Evidence* 2014;9:13.

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What Is Avibactam (Formerly NXL-104)?

- Novel beta-lactamase inhibitor (BLI)
- 1st non-beta-lactam BLI
- 10-100X > Potency than clavulanate or tazobactam
- Active vs KPC, AmpC, and ESBLs
- Not active vs metallo-beta-lactamases (ie, NDM)

Drawz SM, et al. *Antimicrob Agents Chemother* 2014;58:1835.

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Ceftazidime/Avibactam

- Active vs many imipenem-resistant *Enterobacteriaceae*
- MIC90 vs *P. aeruginosa* = 4 mcg/mL
- MIC90 vs MDR R *P. aeruginosa* = >16 mcg/mL
- MIC90 vs AmpC derepressed *P. aeruginosa* = 8 mcg/mL
- Active against KPCs, ESBLs, and AmpC, but…

Castanheira M, et al. *Antimicrob Agents Chemother* 2015;59:3509-3517.

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Ceftazidime/Avibactam and Ceftolozane/Tazobactam vs Ceftazidime, Meropenem, and Piperacillin/Tazobactam-Resistant *P. aeruginosa*

Number of isolates (cumulative %) inhibited at an MIC of:

	≤0.25	0.5	1	2	4	8	16	32	>32
Ceftazidime/ Avibactam		1 (0.3)	4 (1.5)	45 (15.2)	87 (45.1)	100 (71.8)	53 (87.9)	17 (93)	23 (100)
Ceftolozane/ Tazobactam			22 (12.6)	47 (39.4)	51 (68.6)	29 (85.1)	8 (89.7)	4 (92)	14 (100)

Sader HS, et al. *Antimicrob Agents Chemother* 2015;59:3656-3659.
Farrell DJ, et al. *Antimicrob Agents Chemother* 2013;57:6305-6310.

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Ceftolozane/Tazobactam vs Ceftazidime/Avibactam

-	Gram +	Gram –	AmpC	ESBL	KPC	Metallo	MDR P. aerugin-osa	Anaerobe	MDR Acineto-bacter
Ceftolozane/ Tazobactam	–	++	+/–	++	–	–	+	+/–	–
Ceftazidime/ Avibactam	+/–	+++	++	++	++	–	+	+/–	–

Castanheira M, et al. *Antimicrob Agents Chemother* 2015;59:3509-3517.
Sader HS, et al. *Antimicrob Agents Chemother* 2015;59:3656-3659.
Farrell DJ, et al. *Antimicrob Agents Chemother* 2013;57:6305-6310.

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Conclusions: The new agents offer new opportunities

- Oritavancin and Dalbavancin:
  - Revolutionize OPAT?
- Tedizolid
  - Less toxic linezolid? PK/PD differences?
- Ceftolozane/tazobactam
  - Very active against many MDR *P. aeruginosa*
- Ceftazidime/avibactam
  - KPC activity and many MDR *P. aeruginosa*
- Wallet toxicity concerns

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