Die Zahl neuer Antibiotika nimmt zu
Wie setzt man diese sinnvoll ein?

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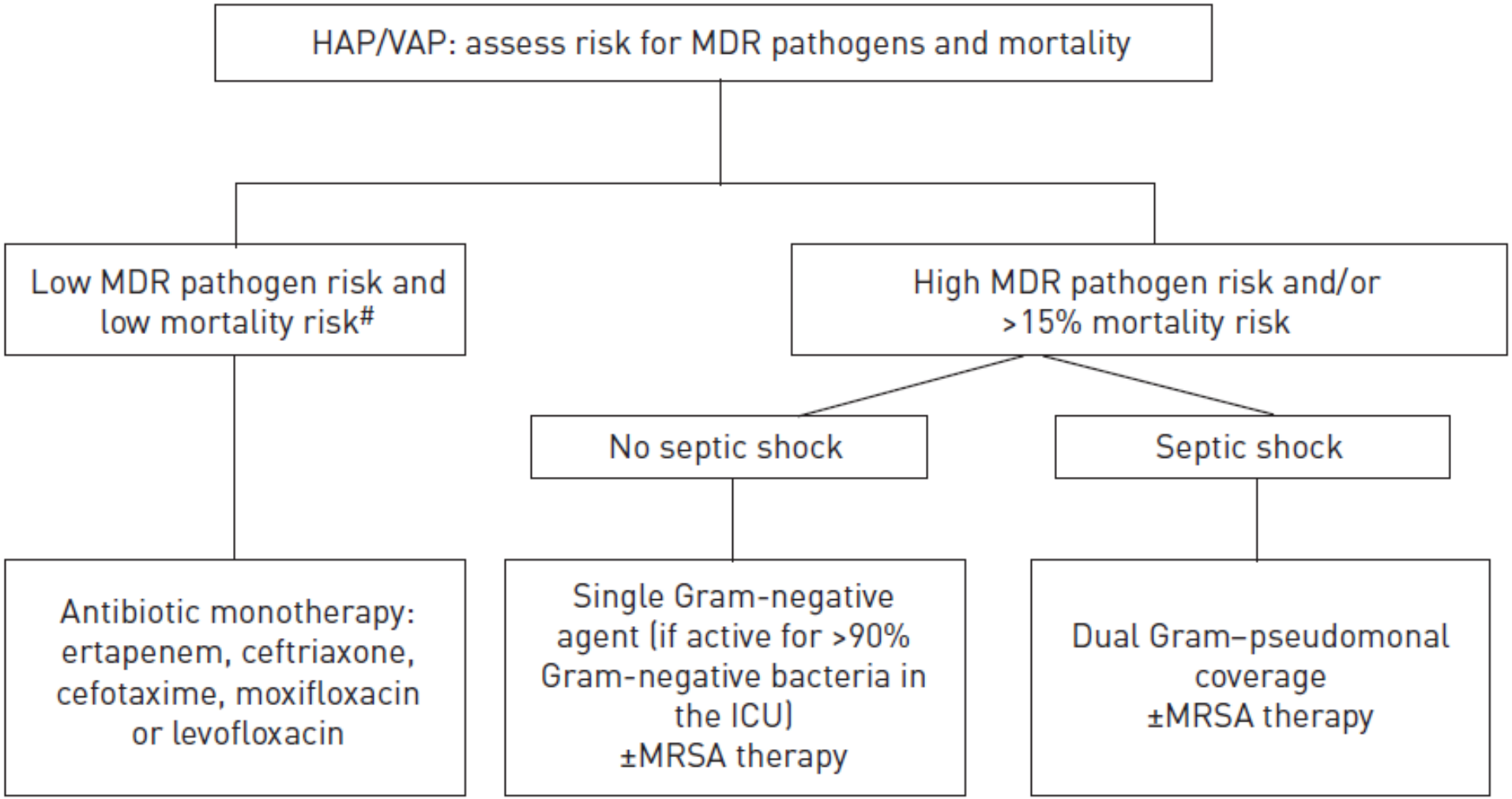
Conflicts of Interest

Research Grants: DFG, BMBF, BMG, EU, WHO

Fees for lectures: AstraZeneca, Basilea, Biotest, Bayer, Boehringer, Berlin Chemie GSK, MSD, Novartis, Pfizer, Roche; Sanofi Aventis

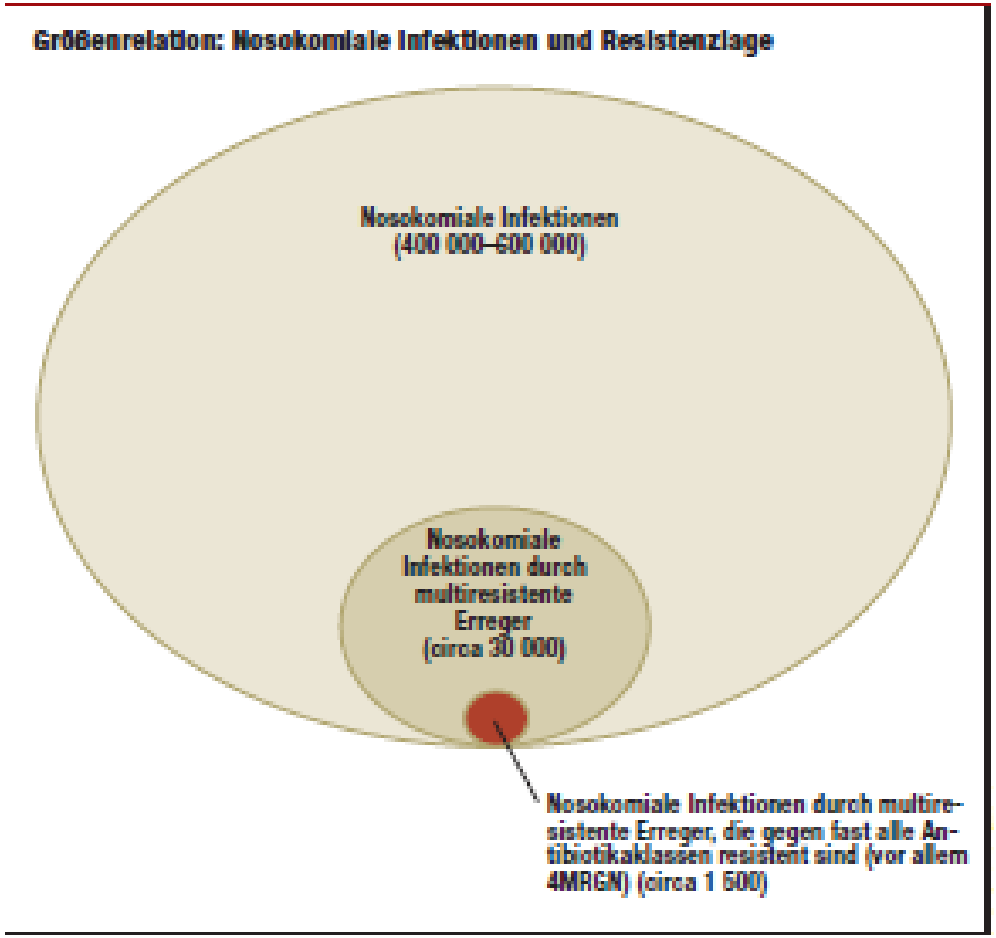
Advisory Board: AstraZeneca, Basilea, Biotest, Bayer, Boehringer, Gilead, GSK, Janssens, Novartis, Pfizer, Roche, SOBI



Torres A. ***Eur Respir J. 2017 Sep 10;50(3).***

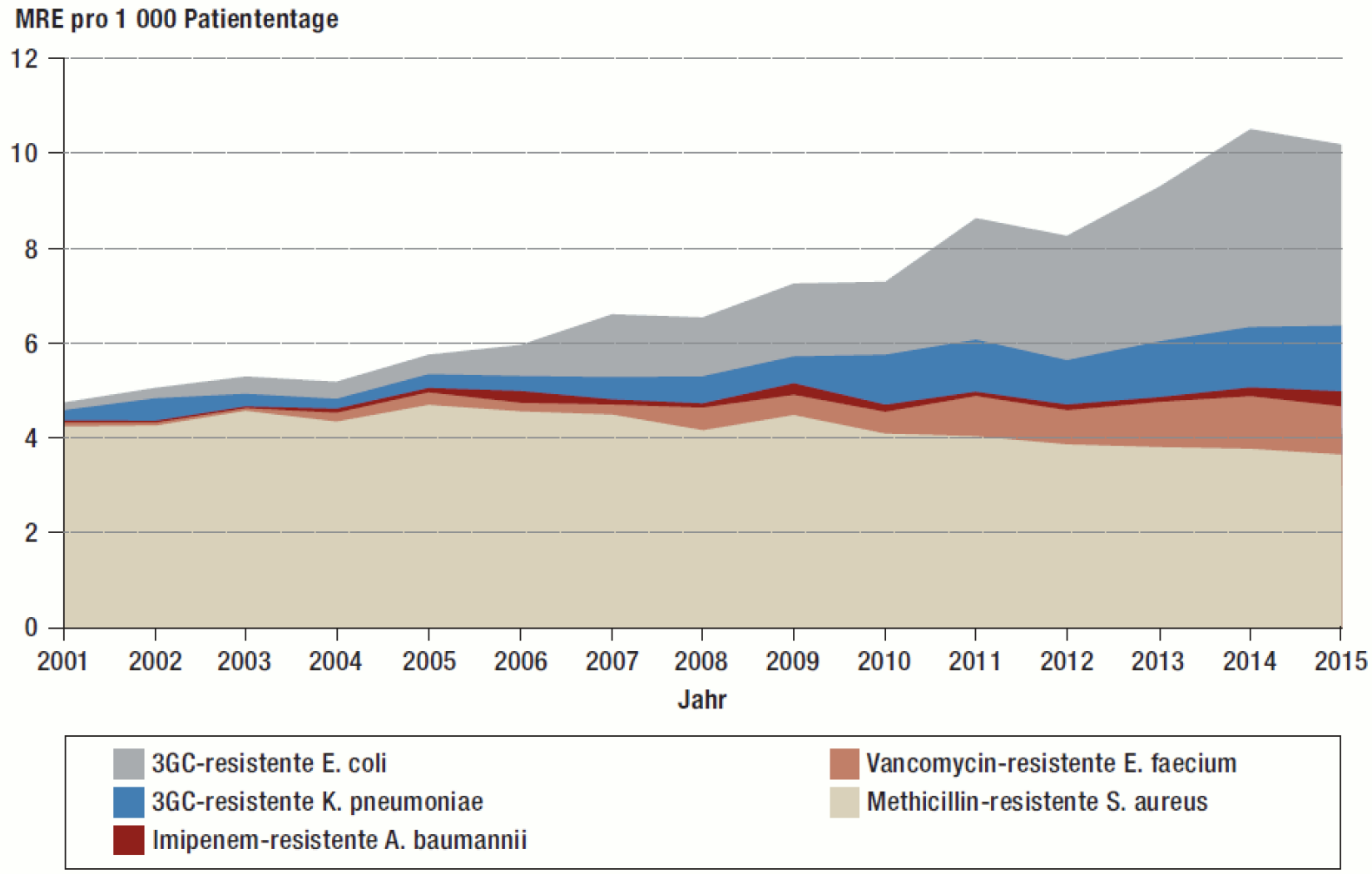
Multiresistente Erreger in Deutschland

- 11.000 MRSA
- 4 000 VRE
- 8 000 multiresistente E. coli
- 2 000 multiresistente K. pneumoniae
- 4 000 multiresistente P. aeruginosa
- Multiresistenz und Multiresistenz ist nicht immer dasselbe
  - 3 MRGN vs. 4 MRGN



Faetkenheuer G, Gastmeier P al. DAEB 2015 10. Apr;112: A674-5.

