Çıkar Çatışması:

- **Danışmanlık: Merck, Pfizer, Gilead, GSK, Astellas, Abdi İbrahim**
- **Araştırma Desteği: Pfizer, Neutec, Astellas**

Akılcı Antibiyotik Kullanımında

Ceftolozan-Tazobaktam'ın Yeri

Dr. Alpay Azap
Ankara Üniversitesi Tıp Fakültesi

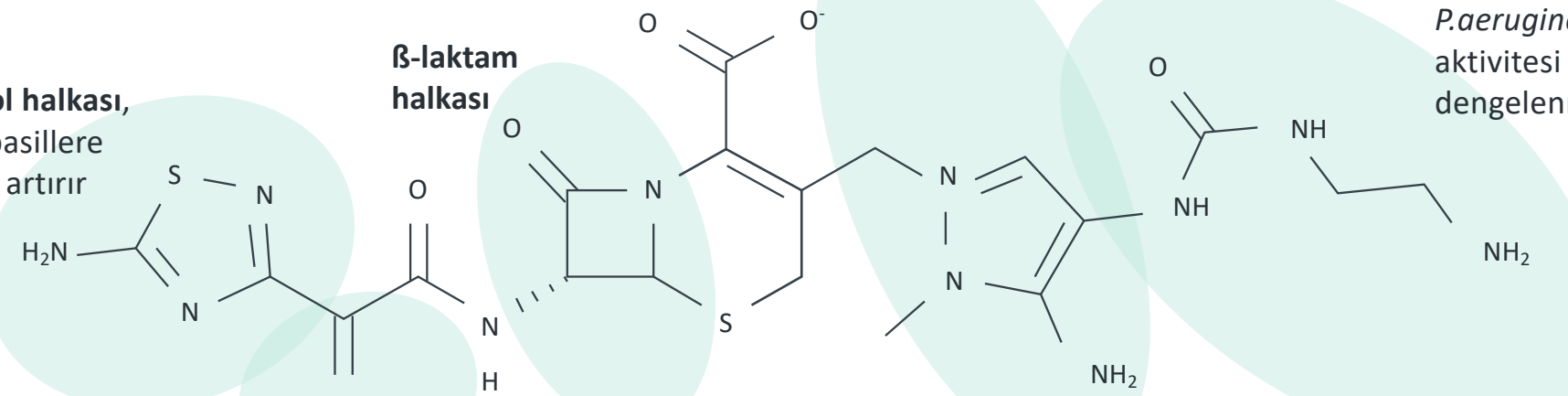
Seftolozan,
P. aeruginosa direnç mekanizmalarına karşı stabil olmak üzere tasarlanmış Sefalosporindir

Pirazol halkası seftolozanın aktif AmpC yerine girmesini önleyen yapısal engelleme sağlar

2-aminoetilüredio grubu, *P.aeruginosa'*da optimum AmpC aktivitesi sergileyecek şekilde dengelenmiştir

ß-laktam halkası

Aminotiadiazol halkası, gram-negatif basillere karşı aktiviteyi artırır



Oksim, ß-laktamaz stabilitesi sağlar.

2-metilpirazol grubu, *P. aeruginosa* karşısında en iyi aktiviteyi sergilediği görülmüştür

Dimetilasetik asit kısım, antipsödomonal aktiviteyi artırır

Murano K Bioorg Med Chem. 2008;16(5):2261–2275; van Duin D Clin Infect Dis. 2016;63(2):234–241; Xipell M Int J Antimicrob Agents. 2017;49(2):266–268.

Seftolozan-Tazobaktam, Yaygın P. aeruginosa Direnç Mekanizmalarına Karşı Stabildir

Direnç Mekanizmaları	Dış Membran Porin Kaybı	ß-laktamaz Enzimi	Efluks Pompası	Efluks Pompası
	OprD	AmpC	MexXY	MexAB
Seftolozan	●	●	●	●
Seftazidim	◐	○	●	○
Sefepim	●	○	○	○
Piperasilin/tazobaktam	●	○	●	○
İmipenem	○	●	●	●
Meropenem	◐	●	○	◐

