The role of new antibiotics in the treatment of severe infections – Safety and efficacy features

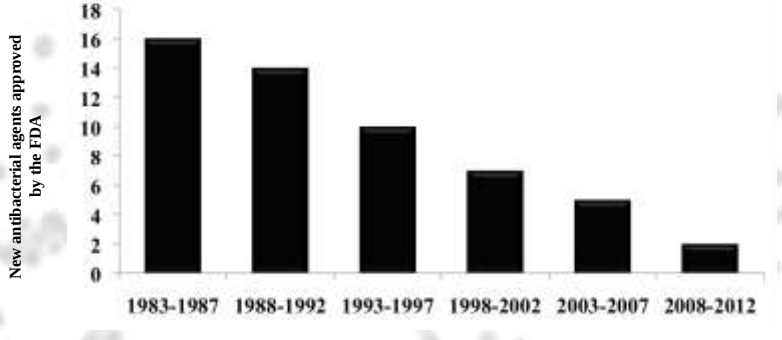
Christian Eckmann

Hannover, Germany

The role of new antibiotics in the treatment of severe infections: Safety and efficacy features

Christian Eckmann
Department of General,
Visceral and Thoracic Surgery
Klinikum Peine
Academic Hospital of
Medical University Hannover
Germany

Introduction of new antibiotic options is steadily declining



IDSA Public Policy. *Clin Infect Dis.* 2011;52(Suppl 5):S397-S428.

Adequate empirical antibiotic therapy in cSSTI

- n=399 cSSTI, of those 277 MRSA
- Univariate OR for treatment success for adequate empirical Ab-therapy: 6.07
- Multivariate OR for treatment success for adequate empirical Ab-therapy: 5.91

Ab, antibiotic; cSSTI, complicated skin and soft tissue infection; MRSA, methicillin-resistant *Staphylococcus aureus*
Szumowski JD, et al. *Antimicrob Agents Chemother*. 2007;51(2):423-428.

Does the trough level of vancomycin play a role in terms of clinical and microbiological efficacy for MRSA cSSTI?

1. Yes
2. No
3. Don’t know
4. Don’t care

Linezolid vs. vancomycin in cSSTI due to MRSA: Clinical value of vancomycin serum trough level

Table 4 Vancomycin trough levels and clinical and microbiologic outcomes in the per-protocol population

	End of treatment			End of study	
	Trough level (μg/mL)	Success n/N (%)	Failure n/N (%)	Success n/N (%)	Failure n/N (%)
Clinical outcome	0–5	23/26 (88.5)	3/26 (11.5)	18/22 (81.8)	4/22 (18.2)
	>5 to 10	55/67 (82.1)	12/67 (17.9)	44/58 (75.9)	14/58 (24.1)
	>10 to 15	30/32 (93.8)	2/32 (6.3)*	28/34 (82.4)	6/34 (17.6)*
	>15	24/25 (96.0)	1/25 (4.0)	20/24 (83.3)	4/24 (16.7)
Microbiologic outcome	0–5	19/26 (73.1)	7/26 (26.9)	17/22 (77.3)	5/22 (22.7)
	>5 to 10	46/67 (68.7)	21/67 (31.3)	40/58 (69.0)	18/58 (31.0)
	>10 to 15	20/33 (60/6)	13/33 (39.4)	20/34 (58.8)	14/34 (41.2)
	>15	19/25 (76.0)	6/25 (24.0)	17/24 (70.8)	7/24 (29.2)*

*Excluded from analysis (n = 1).

Conclusion: Clinical and microbiological success rate is independent from vancomycin serum trough level

Itani KMF, et al. *Am J Surg*. 2010;199(6):804-816.

MRSA – cSSTI
Critique on available drugs

Vancomycin	• Poor tissue penetration • MIC: creep • Difficult identification of strains with reduced susceptibility • Complex monitoring • Toxicity, especially after short treatment
Linezolid	• No data in bacteremia • Resistance problem? • Toxicity, especially following long treatment duration • Cost?
Daptomycin	• Myotoxicity • Eosinophil pneumonia • Right dosage?

MIC, minimum inhibitory concentration.