Antibiotikaresistenz in Deutschland unterschiedliche Entwicklung bei MRSA und MRGN



MDR Pathogens
Risikofaktoren

- Current hospitalization of ≥5 days.
- Antibiotic treatment in the prior 90 days
- High frequency (>25%) of antibiotic resistance in the specific ICU
- Immunosuppressive disease/therapy
- Presence of multiple risk factors for HCAP
  - Hospitalization for 2 days or more in the preceding 90 days
  - Residence in a nursing home or extended care facility
  - Home infusion therapy (including antibiocs)
  - Chronic dialysis within 30 days
  - Home wound care
  - Family member with muldrug-resistant pathogen

Nair GB, Niederman M. Intensive Care Med (2015) 41:34–48

Standardtherapie bei gram positiven Erregern

S. pneumoniae

- **Standard: Amoxicillin; Alternative: Doxycycline, Makrolids**
- **Severe Infection: Beta-Laktam-Makrolid Combination Therapy**

A und B-Streptokokken

- **Standard: Penicillin derivat**
- **Severe Infection: Penicillin-/Clindamycin Combination Therapy**

Staph. Aureus

- **Sensibel: Oxacillin or 1. Gen. Cephalosporin**
- **MRSA: Vancomycin/Linezolid/Daptomycin/Rifampicin/Ceftarolin**

Enterokokken

- **E. faecalis: Ampicillin or Ampicillin/Inhibitor**
- **E. faecium: Vancomycin/Linezolid**

Contents lists available at ScienceDirect

International Journal of Antimicrobial Agents

journal homepage: www.elsevier.com/locate/ijantimicag

Review

Ceftaroline fosamil as a potential treatment option for *Staphylococcus aureus* community-acquired pneumonia in adults

Tobias Welte[a,*], Michal Kantecki[b], Gregory G. Stone[c], Jennifer Hammond[d]

IJAA 2019. Oct;54(4):410-422

		Ceftaroline fosamil	Ceftriaxone
In vitro studies	MIC_{90} values against 7498 MSSA isolates and 10 580 MRSA isolates		
	AWARE programme	MSSA: MIC_{90} 0.25 mg/L	MSSA: MIC_{90} 4 mg/L
		MRSA: MIC_{90} 1 mg/L	MRSA: MIC_{90} 32 mg/L
Clinical studies	Clinical response rates at TOC against *S. aureus* in the ME population		
	FOCUS 1, n/N (%)	8 of 10 (80.0)	7 of 12 (58.3)
	FOCUS 2, n/N (%)	10 of 15 (66.7)	8 of 15 (53.3)
	ASIA CAP, n/N (%)	4 of 4 (100.0)	2 of 4 (50.0)
	Pooled, n/N (%)	22 of 29 (75.9)	17 of 31 (54.8)

Clin Infect Dis. 2014 Jul 1;59(1):51-61

A Phase 3 Randomized Double-Blind Comparison of Ceftobiprole Medocaril Versus Ceftazidime Plus Linezolid for the Treatment of Hospital-Acquired Pneumonia

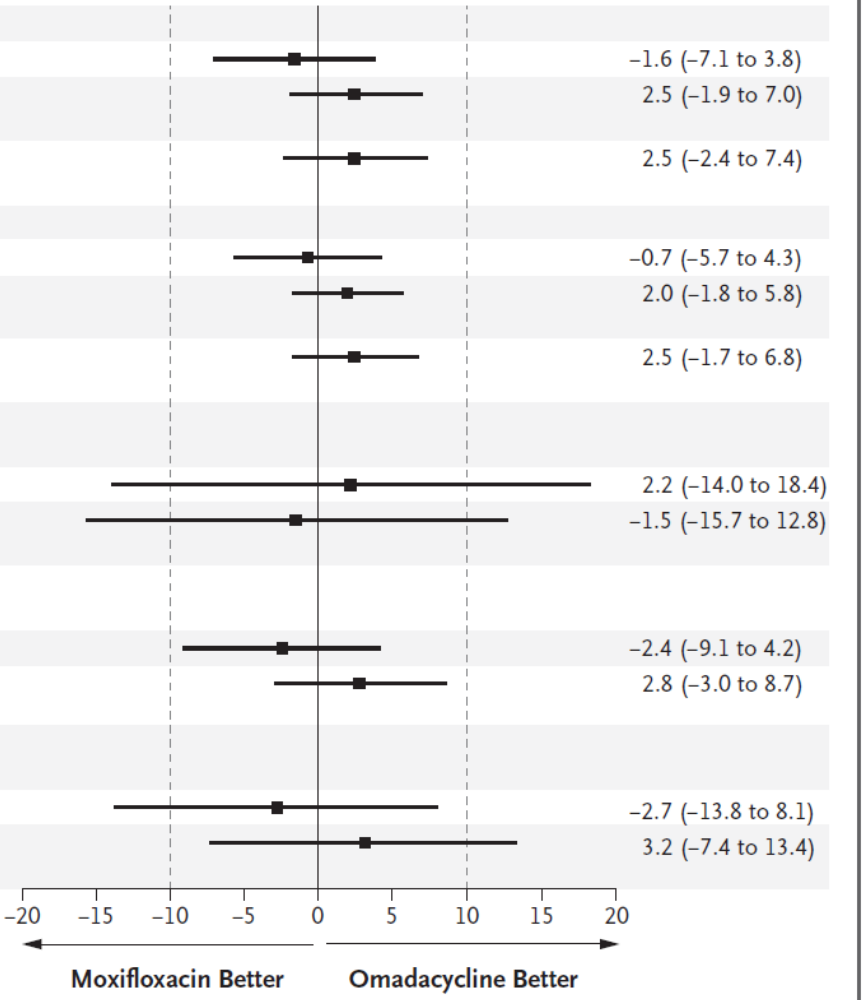
Samir S. Awad,[1] Alejandro H. Rodriguez,[2] Yin-Ching Chuang,[3] Zsuszanna Marjanek,[4] Alex J. Pareigis,[5] Gilmar Reis,[6] Thomas W. L. Scheeren,[7,8] Alejandro S. Sánchez,[9] Xin Zhou,[10] Mikaël Saulay,[11] and Marc Engelhardt[12]

	Ceftobiprole		Ceftazidime/Linezolid			
Analysis Set Group	No.	No.[a] (%)	No.	No.[a] (%)	Difference (%)[b]	(95% CI)[c]
Intent-to-treat						
All patients	391	195 (49.9)	390	206 (52.8)	−2.9	(−10.0 to 4.1)
HAP (excluding VAP)	287	171 (59.6)	284	167 (58.8)	0.8	(−7.3 to 8.8)
VAP	104	24 (23.1)	106	39 (36.8)	−13.7	(−26.0 to −1.5)
HAP, mechanically ventilated	69	21 (30.4)	70	19 (27.1)	3.3	(−11.8 to 18.3)
Clinically evaluable						
All patients	251	174 (69.3)	244	174 (71.3)	−2.0	(−10.0 to 6.1)
HAP (excluding VAP)	198	154 (77.8)	185	141 (76.2)	1.6	(−6.9 to 10.0)
VAP	53	20 (37.7)	59	33 (55.9)	−18.2	(−36.4 to −.0)
HAP (excluding VAP), mechanically ventilated	38	21 (55.3)	37	15 (40.5)	14.7	(−7.6 to 37.1)

Omadacycline for CAP

Stets R et al. NEJM (2019) 380: 517-527

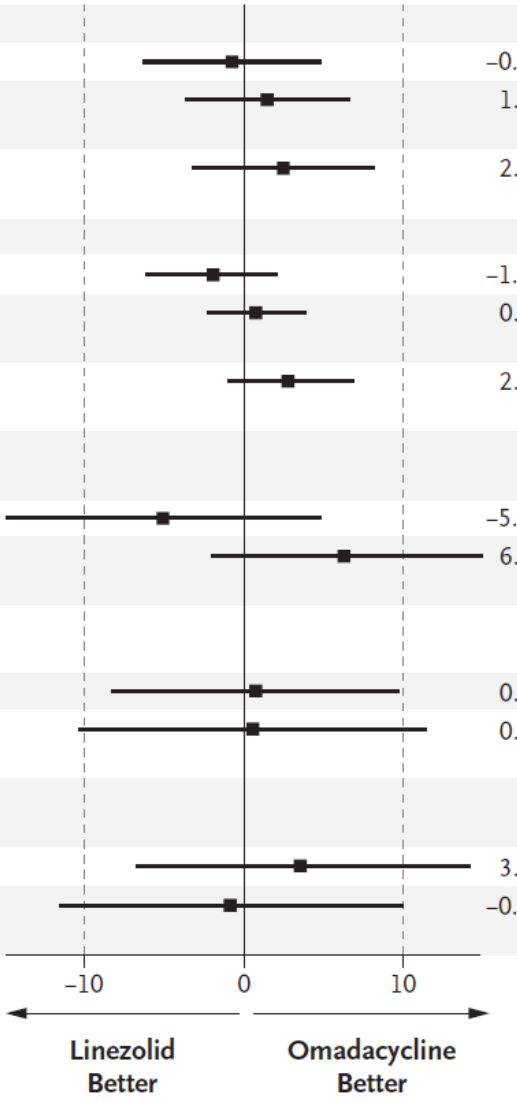
Subgroup	Omadacycline	Moxifloxacin	Percentage-Point Difference (95% CI)
	no. of events/total no. (%)		
ITT population			
Early clinical response	313/386 (81.1)	321/388 (82.7)	−1.6 (−7.1 to 3.8)
Investigator-assessed clinical response at EOT	349/386 (90.4)	341/388 (87.9)	2.5 (−1.9 to 7.0)
Investigator-assessed clinical response at PTE	338/386 (87.6)	330/388 (85.1)	2.5 (−2.4 to 7.4)
Clinical per-protocol population			
Early clinical response	308/356 (86.5)	314/360 (87.2)	−0.7 (−5.7 to 4.3)
Investigator-assessed clinical response at EOT	336/357 (87.0)	329/357 (84.8)	2.0 (−1.8 to 5.8)
Investigator-assessed clinical response at PTE	316/340 (92.9)	312/345 (90.4)	2.5 (−1.7 to 6.8)
Patients with PSI risk class II in the ITT population			
Early clinical response	43/57 (75.4)	41/56 (73.2)	2.2 (−14.0 to 18.4)
Investigator-assessed clinical response at PTE	47/57 (82.5)	47/56 (83.9)	−1.5 (−15.7 to 12.8)
Patients with PSI risk class III in the ITT population			
Early clinical response	191/227 (84.1)	187/216 (86.6)	−2.4 (−9.1 to 4.2)
Investigator-assessed clinical response at PTE	206/227 (90.7)	190/216 (88.0)	2.8 (−3.0 to 8.7)
Patients with PSI risk class IV in the ITT population			
Early clinical response	79/102 (77.5)	93/116 (80.2)	−2.7 (−13.8 to 8.1)
Investigator-assessed clinical response at PTE	85/102 (83.3)	93/116 (80.2)	3.2 (−7.4 to 13.4)