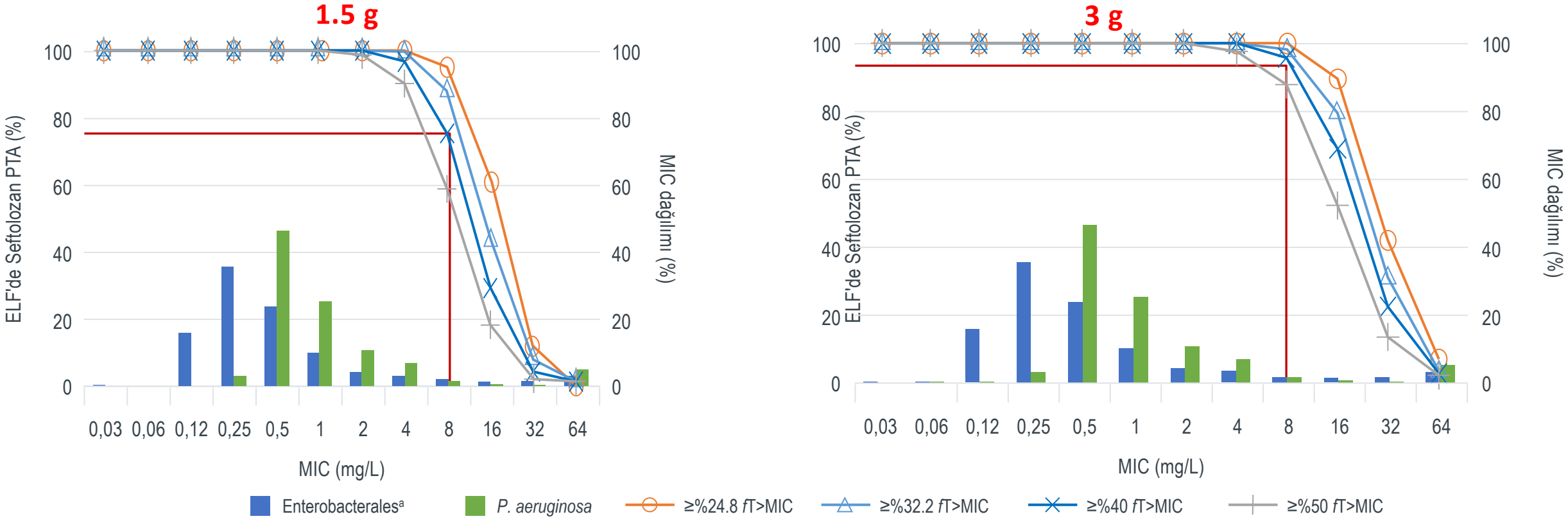
○ **Aktivite büyük ölçüde azalır** ● **Aktivite korunur**

Castanheira M ve ark. Antimicrob Agents Chemother. 2014;58:6844-50.

Faz 1 PK/PD Çalışması

- Diğer sefalosporinlere benzer Süre bağımlı bakterisidal (%fT.MIC)
- T1/2: 2-3 saat Proteine bağlanma:%20, Dağılım hacmi: 12-18 litre

Pnömoniyle hastaneye yatırılan hastalarda ELF PTA oranları, 1.5 g ve 3 g doz (2012 ABD/AB gözlem verileri)



Xiao AJ ve ark. J Clin Pharm. 2016;56(1):56–66.

Seftolozan-Tazobaktam İn-vitro etkinlik

- P. aeruginosa:
  - AmpC (+) %97
  - Efflux (+) %94-99.7

- CANWARD, 3229 P. aeruginosa %98 duyarlı

AK-R suşlarda %85 CİP-R suşlarda:%95

- Enterobacterales:

Türe ve direnç paternine göre değişken

- ASPECT-NP: %43,
  - ESBL (+) E.coli: %90
  - ESBL (+) Klebsiella: %36

Karbapenamaz (+) GNAB
Acinetobacter spp
Gram pozitif bakteriler
C. difficile

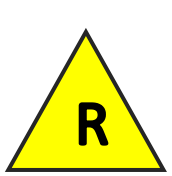


TABLE 1 Antimicrobial activity of ceftolozane-tazobactam and comparator agents by region/country[g]

	Antimicrobial agent					
Gram-negative bacteria	Ceftolozane-tazobactam	Piperacillin- tazobactam	Meropenem	Ceftazidime-avibactam	Cefepime	Ceftazidime
Pseudomonas aeruginosa (all)						
United States[c]	98	78	76		84	83
United States[a,d]	82	37	25	87	40	50
United States[e]	95	73	74		76	78
Asia Pacific	92	74	78		80	79
China	89	67	67	87	75	72
Spain	91	60	24		41	45
Eastern Europe	81	57	55			63
Western Europe	94	77	79			80
Pseudomonas aeruginosa (MDR)						
United States[c]	88	21	20		34	34
United States[d]	89	41	30	91	46	57
United States[c,e]	74	8	6		6	10
Asia Pacific[b]	73	43	0		48	53
China[b]	68	36	8	66	46	44
Spain	88	0	0			0
Pseudomonas aeruginosa (XDR)						
United States[c]	83	9	11	–	23	25
United States[d]	57	14	7	71	21	21
United States[e]	75					
Spain	83					
Enterobacterales (all)						
United States[c]	90	86	96		86	81
United States[d]	92	75		100	49	38
China	72			95		
Eastern Europe	79	66	92			57
Western Europe	95	85	98			81
Klebsiella pneumoniae (all)						
United States[c]	90	85	93		81	79
Asia Pacific	82	80	94		75	72
China	53	53	61	94	39	41
Spain	73	67	88		64	54
Eastern Europe	57	40	79			34
Western Europe	85	71	90			68