Dalbavancin: Overview

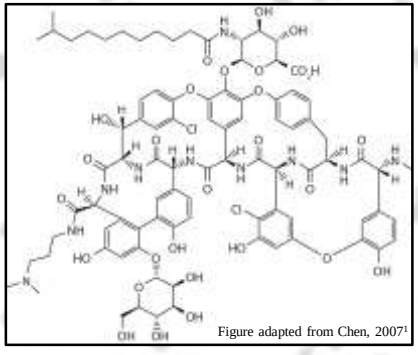


Figure adapted from Chen, 2007[1]

- For adults with ABSSSI, a two-dose regimen is recommended: 1000 mg IV, followed by 500 mg IV one week later[2]
- IV infusions should be administered over a 30-minute time period[2]

Dalbavancin was recently approved by the FDA and the Marketing Authorization Application has been submitted to the EMA

ABSSSI, acute bacterial skin and skin structure infection; EMA, European Medicines Agency; FDA, US Food and Drug Administration; IV, intravenous
1. Chen AY, et al. *Int J Clin Pract.* 2007;61:853-863; 2. Dalvance [prescribing information]. Durata Therapeutics, Chicago IL; 2014.

Dalbavancin vs. linezolid/vancomycin in the treatment of ABSSSI

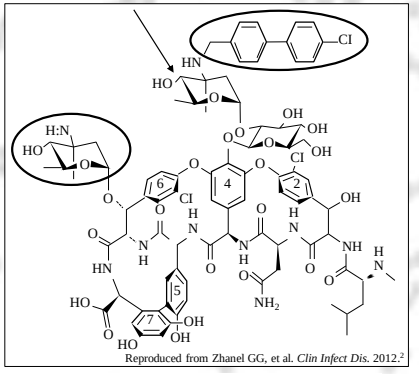
End Point	Dalbavancin	Vancomycin–Linezolid	Absolute Difference (95% CI)
	number/total number (percent)		*percentage points*
Primary end point			
DISCOVER 1	240/288 (83.3)	233/285 (81.8)	1.5 (−4.6 to 7.9)
DISCOVER 2	285/371 (76.8)	288/368 (78.3)	−1.5 (−7.4 to 4.6)
Both trials	525/659 (79.7)	521/653 (79.8)	−0.1 (−4.5 to 4.2)
Sensitivity analysis			
DISCOVER 1	259/288 (89.9)	259/285 (90.9)	−1.0 (−5.7 to 4.0)
DISCOVER 2	325/371 (87.6)	316/368 (85.9)	1.7 (−3.2 to 6.7)
Both trials	584/659 (88.6)	575/653 (88.1)	0.6 (−2.9 to 4.1)
Secondary end point			
Clinical status	517/570 (90.7)	502/545 (92.1)	−1.5 (−4.8 to 1.9)
Sensitivity analysis of clinical status†	533/570 (93.5)	517/545 (94.9)	−1.4 (−4.2 to 1.4)
Investigator's assessment of outcome	547/570 (96.0)	527/545 (96.7)	−0.7 (−3.0 to 1.5)

†The degree of fluctuance or localized heat or warmth had to be improved from baseline.

Boucher HW, et al. *N Engl J Med*. 2014;370(23):2169-2179.

Oritavancin: Overview

- Semisynthetic lipoglycopeptide[1]
- Three structural differences from vancomycin provide enhanced activity against vancomycin-resistant and vancomycin-susceptible organisms, including VSE and VRE[2]



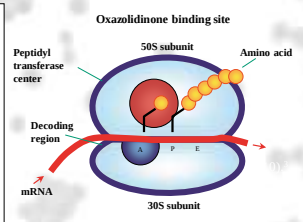
Reproduced from Zhanel GG, et al. *Clin Infect Dis*. 2012.[2]

Oritavancin was recently approved by the FDA and the Marketing Authorization Application has been submitted to the EMA

EMA, European Medicines Agency; FDA, US Food and Drug Administration; VSE, vancomycin-susceptible enterococci; VRE, vancomycin-resistant enterococci. 1. Orbactiv (oritavancin) [prescribing information]. Parsippany, NJ: The Medicines Company; 2014; 2. Zhanel GG, et al. *Clin Infect Dis*. 2012;54(Suppl 3):S214-S219.