Omadacycline for SSSI

O'Riordan W et al. N Engl J Med 2019;380:528-38

Subgroup	Omadacycline	Linezolid	Percentage-Point Difference (95% CI)
	no. of events/total no. (%)		
Modified ITT population			
Early clinical response	268/316 (84.8)	266/311 (85.5)	−0.7 (−6.3 to 4.9)
Investigator-assessed clinical response at EOT	281/316 (88.9)	272/311 (87.5)	1.5 (−3.6 to 6.6)
Investigator-assessed clinical response at PTE	272/316 (86.1)	260/311 (83.6)	2.5 (−3.2 to 8.2)
Clinical per-protocol population			
Early clinical response	276/298 (92.6)	278/294 (94.6)	−1.9 (−6.1 to 2.1)
Investigator-assessed clinical response at EOT	271/278 (97.5)	264/273 (96.7)	0.8 (−2.2 to 3.9)
Investigator-assessed clinical response at PTE	259/269 (96.3)	243/260 (93.5)	2.8 (−1.0 to 6.9)
Patients with cellulitis or erysipelas in the modified ITT population			
Early clinical response	97/123 (78.9)	99/118 (83.9)	−5.0 (−14.9 to 4.9)
Investigator-assessed clinical response at PTE	112/123 (91.1)	100/118 (84.7)	6.3 (−2.0 to 15.0)
Patients with wound infection in the modified ITT population			
Early clinical response	91/102 (89.2)	92/104 (88.5)	0.8 (−8.2 to 9.7)
Investigator-assessed clinical response at PTE	83/102 (81.4)	84/104 (80.8)	0.6 (−10.3 to 11.4)
Patients with major abscess in the modified ITT population			
Early clinical response	80/91 (87.9)	75/89 (84.3)	3.6 (−6.7 to 14.2)
Investigator-assessed clinical response at PTE	77/91 (84.6)	76/89 (85.4)	−0.8 (−11.5 to 10.0)



Pharmacotherapy. 2020 Mar;40(3):221-238

Evaluation of Eravacycline: A Novel Fluorocycline

Sara Alosaimy,[1] Jacinda C. Abdul-Mutakabbir,[1] Razie Kebriaei,[1] Sarah C. J. Jorgensen,[1] and Michael J. Rybak[1,2,3]*

[1]Anti-Infective Research Laboratory, Department of Pharmacy Practice, Eugene Applebaum College of Pharmacy and Health Sciences, Wayne State University, Detroit, Michigan; [2]Department of Pharmacy, Detroit Medical Center, Detroit, Michigan; [3]Division of Infectious Diseases, Department of Medicine, School of Medicine, Wayne State University, Detroit, Michigan

Aerobic bacteria	
Gram-positive	*Staphylococcus aureus*
	Streptococcus anginosus group
	Enterococcus faecalis
	Enterococcus faecium
Gram-negative	*Citrobacter freundii*
	Enterobacter cloacae
	Escherichia coli
	Klebsiella pneumoniae
	Klebsiella oxytoca
Anaerobic bacteria	
Gram-positive	*Clostridioides perfringens*
Gram-negative	*Bacteroides ovatus*
	Bacteroides thetaiotaomicron
	Bacteroides uniformis
	Bacteroides caccae
	Bacteroides vulgatus
	Parabacteroides distasonis
	Bacteroides fragilis

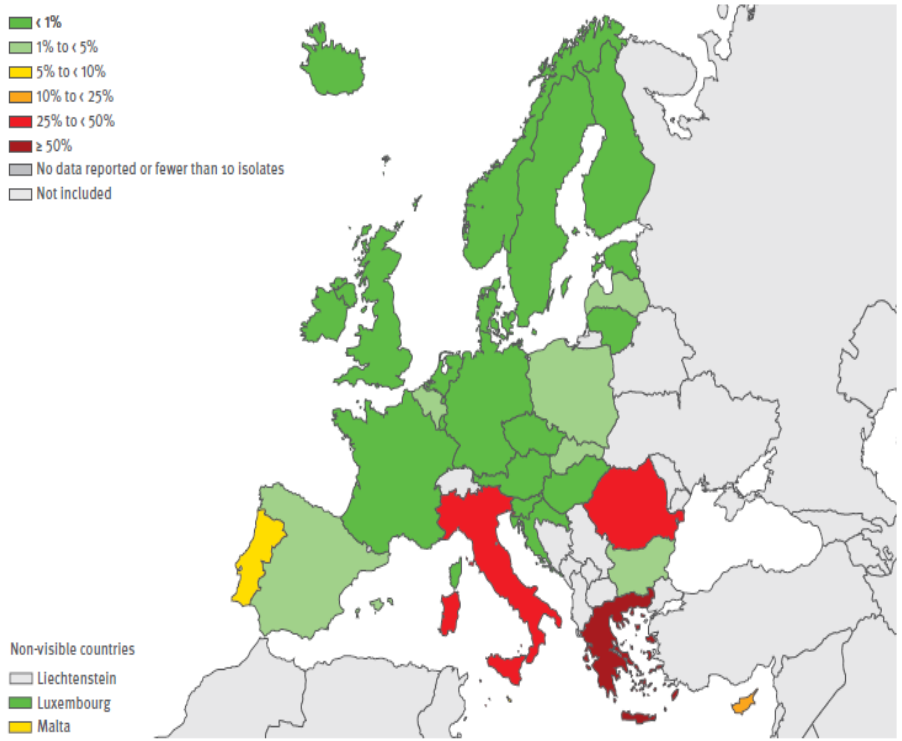
Study Design	ERV Arm	Comparator Arm	Duration	Primary Outcome	Result
cIAI					
Phase II Randomized, Double-blind, Double-dummy, Multicenter, multinational (N=143)[52]	1.0 IV mg/kg[a] q12h (n=56) Or 1.5 mg/kg IV q24h[a] (n=53)	ERT 1 g IV q24h (n=30)	4–14 days for treatment, 10–14 days for TOC visit, 28–42 days after last dose for follow-up	Clinical response in ME patients at the TOC visit 10 –14 days after the last dose of study drug therapy	• ERV 1.0 mg/kg 100.0% and ERT 92.3%: 95% CI (−6.7%–40.9%) • ERV 1.5 mg/kg 92.3% and ERT 92.3%: 95% CI (−23.1%–25.2%)
IGNITE1: Phase III Randomized, Double-blind, Double-dummy, Comparative, Noninferiority, Multicenter, multinational (N=541)[b,73]	1.0 mg/kg q12h[a] (n=270)	ERT 1 g IV q24h (n=268)	4–14 days for treatment, 25–31 days for TOC visit, 38–50 days after last dose for follow-up	Clinical response at TOC in the micro-ITT, MITT and CE populations	• ERV 86.8% and ERT 87.6%: 95% CI (−7.1 to 5.5) in the micro-ITT population • ERV 87.0% and ERT 88.8%: 95% CI (−7.4 to 3.8) in the MITT population • ERV 91.4% and ERT 95.0%: 95% CI (−8.9 to 1.5) in the CE population
IGNITE4: Phase III Randomized, Double-blind, Double-dummy, Comparative, Noninferiority, Multicenter, multinational (N=500)[b,72]	1.0 mg/kg IV q12h[a] (n=250)	MEM 1 g IV q8h (n=249)	4–14 days for treatment, 25–31 days for TOC visit, 38–50 days after last dose for follow-up	Clinical response at TOC in the micro-ITT population	• ERV 90.8% and MEM 91.2%: 95% CI (−6.3 to 5.3)
cUTI					
IGNITE2: Phase III Randomized, Double-blind, Double-dummy, Comparative, Noninferiority, Multicenter, multinational (N=1045)[b,74]	1.5 mg/kg[a] IV q24h, then transition to 200 mg PO q12h (n=502) Or 1.5 mg/kg IV[a] q24h, then transition to 250 mg PO q12h (n=45)	LEV 750 mg IV q24h, then 750 mg PO q24hr (n=498)	3–7 days for IV treatment and transition to PO to maintain 7 days of total treatment, 2-3 wk after last dose for follow-up	Responder outcome defined as clinical cure and microbiological success at PT	• ERV 60.4% and LEV 66.9%: 95% CI (−14.1 to 1.2)
IGNITE3: Phase III Randomized, Double-blind, Double-dummy, Comparative, Noninferiority, Multicenter, multinational (N=1201)[b,74]	1.5 mg/kg[a] IV q24h (n=601)	ERT 1g IV q24h (n=600)	5–10 days for treatment, 2–3 wk after last dose for follow-up	Responder outcome defined as clinical cure and microbiological success at PT	• ERV 84.8% and ERT 94.8%: 95% CI (−14.1 to −6.0)

Carbapenem resistant Enterobacteriacae

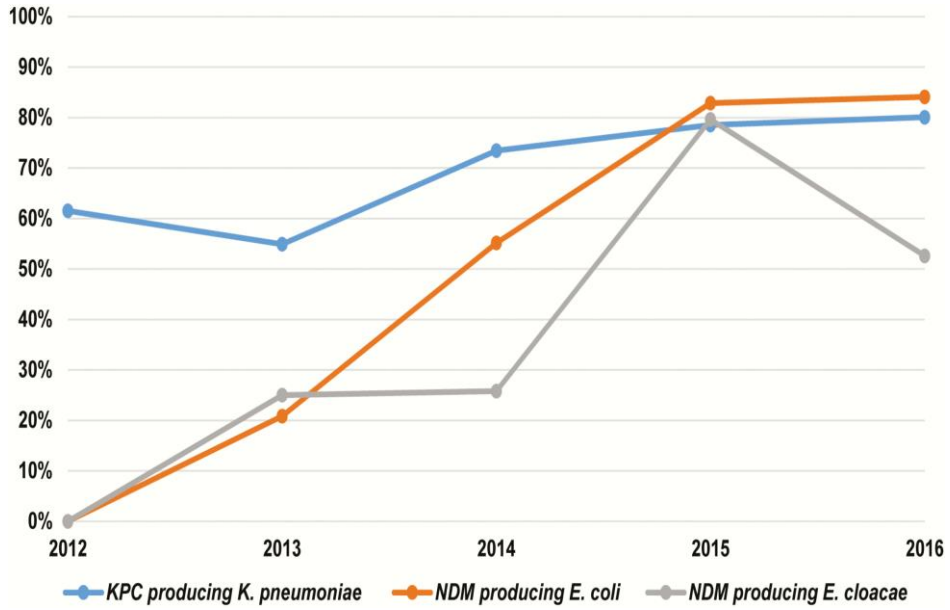
https://ecdc.europa.eu/sites/portal/files/documents/AMR%202016_Final-with-cover-for-web-2017.pdf