Walkty A. J Antimicrob Chemother 73:703–708.
Lizza BD, Antimicrob Agent Chem, 2021;65:e02318-20

Clinical Infectious Diseases
MAJOR ARTICLE

Modifiable Risk Factors for the Emergence of Ceftolozane-tazobactam Resistance

Pranita D. Tamma,[1] Stephan Beisken,[2] Yehudit Bergman,[3] Andreas E. Posch,[4] Edina Avdic,[5] Sima L. Sharara,[6] Sara E. Cosgrove,[7] and Patricia J. Simner[8]

Porin kaybı ve eflux pompası aktivasyonuna dayanıklı C/T'a direnç:

- AmpC-AmpR bölgesinde mutasyon
- Hedef molekülde (PBP3) mutasyon
- Multidrug eflux pompasında mutasyon
- DNA-polimeraz alt ünitelerinde mutasyon

Johns Hopkins, 28 Karba-R C/T duyarlı hasta, >72s C/T tdv

Tedavi öncesi vs sonrası MİK değerinde 4 kat artış: %50

Direnç gelişen hastalarda

- odak kontrolü yetersiz
- uzamış infüzyon (3s) yapılmamış

Direnç çoğunlukla AMpC mutasyonu sonucu gelişmiş.

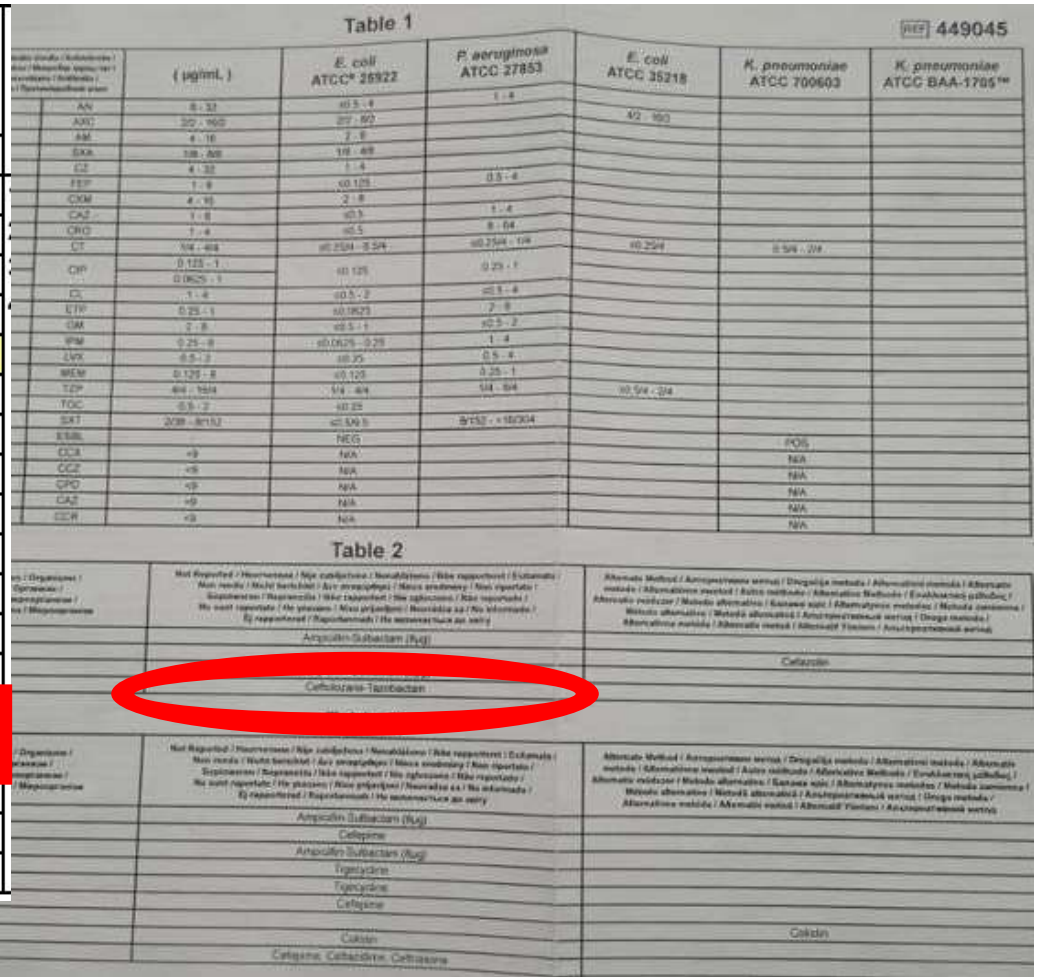
CAZ-AVI'ye de direnç gelişmiş (C/T kullanımıyla)