Tedizolid phosphate mechanism of action

- Tedizolid binds to the 50S subunit of the bacterial ribosome, inhibiting protein synthesis[1]
- Organisms resistant to oxazolidinones via chromosomal mutations are generally cross-resistant to tedizolid
- In a limited number of *Staphylococcus aureus* strains, the presence of the *cfr* gene did not result in resistance to tedizolid phosphate in the absence of chromosomal mutations[2]



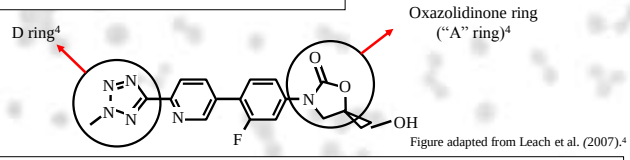
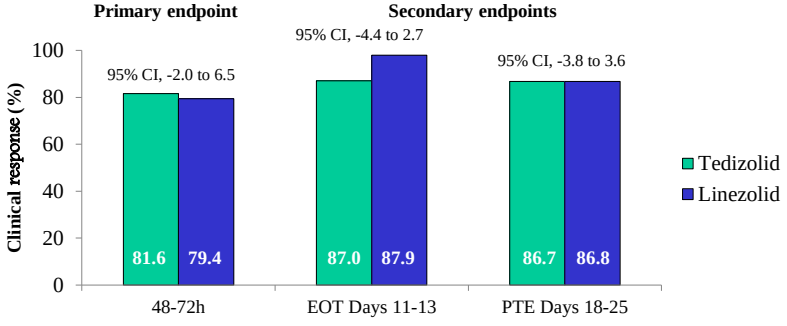


Figure adapted from Leach et al. (2007).[4]

cfr = chloramphenicol-florfenicol resistance
1. Shaw KJ, et al. *Antimicrob Agents Chemother*. 2008;52:4442-4447; 2. SIVEXTRO [prescribing information]. Cubist Pharmaceuticals; Lexington, MA; 2014; 3. Locke JB, et al. *Antimicrob Agents Chemother*. 2010;54:5337-5343; 4. Leach KL, et al. *Mol Cell*. 2007;26:393-402.

Tedizolid vs. linezolid in the treatment of ABSSSI

- Pooled analysis of two randomized, double-blind, Phase 3, multicenter trials (ESTABLISH-1 and ESTABLISH-2)
- n=1333 patients with ABSSSI (FDA criteria)
- 1 × 200 mg oral tedizolid for 6 days vs. 2 × 600 mg oral linezolid for 10 days



ABSSSI, acute bacterial skin and skin structure infection; EOT, end of treatment; FDA, US Food and Drug Administration; PTE, post-treatment evaluation.
Shorr, et al. *Antimicrob Agents Chemother*. 2015;59(2):864-871.

Decision matrix
Likelihood of resistant pathogens in cIAI

	MRSA	VRE	ESBL	KPC, MBL	(MDR) *Pseudo-monas* spp.	*Acineto-bacter* spp.
Primary peritonitis	+	+	++	-	-	-
Secondary peritonitis - CA	-	-	+	-	-	-
Secondary peritonitis - postoperative	+	++	+++	+	+	-
Tertiary peritonitis	++	+++	+++	+	++	-
CA-cIAI without risk factors	-	-	-	-	-	-
CA-cIAI with risk factors	-	-	+	-	++	-
HA-cIAI	+	-	++	-	++	+

CA, community-acquired; cIAI, complicated intra-abdominal infection; ESBL, extended-spectrum β-lactamase; HA, healthcare-associated; KPC, *Klebsiella pneumoniae* carbapenemase; MBL, metallo-β-lactamase; MDR, multidrug resistant; VRE, vancomycin-resistant *Enterococcus.*
Eckmann C, et al. *Eur J Infect Dis*. 2012;6:22–27.