Wang Qi et al. CID, Volume 67, Issue suppl_2, 1 December 2018, Pages S196–S205,

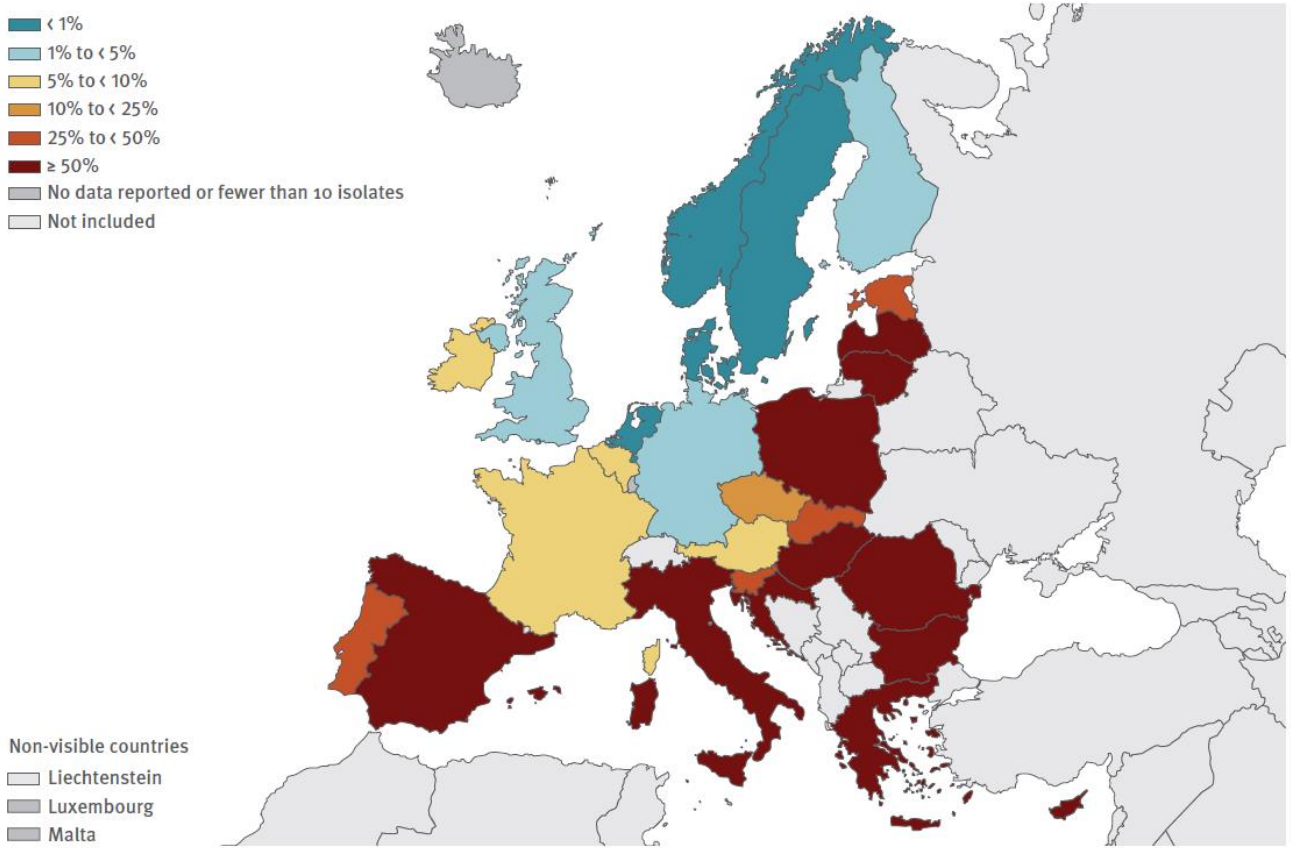
Europe



China



Anteil von 4-MRGN bei invasiven Acinetobacter-Infektionen in Europa



ECDC. Surveillance of antimicrobial surveillance in Europe 2017.

Risk of Death is Higher in Patients Infected with Resistant Strains

		Deaths (%)		
	Outcome (number of studies included)	**Resistant**	**Not resistant**	**RR (95% CI)**
***Escherichia coli* resistant to:**				
3rd gen. cephalosporins	Bacterium attributable mortality (n=4)	23.6	12.6	2.02 (1.41 to 2.90)
Fluoroquinolones	Bacterium attributable mortality (n=1)	0	0	
***Klebsiella pneumoniae* resistant to:**				
3rd gen. cephalosporins	Bacterium attributable mortality (n=4)	20	10.1	1.93 (1.13 to 3.31)
Carbapenems	Bacterium attributable mortality (n=1)	27	13.6	1.98 (0.61 to 6.43)
***Staphylococcus aureus* resistant to:**				
Methicillin (MRSA)	Bacterium attributable mortality (n=46)	26.3	16.9	1.64 (1.43 to 1.87)

Therapieoptionen bei schweren Infektionen mit 3 und 4-MRGN

Verbleibende wirksame Antibiotikaklassen

- **Carbapeneme**
    - **als Monotherapie wirksam**
    - **Nachteil: Gefahr der Selektion Carbapenemresistenter Erreger (CRO) > 4 MRGN > und dann?**
- **Colistin - alleine oder in Kombination?**
- **Alternativen?**

Ceftolozan/Tazobactam vs. Other agents for bacteremia and NP due to MDR Pseudomonas

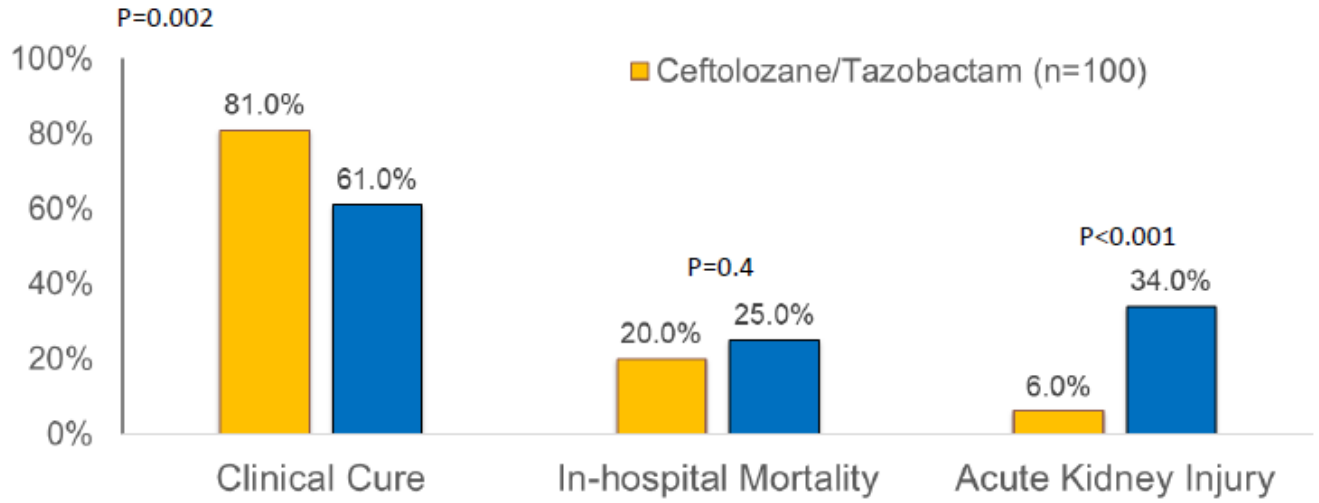
- Multicenter case-control study from Italy

Treatment and outcome	Number (%) of patients			
Variable	Overall	Colistin/ aminoglycoside group* (n=32)	Ceftolozane-tazobactam group* (n=16)	p
Overall duration of treatment	12.3±6.6	12.3±7.7	12.1±5.8	0.93
14-day clinical cure	31 (64.6)	18 (56.3)	13 (81.3)	0.11
30-day mortality	12 (25.0)	9 (28.1)	3 (18.8)	0.72
AKI development during antibiotic therapy	8 (16.7)	8 (25.0)	0	**0.04**

Vena A, *et al.* Clin infect Dis 2020;ciaa003

Effectiveness of Ceftolozan-Tazobactam vs. Polymyxin or Aminoglykosid containing regimens

- 200 patients from 6 US Medical Centers with MDR *P.* aeruginosa; 42% with Severe sepsis or septic shock; 69% were in an ICU at the onset of the infection
  - Ceftolozane/tazobactam was associated with a 20% improvement in clinical cure and a 28% decrease in AKI
    - This equates to a number needed to treat (NNT) with ceftolozane/tazobactam for a clinical cure of 5 and a number needed to harm (NNH) with an AKI event with a polymyxin or aminoglycoside of 4



Pogue J, *et al.* Clin Infect Dis 2020;71:304

MDR Pseudomonas spp. Therapie

Bronchiallavage:

- **Pseudomonas aeruginosa 10^5 cfu/ml**
  - **Meropenem MIC = 8 mg/l (R)**
  - **Alle anderen Betalaktame, auch Ceftazidim resistent**
  - **Ciprofloxacin resistent**
  - **Colistin MIC = 1 mg/l (S)**
  - **Tobramcin MIC < 1 mg/l (S)**
  - **Fosfomycin = 8 mg/l (S)**

Pseudomonas Treatment
Prolonged Infusion

2196 articles were identified and screened, 22 studies (1876 patients) were included in the meta-analysis.

Carbapenems, penicillins, and cephalosporins were studied.

Prolonged infusion was associated with lower all-cause mortality than short-term infusion (risk ratio [RR] 0·70, 95% CI 0·56-0·87).

Heterogeneity was not observed (p=0·93, I^2=0%). The funnel plot and the Egger's test (p=0·44) showed no evidence of publication bias.

Spektum neuer β-Laktam und β-Laktam Kombinationsantibiotika gegenüber multi-resistenten Gram-negativen Bakterien

Agents (references)	Company	Activity against indicated enzymes or multidrug-resistant strains						
		ESBL	KPC	MβL	AmpC	OXA	MDR-PA	MDR-Ab
Ceftazidime-avibactam	Pfizer	+	+		+	+		
Aztreonam-avibactam	Pfizer	+	+	+	+	+		
Ceftaroline-avibactam	Pfizer	+	+		+	+		
Meropenem-vaborbactam	Melinta	+	+		+			
Imipenem/cilastatin-relebactam	Merck	+	+		+		+	
Meropenem-nacubactam	Roche	+	+		+	+[a]	+[a]	
Cefepime-zidebactam	Wockhardt	+	+	+	+	+	±	+
Cefepime-VNRX-5133	VenatoRx	+	+	+	+	+	+	
Cefepime-AAI101	Allecra	+	+		+	+		
Cefiderocol	Shionogi	+	+	+	+	+	+	+

Shio-Shin J et al. Drugs (2019) 79:705–714

ASPECT - NP

Studiendesign

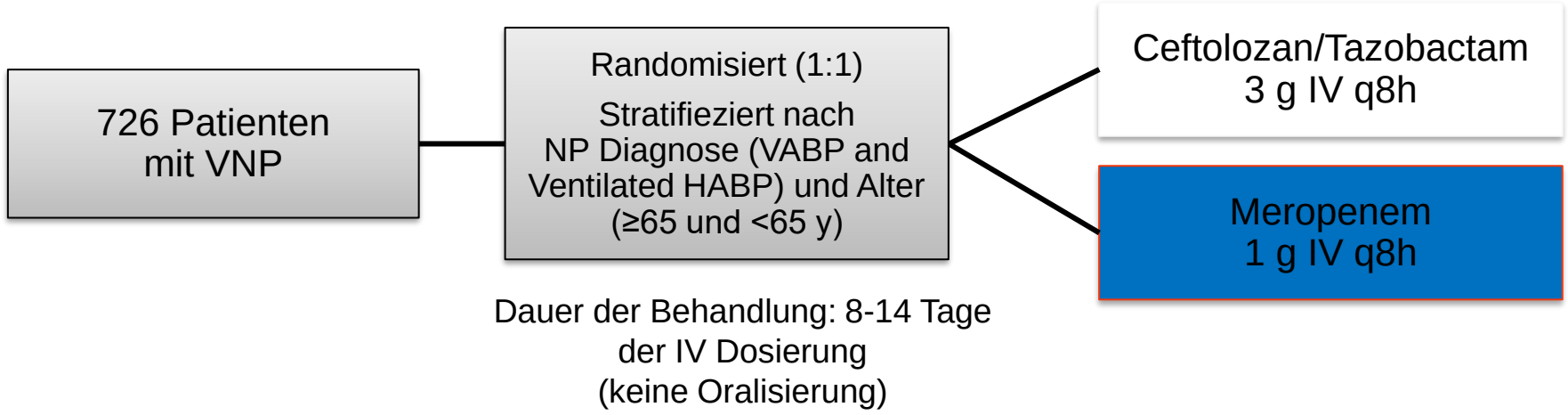
Phase 3 Studie:

•randomisiert, kontrolliert, doppelblind, multizentrisch bei Erwachsenen Patienten mit nosokomialer Pneumonie (Ventilator-Associated Bacterial Pneumonia [VABP] or Ventilated Hospital-Acquired Bacterial Pneumonia [HABP])

primärer Endpunkt:

•nach US FDA: Nichtunterlegenheit (NI) basierend auf der Gesamtmortalitätsrate an Tag 28 in der ITT Population (NI margin 10%, 95% CI)

•nach EMA: Nichtunterlegenheit (NI) basierend auf der klinischen Ansprechrate am TOC-Visit (7-14 Tage nach EOT) in der CE Population (NI margin 12.5%, 97.5% CI)



Dauer der Behandlung: 8-14 Tage
der IV Dosierung
(keine Oralisierung)

Ceftolozane–tazobactam versus meropenem for treatment of nosocomial pneumonia (ASPECT-NP): a randomised, controlled, double-blind, phase 3, non-inferiority trial

Lancet Infect Dis 2019
Published Online
September 25, 2019

Marin H Kollef, Martin Nováček, Ülo Kivistik, Álvaro Réa-Neto, Nobuaki Shime, Ignacio Martin-Loeches, Jean-François Timsit, Richard G Wunderink, Christopher J Bruno, Jennifer A Huntington, Gina Lin, Brian Yu, Joan R Butterton, Elizabeth G Rhee

	Ceftolozane–tazobactam group	Meropenem group	% difference (95% CI)*
28-day all-cause mortality (ITT population)†			
Overall	87/362 (24·0%)	92/364 (25·3%)	1·1 (–5·1 to 7·4)‡
Ventilator-associated pneumonia	63/263 (24·0%)	52/256 (20·3%)	–3·6 (–10·7 to 3·5)§
Ventilated hospital-acquired pneumonia	24/99 (24·2%)	40/108 (37·0%)	12·8 (0·2 to 24·8)§
28-day all-cause mortality (microbiological ITT population)†	53/264 (20·1%)	63/247 (25·5%)	4·4 (–2·8 to 11·8)‡
Clinical cure at test of cure (ITT population)†			
Overall	197/362 (54·4%)	194/364 (53·3%)	1·1 (–6·2 to 8·3)‡
Ventilator-associated pneumonia	147/263 (55·9%)	146/256 (57·0%)	–1·1 (–9·6 to 7·4)§
Ventilated hospital-acquired pneumonia	50/99 (50·5%)	48/108 (44·4%)	6·1 (–7·4 to 19·3)§
Clinical cure at test of cure (clinically evaluable population)¶			
Overall	139/218 (63·8%)	143/221 (64·7%)	–1·3 (–10·2 to 7·7)‡
Ventilator-associated pneumonia	105/159 (66·0%)	111/172 (64·5%)	1·5 (–8·7 to 11·6)§
Ventilated hospital-acquired pneumonia	34/59 (57·6%)	32/49 (65·3%)	–7·7 (–25·0 to 10·6)§
Microbiological eradication at test of cure (microbiological ITT population)†	193/264 (73·1%)	168/247 (68·0%)	4·5 (–3·4 to 12·5)‡

Lancet Infect Dis 2019

Published Online
September 25, 2019

Ceftolozane–tazobactam versus meropenem for treatment of nosocomial pneumonia (ASPECT-NP): a randomised, controlled, double-blind, phase 3, non-inferiority trial

Marin H Kollef, Martin Nováček, Ülo Kivistik, Álvaro Réa-Neto, Nobuaki Shime, Ignacio Martin-Loeches, Jean-François Timsit, Richard G Wunderink, Christopher J Bruno, Jennifer A Huntington, Gina Lin, Brian Yu, Joan R Butterton, Elizabeth G Rhee

	Ceftolozane–tazobactam group	Meropenem group	% difference (95% CI)*
Gram-negative pathogens	157/259 (60·6%)	137/240 (57·1%)	3·5 (–5·1 to 12·1)
Enterobacteriaceae	120/195 (61·5%)	105/185 (56·8%)	4·8 (–5·1 to 14·5)
ESBL-producing Enterobacteriaceae	48/84 (57·1%)	45/73 (61·6%)	–4·5 (–19·3 to 10·7)
Pseudomonas aeruginosa	36/63 (57·1%)	39/65 (60·0%)	–2·9 (–19·4 to 13·8)
Multidrug-resistant *P aeruginosa*	13/24 (54·2%)	6/11 (54·5%)	–0·4 (–31·2 to 31·7)
Extensively drug-resistant *P aeruginosa*	4/10 (40·0%)	2/5 (40·0%)	0·0 (–43·6 to 40·3)

Data are n/N (%). *Unstratified Newcombe CIs; inferences drawn from these intervals might therefore not be reproducible.

JAMA | Original Investigation

Effect of Piperacillin-Tazobactam vs Meropenem on 30-Day Mortality for Patients With *E coli* or *Klebsiella pneumoniae* Bloodstream Infection and Ceftriaxone Resistance

A Randomized Clinical Trial

Patrick N. A. Harris, MBBS; Paul A. Tambyah, MD; David C. Lye, MBBS; Yin Mo, MBBS; Tau H. Lee, MBBS; Mesut Yilmaz, MD; Thamer H. Alenazi, MD; Yaseen Arabi, MD; Marco Falcone, MD; Matteo Bassetti, MD, PhD; Elda Righi, MD, PhD; Benjamin A. Rogers, MBBS, PhD; Souha Kanj, MD; Hasan Bhally, MBBS; Jon Iredell, MBBS, PhD; Marc Mendelson, MBBS, PhD; Tom H. Boyles, MD; David Looke, MBBS; Spiros Miyakis, MD, PhD; Genevieve Walls, MB, ChB; Mohammed Al Khamis, MD; Ahmed Zikri, PharmD; Amy Crowe, MBBS; Paul Ingram, MBBS; Nick Daneman, MD; Paul Griffin, MBBS; Eugene Athan, MBBS, MPH, PhD; Penelope Lorenc, RN; Peter Baker, PhD; Leah Roberts, BSc; Scott A. Beatson, PhD; Anton Y. Peleg, MBBS, PhD; Tiffany Harris-Brown, RN, MPH; David L. Paterson, MBBS, PhD; for the MERINO Trial Investigators and the Australasian Society for Infectious Disease Clinical Research Network (ASID-CRN)

	30-d Mortality, No./Total No. (%)		Risk Difference, % (1-Sided 97.5% CI)[a]	*P* Value for Noninferiority
	Piperacillin-Tazobactam	Meropenem		
Primary analysis	23/187 (12.3)	7/191 (3.7)	8.6 (−∞ to 14.5)	.90
Per-protocol analysis	18/170 (10.6)	7/186 (3.8)	6.8 (−∞ to 12.8)	.76

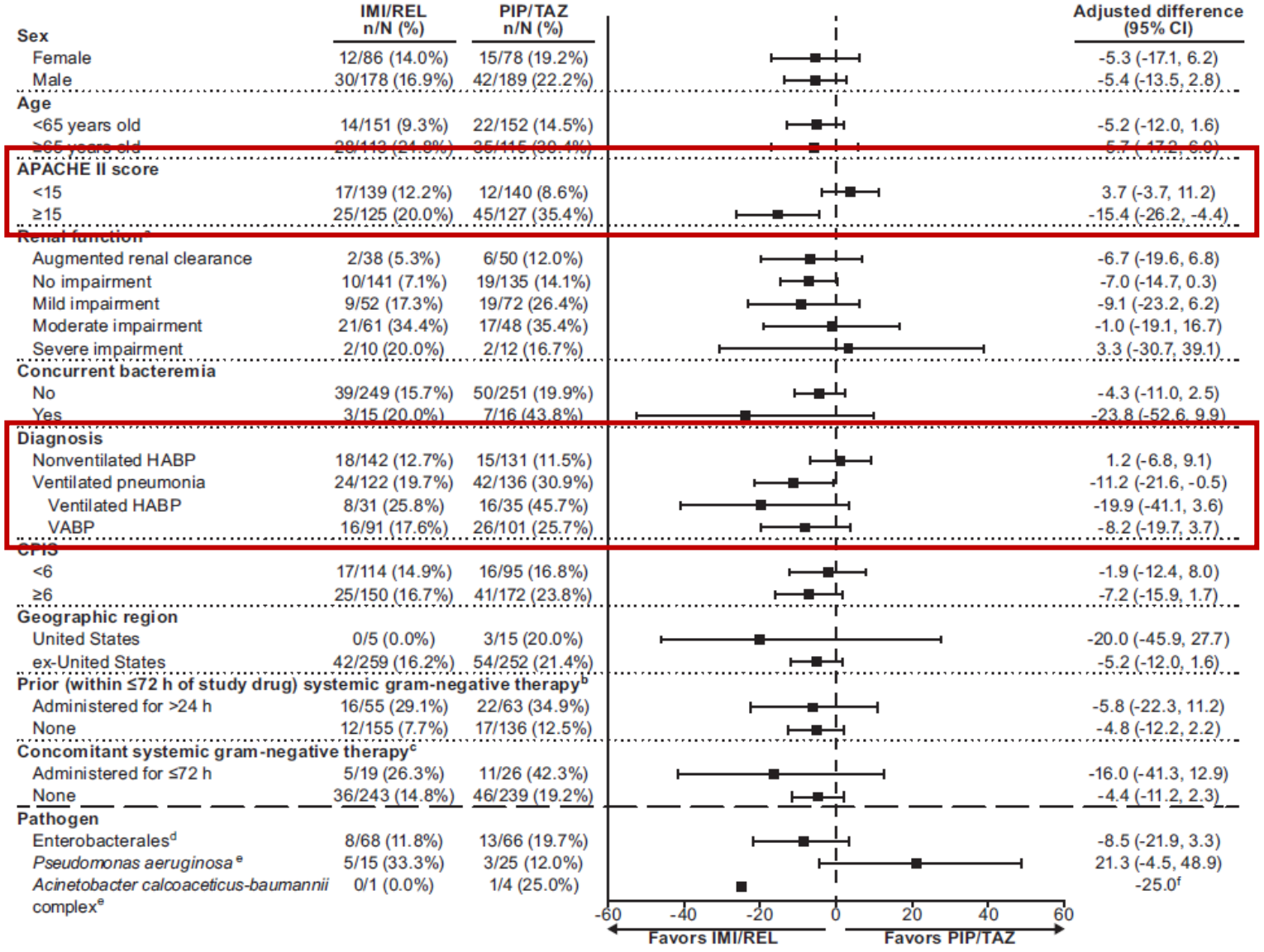
A Randomized, Double-blind, Multicenter Trial Comparing Efficacy and Safety of Imipenem/Cilastatin/Relebactam Versus Piperacillin/Tazobactam in Adults With Hospital-acquired or Ventilator-associated Bacterial Pneumonia (RESTORE-IMI 2 Study)

Ivan Titov,[1] Richard G. Wunderink,[2] Antoine Roquilly,[3] Daniel Rodríguez Gonzalez,[4] Aileen David-Wang,[5] Helen W. Boucher,[6] Keith S. Kaye,[7] Maria C. Losada,[8] Jiejun Du,[8] Robert Tipping,[8] Matthew L. Rizk,[8] Munjal Patel,[8] Michelle L. Brown,[8] Katherine Young,[8] Nicholas A. Kartsonis,[8] Joan R. Butterton,[8] Amanda Paschke,[8] and Luke F. Chen[8]

Endpoint	IMI/REL, no./No. (%)[a]	PIP/TAZ, no./No. (%)[a]	Adjusted Difference[b], % (95% CI)
Primary endpoint			
Day 28 all-cause mortality (MITT)	42/264 (15.9)	57/267 (21.3)	−5.3 (−11.9 to 1.2)[c]
Key secondary endpoint			
Favorable clinical response at EFU (MITT)	161/264 (61.0)[d]	149/267 (55.8)[d]	5.0 (−3.2 to 13.2)[e]
Other secondary endpoints			
Day 28 all-cause mortality (mMITT)	36/215 (16.7)	44/218 (20.2)	−3.5 (−10.9 to 3.6)
Favorable microbiologic response at EFU (mMITT)	146/215 (67.9)[d]	135/218 (61.9)[d]	6.2 (−2.7 to 15.0)
Favorable clinical response at EFU (CE)	101/136 (74.3)	100/126 (79.4)	−3.7 (−13.6 to 6.4)

Clin Infect Dis. 2020 Aug 12: Online ahead of print.