Ceftazidime/avibactam in cIAI

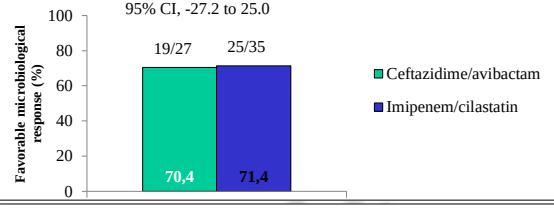
- Ceftazidime/avibactam is an intravenous (IV) antimicrobial that consists of a combination of ceftazidime and the non-β-lactam β-lactamase inhibitor avibactam
- Phase 2, prospective, randomized, double-blind, active-controlled trial evaluated the efficacy and safety of ceftazidime/avibactam plus metronidazole compared with meropenem in adult hospitalized patients with cIAI
- Primary endpoint: clinical response at TOC visit in the ME population

Favorable clinical response	Ceftazidime/avibactam + metronidazole	Meropenem	Difference (95% CI)
ME at TOC, n (%)	62/68 (91.2)	71/76 (93.4)	-2.2 (-20.4 to 12.2)
ME at LFU, n (%)	66/68 (97.1)	74/76 (97.4)	-0.3 (-17.1 to 15.4)

CI, confidence interval; LFU, late- follow up; ME, microbiologically evaluable; TOC, test-of-cure.
Lucasti et al. *J Antimicrob Chemother*. 2013;68:1183-92.

Ceftazidime/avibactam in cUTI

- A Phase 2, prospective, randomized trial (NCT00690378) compared the efficacy and safety of ceftazidime/avibactam to imipenem/cilastatin in hospitalized adults with cUTI and acute pyelonephritis
- The primary endpoint was microbiological response at the test-of-cure visit (5-9 days posttherapy) in the microbiologically evaluable population

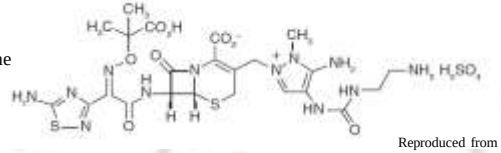


CI, confidence interval; cUTI, complicated urinary tract infection.
Vazquez et al. *Curr Med Res Opin*. 2012;28:1921-31.

Ceftolozane/tazobactam overview

- Antipseudomonal cephalosporin + β-lactamase inhibitor
- Fixed 2:1 ratio
- Active against:
  - *Pseudomonas aeruginosa*, including drug-resistant strains
  - *Escherichia coli*, including ESBL-positive strains
  - *Klebsiella pneumoniae*, including ESBL-positive strains

Ceftolozane



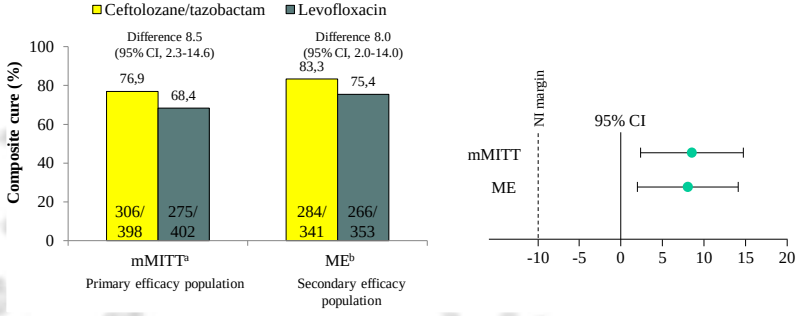
Reproduced from Eckmann & Solomkin (2015)

Completed Phase 3 trials for treatment of cIAI and cUTI
Phase 3 trial underway for nosocomial pneumonia

cIAI, complicated intra-abdominal infection; cUTI, complicated urinary tract infection; ESBL, extended spectrum β-lactamase.
Zhanel, et al. *Drugs*. 2014;74:31-51. Eckmann C, Solomkin J. *Expert Opin Pharmacother*. 2015;16(2):271-280

ASPECT-cUTI: Primary and key secondary endpoints

- Ceftolozane/tazobactam was superior to high-dose levofloxacin in seriously ill patients with cUTI

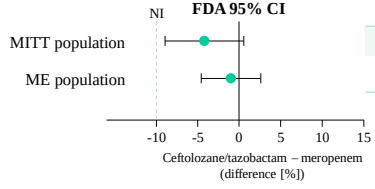


CI, confidence interval; cUTI, complicated urinary tract infection; ME, microbiologically evaluable; mMITT, microbiological modified intention-to-treat; NI, noninferiority. [a]Using a treatment-failure approach, where indeterminate responses are imputed as failures; [b]Using a data-as-observed approach, where indeterminate responses are excluded from the analysis. Wagenlehner, et al. *Lancet*. 2015 [In Press].