Titov I et al. Clin Infect Dis. 2020 Aug 12: Online ahead of print.



JAMA | Original Investigation

JAMA. 2018;319(8):788-799. doi:10.1001/jama.2018.0438

Effect of Meropenem-Vaborbactam vs Piperacillin-Tazobactam on Clinical Cure or Improvement and Microbial Eradication in Complicated Urinary Tract Infection

The TANGO I Randomized Clinical Trial

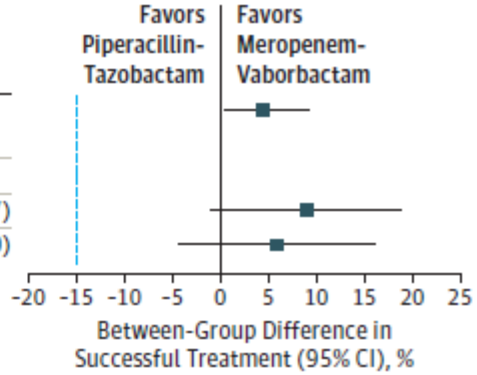
Keith S. Kaye, MD, MPH; Tanaya Bhowmick, MD; Symeon Metallidis, MD; Susan C. Bleasdale, MD; Olexiy S. Sagan, MD; Viktor Stus, MD, PhD; Jose Vazquez, MD; Valerii Zaitsev, PhD; Mohamed Bidair, MD; Erik Chorvat, MD; Petru Octavian Dragoescu, MD; Elena Fedosiuk, MD; Juan P. Horcajada, MD, PhD; Claudia Murta, MD; Yaroslav Sarychev, MD; Ventsislav Stoev, MD; Elizabeth Morgan, BS; Karen Fusaro, BS; David Griffith, BS; Olga Lomovskaya, PhD; Elizabeth L. Alexander, MD; Jeffery Loutit, MBChB; Michael N. Dudley, PharmD; Evangelos J. Giamarellos-Bourboulis, MD, PhD

Drug resistance (FDA/CLSI criteria) in the most common baseline urinary gram-negative pathogens (microbiologic MITT population)[a,g,h]		
E coli	n = 124	n = 115
Meropenem	0	0
Piperacillin-tazobactam	7 (5.6)	6 (5.2)
K pneumoniae	n = 30	n = 27
Meropenem	1 (3.3)	2 (7.4)
Piperacillin-tazobactam	15 (50)	9 (33.3)

JAMA. 2018;319(8):788-799. doi:10.1001/jama.2018.0438

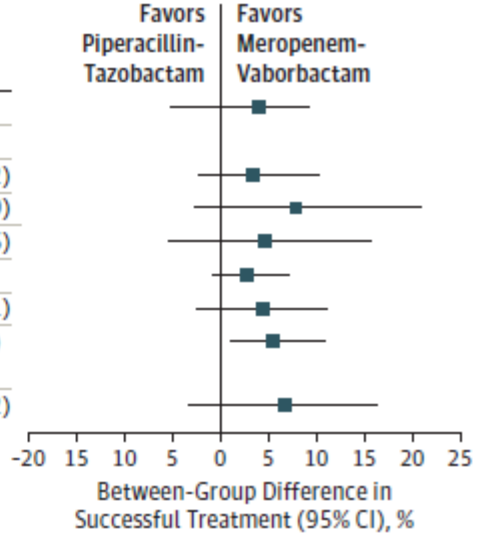
A Primary end points

	No. of Patients Successfully Treated/Total No. (%)		Between-Group Difference (95% CI), %
	Meropenem-Vaborbactam	Piperacillin-Tazobactam	
FDA primary: overall success at end of intravenous treatment (microbiologic MITT analysis)[a,b]	189/192 (98.4)	171/182 (94.0)	4.5 (0.7 to 9.1)
EMA primary: microbial eradication at test of cure			
Microbiologic MITT analysis[b]	128/192 (66.7)	105/182 (57.7)	9.0 (-0.9 to 18.7)
Microbiologic evaluable analysis	118/178 (66.3)	102/169 (60.4)	5.9 (-4.2 to 16.0)



B Secondary end points

	No. of Patients Successfully Treated/Total No. (%)		Between-Group Difference (95% CI), %
	Meropenem-Vaborbactam	Piperacillin-Tazobactam	
Overall success at test of cure[a]	143/192 (74.5)	128/182 (70.3)	4.1 (-4.9 to 9.1)
Overall success at end of intravenous treatment[a]			
Acute pyelonephritis	117/120 (97.5)	95/101 (94.1)	3.4 (-2.0 to 10.2)
Complicated UTI, removable infection source[c]	35/35 (100)	35/38 (92.1)	7.9 (-2.5 to 20.9)
Complicated UTI, nonremovable infection source	37/37 (100)	41/43 (95.3)	4.7 (-5.1 to 15.6)
Clinical cure at end of intravenous treatment[d]	189/192 (98.4)	174/182 (95.6)	2.8 (-0.7 to 7.1)
Clinical cure at test of cure	174/192 (90.6)	157/182 (86.3)	4.4 (-2.2 to 11.1)
Microbial eradication at end of intravenous treatment (FDA criteria)	188/192 (97.9)	168/182 (92.3)	5.6 (1.4 to 10.7)
Microbial eradication at test of cure (FDA criteria)	132/192 (68.8)	113/182 (62.1)	6.7 (-3.0 to 16.2)



	ESBL				Carbapenemasen		
	Klasse A			Klasse C	Klasse A	Klasse B	Klasse D
	TEM	SHV	CTX-M	AmpC	KPC	MBL	OXA-48
4G Cephalosporine							
Piperacillin/Tazobactam							
Carbapeneme							
Aztreonam							

Ambler	Enzyme	Ceftolozan/ Tazobactam	Ceftazidim/ Avibactam	Meropenem/ Vaborbactam	Imipenem/ Relebactam	Aztreonam	Aztreonam/ Avibactam
A	ESBL	+	+	+	+	-	+
	KPC	-	+	+	+	-	+
B	MBL	-	-	-	-	+	+
C	AmpC	variabel	+	+	+	-	+
D	OXA-48	-	+	-	-	variabel	variabel

1. ClinicalTrials.gov NCT01499290, NCT01500239, NCT0172602. 2. ClinicalTrials.gov NCT01595438, NCT01599806. 3. ClinicalTrials.gov NCT01644643. 4. ClinicalTrials.gov NCT01808092.

Ceftazidime-Avibactam - Phase III Clinical Trial Programme

7 prospective, international, multicentre, randomised Phase III studies

RECLAIM 1, 2 and 3[1] **Adults with cIAI**	RECAPTURE 1 and 2[2] **Adults with cUTI (including acute pyelonephritis)**	REPRISE[3] **Adults with cIAI or cUTI due to CAZ-resistant pathogens**	REPROVE[4] **Adults with NP including VAP**
Double-blind randomisation (1:1): •Ceftazidime-avibactam 2000-500 mg q8h + metronidazole 500 mg IV q8h *or* •Meropenem 1000 mg q8h **Primary objective:** •RECLAIM 1 and 2: –Assess non-inferiority of CAZ-AVI re: clinical cure at TOC visit in patients with ≥1 identified pathogen (mMITT populations) •RECLAIM 3: –Proportion of patients with clinical cure at TOC visit (CE population)	**Double-blind randomisation (1:1):** • Ceftazidime-avibactam 2000-500 mg q8h *or* • Doripenem 500 mg q8h **Primary objective:** Assess non-inferiority of CAZ-AVI on co-primary endpoints (mMITT populations): 1) Resolution of UTI-specific symptoms 2) Resolution/improvement of flank pain 3) Per-patient microbiological eradication and symptomatic resolution	**Open-label randomisation (1:1):** • Ceftazidime-avibactam 2000-500 mg q8h (+ metronidazole 500 mg q8h for cIAI) *or* • Best available therapy (BAT) **Primary objective:** Estimate per-patient clinical response to CAZ-AVI and BAT at TOC visit in cUTI and cIAI caused by CAZ-resistant Gram-negative pathogens	**Double-blind randomisation (1:1):** • Ceftazidime-avibactam 2000-500 mg q8h *or* • Meropenem 1000 mg q8h • *Plus* open-label empiric linezolid + aminoglycoside **Primary objective:** Assess non-inferiority of CAZ-AVI on clinical cure rate at TOC visit in cMITT and CE populations

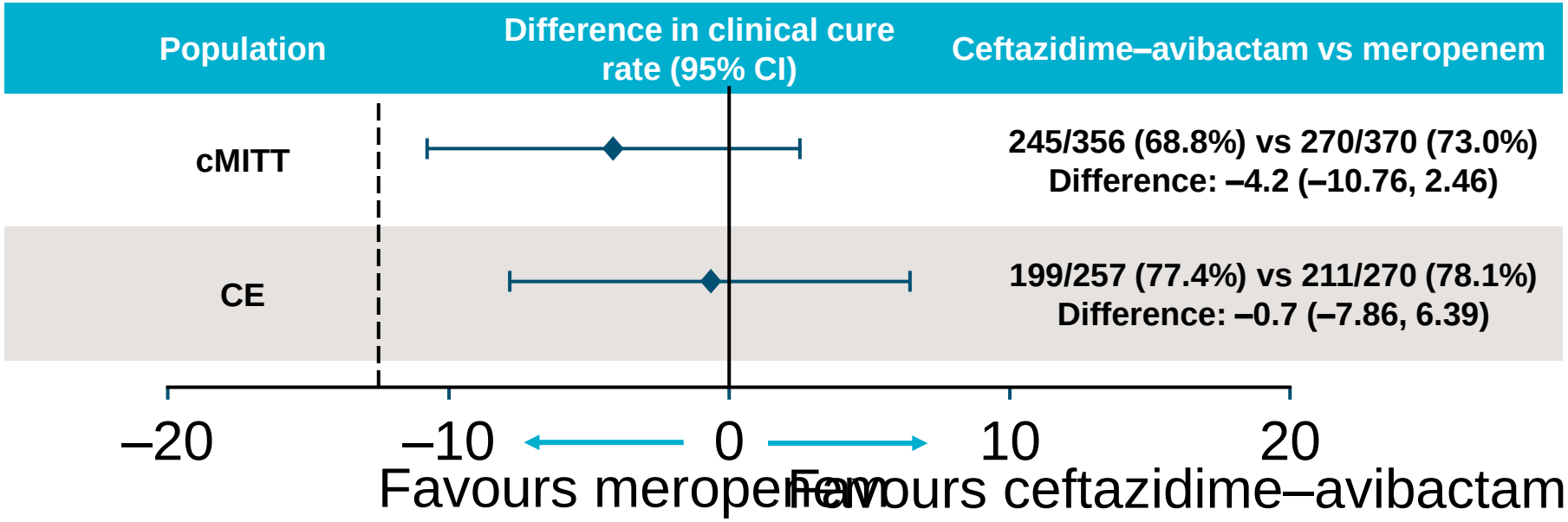
Consistent dosing across all seven trials
Comparators >97% carbapenems across all seven trials

Ceftazidime-Avibactam Dosage and Administration

	cIAI	cUTI/NP/ Aerobic Gram-negative infections
Recommended dose	Ceftazidime-avibactam 2000-500 mg q8h plus metronidazole q8h	Ceftazidime-avibactam 2000-500 mg q8h
IV infusion time	2 h	
Treatment duration	5–14 days	
Dose adjustments	Reduced dose and/or less frequent dosing for CrCL ≤50 mL/min Ceftazidime is almost exclusively excreted by glomerular filtration and the dose should be reduced when the glomerular filtration rate is <50 mL/min[3]	
Patients' age	≥18 years	

http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/004027/WC500210234.pdf

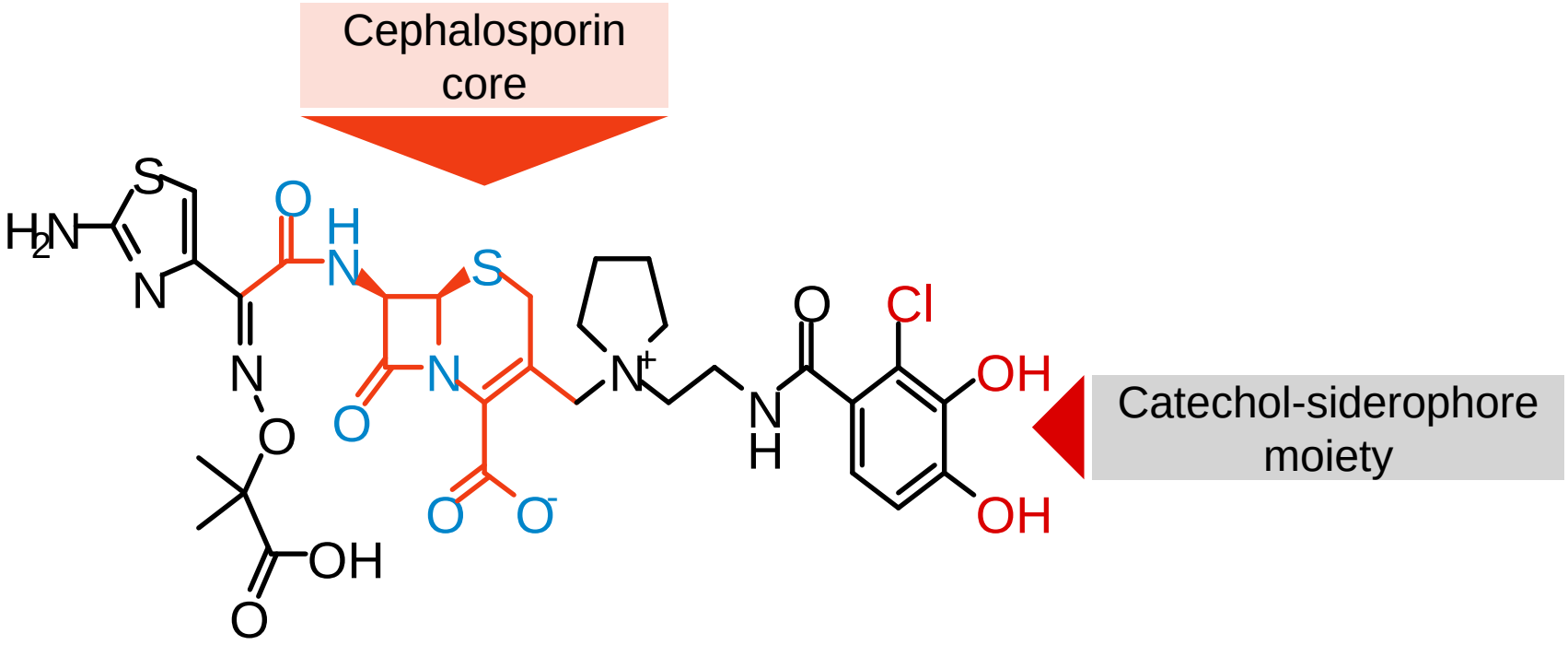
Primary efficacy results: Clinical cure rates at TOC visit (cMITT and CE populations)



The primary endpoint was met: ceftazidime–avibactam was non-inferior to meropenem in both co-primary populations

Torres A. et al.. *Lancet Infect Dis (in press)*

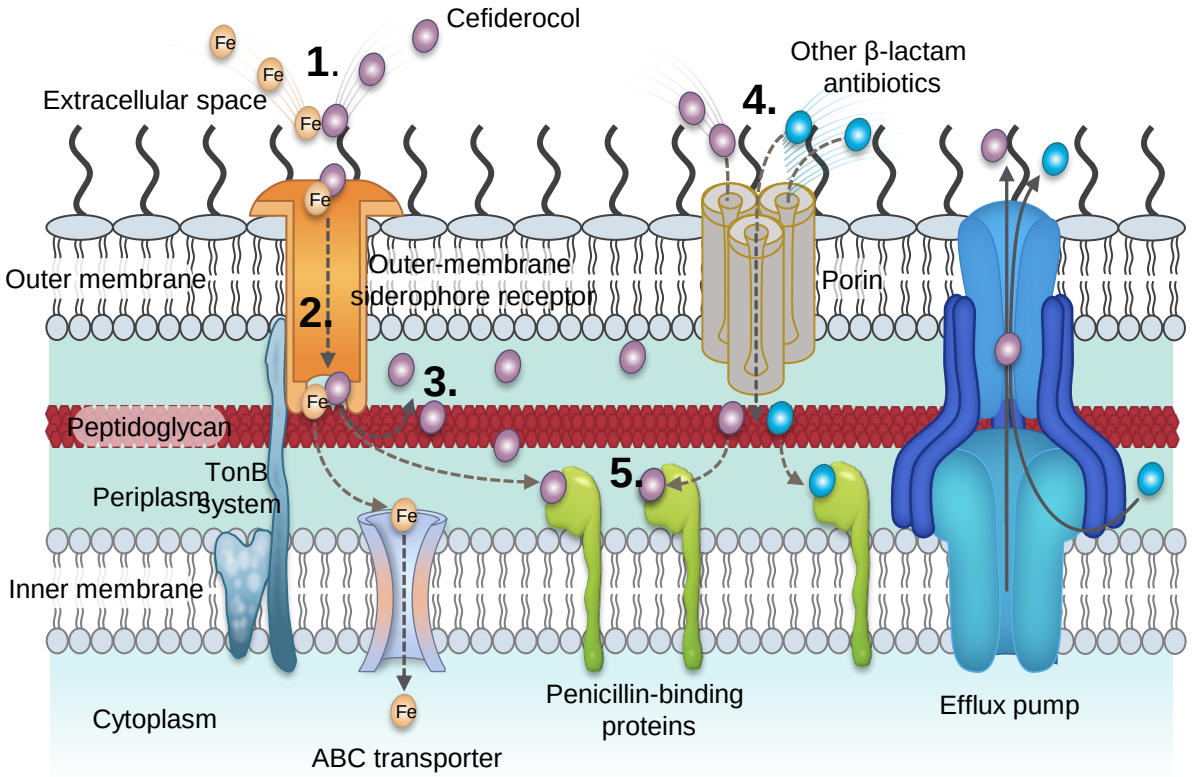
Cefiderocol



Ito A, et al. *Antimicrob Agents Chemother* 2016;60:7396–401.

Novel mechanism of cefiderocol entry into the periplasm

Cefiderocol is actively transported across the outer membrane via an iron-uptake mechanism[1,2]



1. Cefiderocol chelates extracellular iron
2. Chelated complex is actively transported into the periplasm by outer-membrane receptors
3. Once in the periplasm, cefiderocol dissociates from iron ions
4. Like other beta-lactam antibiotics, cefiderocol also enters the periplasm via diffusion through porins
5. Once inside the periplasm, cefiderocol binds and inhibits PBPs

Cefiderocol's unique mechanism of entry enables it to overcome resistance mediated by changes to porin channels and efflux-pump overexpression

Ito A, et al. *Antimicrob Agents Chemother* 2016;60:7396–401; Ito A, et al. Poster Saturday-114 presented at ASM Microbe 2017, New Orleans, LA.

Hackel MA, et al. Antimicrob Agents Chemother 2017;61:e00093-17;

In vitro activity of cefiderocol and comparators against non-fermenters (SIDERO-WT-2014-2016 European isolates)

Drug, MIC mg/L	*P. aeruginosa* (n=2,767)		CarbNS- *P. aeruginosa* (n=727)		*A. baumannii* (n=2,014)		CarbNS- *A. baumannii* (n=1,438)		*S. maltophilia* (n=627)		*B. cepacia* complex (n=81)	
	MIC_{50}	MIC_{90}	MIC_{50}	MIC_{90}	MIC_{50}	MIC_{90}	MIC_{50}	MIC_{90}	MIC_{50}	MIC_{90}	MIC_{50}	MIC_{90}
Cefiderocol	0.12	0.5	0.25	1	0.12	2	0.25	2	0.06	0.25	0.015	0.5
Cefepime	4	16	16	64	64	>64	64	>64	32	64	16	>64
Ceftazidime/avibactam	2	8	8	64	32	>64	32	>64	16	>64	4	8
Ceftolozane/tazobactam	0.5	4	1	>64	16	>64	32	>64	8	>64	2	32
Ciprofloxacin	0.25	>8	8	>8	>8	>8	>8	>8	2	8	1	>8
Colistin	1	2	1	2	1	8	1	>8	1	8	>8	>8
Meropenem	0.5	16	8	>64	64	>64	64	>64	>64	>64	4	16

MIC ≤4 mg/L MIC >4–<32 mg/L MIC ≥32 mg/L

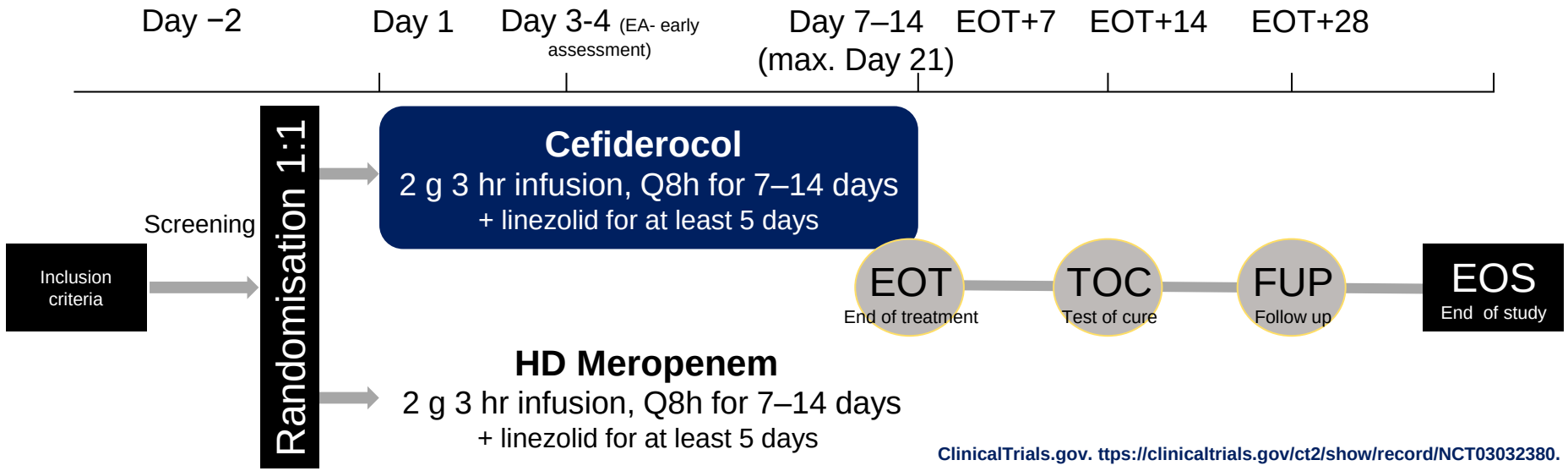
* Portsmouth S, Lancet Inf Dis 2018; 18:1319-28 ; Basseti M, Inf and Drug Res 2019: 12 3607-23; www.ema.europa.eu/medicines/human/EPAR/fetcroja