ASPECT-cIAI: Primary and key secondary endpoints

- Ceftolozane/tazobactam plus metronidazole was noninferior to meropenem in patients with cIAI

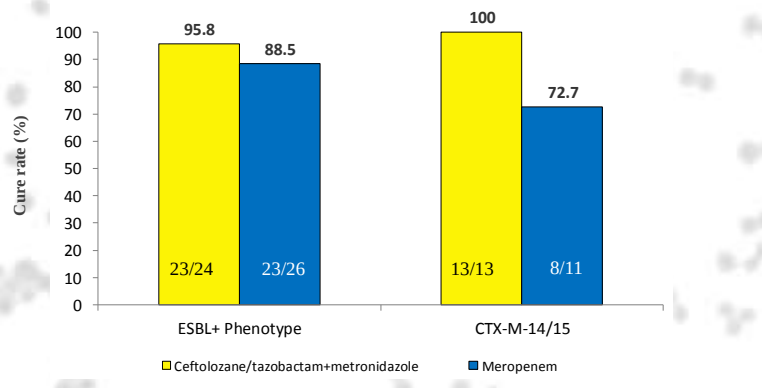
Clinical cure rates at TOC



Ceftolozane/tazobactam + metronidazole n/N (%)	Meropenem n/N (%)	Percentage difference (99% CI)
323/389 (83.0)	364/417 (87.3)	-4.2 (-8.9 to 0.5)
259/275 (94.2)	304/321 (94.7)	-1.0 (-4.5 to 2.6)

CI, confidence interval; CE, clinically evaluable; cIAI, complicated intra-abdominal infection; EMA, European Medicines Agency; FDA, US Food and Drug Administration; ITT, intent-to-treat; ME, microbiologically evaluable; MITT, microbiological intent-to-treat; NI, noninferiority; TOC, test-of-cure.
Eckmann, et al. ECCMID 2014. Poster P0266a.; Solomkin J, et al. *Clin Infect Dis*. 2015 Feb 10. [Epub ahead of print].

Ceftolozane/tazobactam vs. meropenem in patients with cIAI due to ESBLs



cIAI, complicated intra-abdominal infection; ESBL, extended-spectrum β-lactamase.
Solomkin J, et al. *Clin Infect Dis*. 2015 Feb 10. [Epub ahead of print].

Possible stewardship role of tedizolid and ceftolozane/tazobactam

- Tedizolid[1]
  - Available IV and oral
  - Can reduce IV treatment days in cSSTI
  - Can reduce costs and risks of in-hospital treatment
- Ceftolozane/Tazobactam[2]
  - Rise in ESBL so can help reduce carbapenem use (carbapenem stewardship)
  - Alternative to quinolones or aminoglycosides in β-lactam hypersensitivity?

1. Shorr, et al. Antimicrob Agents Chemother. 2015;59(2):864-871; 2. Eckmann C, Solomkin J. Expert Opin Pharmacother. 2015;16:271-80.
cSSTI, complicated skin and soft tissue infection; ESBL, extended-spectrum β-lactamase; IV, intravenous.

Is antibiotic class restriction practised at your institution to address antimicrobial resistance?

1. Yes
2. No

We live in a bacterial world where we will never be able to stay ahead of the mutation curve. A test of our resilience is how far behind the curve we allow ourselves to fall.

– US CDC , World Economic Forum, 2013

US CDC 2013. http://www.cdc.gov/drugresistance/threat-report-2013/pdf/ar-threats-2013-508.pdf

Q&A with panel discussion

All

Thank you

- We appreciate your feedback on this symposium
- Please turn to the back of your program book where you will find an evaluation form, which we ask you to complete and hand to a hostess
- Please remember to return your keypad