Cefiderocol - Klinische Daten

Studie	APEKS-NP (n=300)	APEKS-cUTI (n=452)	CREDIBLE (n=150)
Indikation	HAP/VAP/HCAP	Komplizierte Harnwegsinfektion (cUTI) mit/ohne akute Pyelonephritis	HAP/VAP/HCAP BSI/Sepsis cUTI
Therapie	Fetcroja® im Vergleich zu Hochdosis-Meropenem	Fetcroja® im Vergleich zu Imipenem/Cilastatin	Fetcroja® Best Available Therapy (29 verschiedene AB-Regime)
Studiendesign	Multizentrisch, randomisiert, doppelblind, Non-Inferiorität	Multizentrisch, randomisiert, doppelblind Non-Inferiorität	Multizentrisch, randomisiert, Open-label Nicht vergleichend (deskriptiv)
Primärer Endpunkt	Gesamtmortalität (Tag 14)	Kombiniertes klinisches und mikrobiologisches Ansprechen	Klinisches Ansprechen (cUTI: mikrobiologisches Ansprechen) Kein Vergleich

Study overview

Study design	Multicentre (multinational), double-blind, parallel group, randomised, active-controlled, non-inferiority study
Primary objective	Day 14 all-cause mortality of cefiderocol versus high dose, extended-infusion meropenem, in patients with HABP, VABP, HCABP caused by Gram-negative pathogens
Sample size	300 patients (1:1 randomisation)

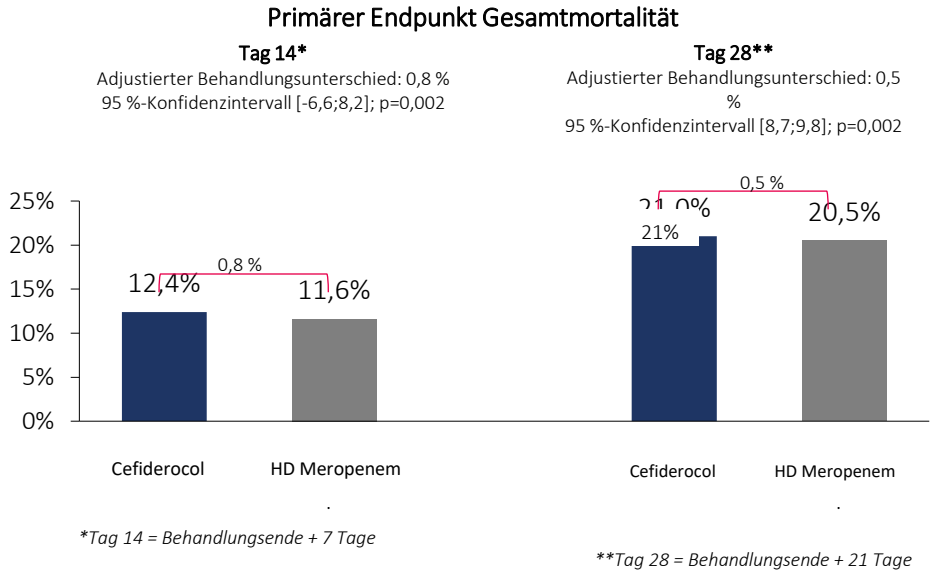


ClinicalTrials.gov. ttps://clinicaltrials.gov/ct2/show/record/NCT03032380.

Cefiderocol - Vergleichbare Effektivität mit Hochdosis-Meropenem bei nosokomialer Pneumonie*

Klinische Wirksamkeit bei gramnegativer nosokomialer Pneumonie

- Studie in 19 Ländern (EU: 9) und 119 (EU: 45) Kliniken, n=300
- Meropenem wurde hochdosiert (2 g) und über 3 Stunden infundiert (Wirksamkeit bei Carbapenem-resistenten Erregern gemäß ATS-Empfehlung, Verblindung).



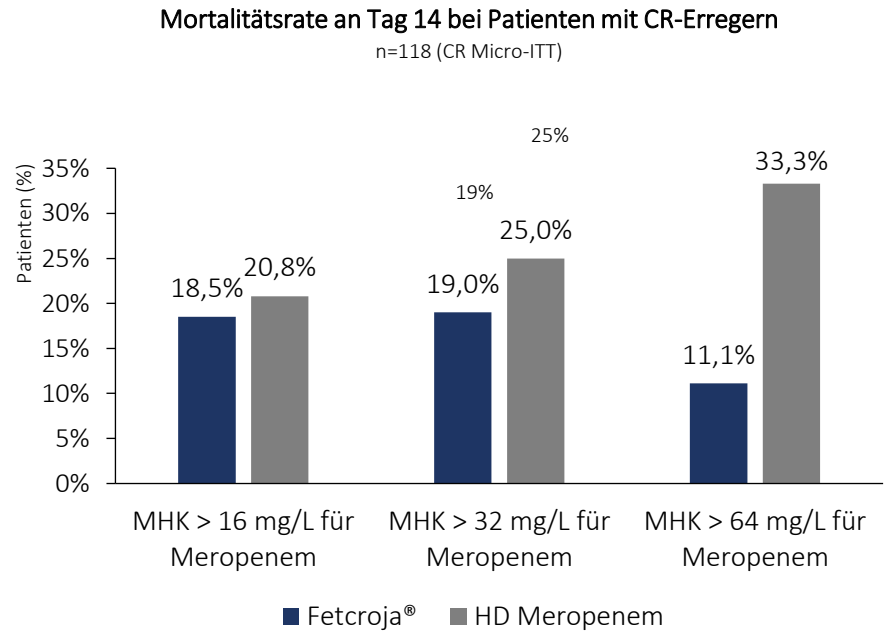
Besonderheit:
Bisher einzige Vergleichsstudie gegen Hochdosis-Meropenem mit verlängerter Infusionszeit belegt signifikant die klinische Wirksamkeit von Cefiderocol auch bei Carbapenem-resistenten gramnegativen Erregern.

Die klinischen und mikrobiologischen Ansprechraten waren vergleichbar gut zu HD-Meropenem.

* Modifiziert nach Wunderink RG et al. Lancet Infect Dis. 2020 Oct 12:S1473-3099(20)30731-3.

Cefiderocol - In der Subgruppenanalyse bei Carbapenem-resistenten Erregern überlegen

Bei Problemerregern niedrigere Gesamtmortalität im Vergleich zu Hochdosis-Meropenem



Subgruppenanalyse (n=118):

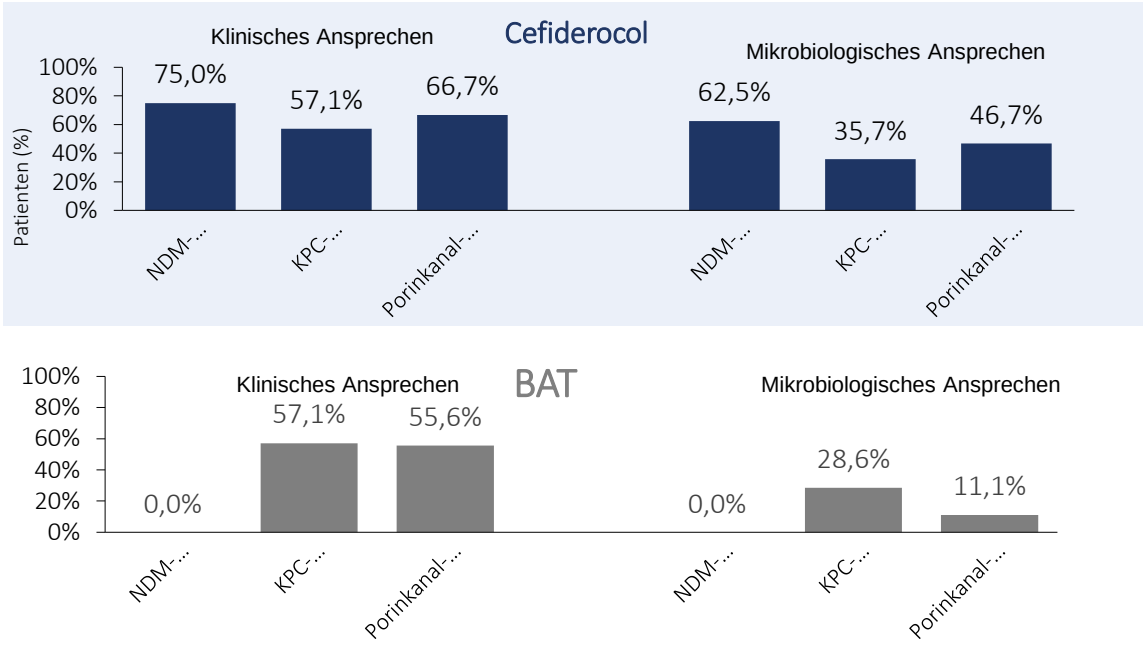
- Bei Carbapenem-resistenten Erregern zeigt Cefiderocol seine überlegene Wirksamkeit im Vergleich zu Hochdosis-Meropenem

* Modifiziert nach Wunderink RG et al. Lancet Infect Dis. 2020 Oct 12:S1473-3099(20)30731-3.

Cefiderocol – Behandlung in Salvage-Situationen bei lebensbedrohlich Erkrankten mit Carbapenem-resistenten gramnegativen Infektionen

CREDIBLE: Deskriptive, Open-label-Datensammlung zu Wirksamkeit und Verträglichkeit

Klinisches und mikrobiologisches Ansprechen (TOC) von ***Enterobacterales*** mit **Carbapenemase oder Porinkanal-Mutation**



Besonderheit:
Cefiderocol wirkt deutlich besser bei Resistenz durch Metallo-betalaktamasen, KPC-Mutation und Porinkanal-Mutation

Modifiziert nach: Bassetti M. et al. Lancet Infect Dis. 2020 Oct 12:S1473-3099(20)30796-9.

Fortschritte in der antibiotischen Therapie der schweren Infektion
Sind wir in den letzten 10 Jahren vorangekommen?

- **Es hat in den letzten 10 Jahren keinen Durchbruch im Management der schweren Infektion gegeben**
- **Aber: es gibt kleine Fortschritte in jeder Hinsicht, vor allem gibt es neue Antibiotika**
- **Der Forschungsbedarf ist dennoch weiter hoch**
- **Zukünftige Forschung wird nur dann zu wesentlichen Ergebnissen führen, wenn national wie international kooperativ geforscht wird**