Clin Infect Dis. 2021;73(11):e4599–606

Antimikrobiyal duyarlılık testi:

- Otomatize sistemlerde (Phoenix, Vitek) yer alıyor.
- EUCAST'ta MİK ve disk difüzyon test sınır değerleri belirlenmiş

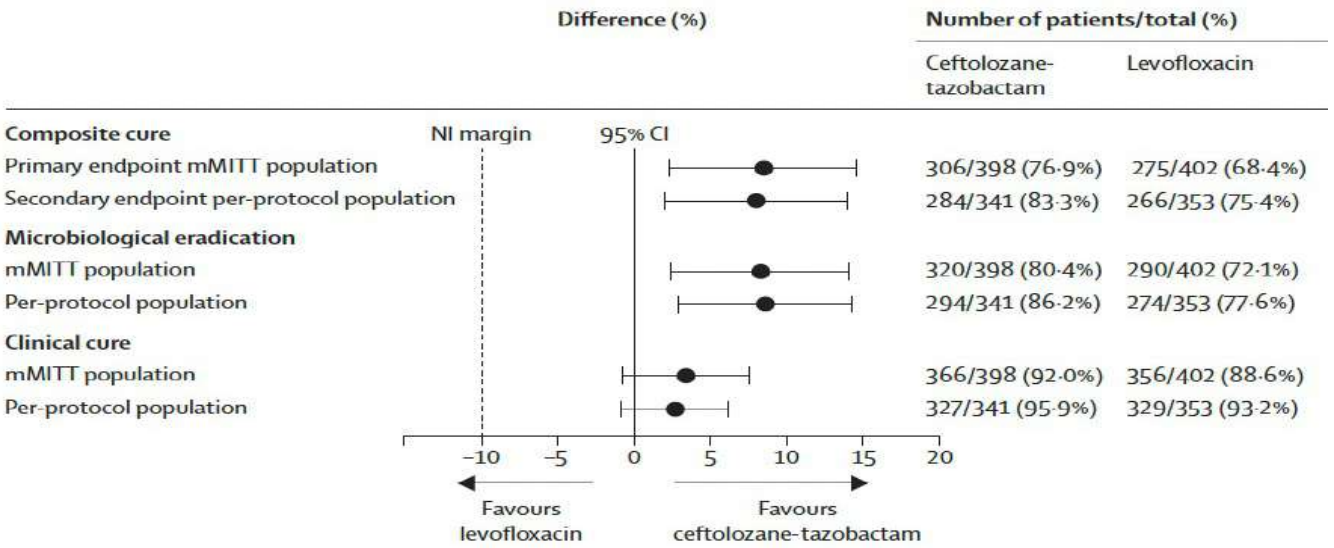
Cephalosporins	MIC breakpoint (mg/L)		Disk content (µg)	Zone diameter breakpoint (mm)	
	S ≤	R >		S ≥	R <
Cefaclor	-	-		-	-
Cefadroxil	-	-		-	-
Cefalexin	-	-		-	-
Cefazolin	-	-		-	-
Cefepime[1]	8	8	30	21	21
Cefixime	-	-		-	-
Cefotaxime	-	-		-	-
Cefoxitin	NA	NA		NA	NA
Cefpodoxime	-	-		-	-
Ceftaroline	-	-		-	-
Ceftazidime[2]	8	8	10	17	17
Ceftazidime-avibactam, *P. aeruginosa*	8[3]	8[3]	10-4	17	17
Ceftibuten	-	-		-	-
Ceftobiprole	IE	IE		IE	IE
Ceftolozane-tazobactam, *P. aeruginosa*	4[4]	4[4]	30-10	24	24
Ceftriaxone	-	-		-	-
Cefuroxime iv	-	-		-	-
Cefuroxime oral	-	-		-	-



Ceftolozane-tazobactam compared with levofloxacin in the treatment of complicated urinary-tract infections, including pyelonephritis: a randomised, double-blind, phase 3 trial (ASPECT-cUTI)

Florian M Wagenlehner, Obiamiwe Umeh, Judith Steenbergen, Guojun Yuan, Rabih O Darouiche

- Seftolozan/TZP (3 x 1.5g)
  Vs
  Levofloxacin 750 mg



	Ceftolozane-tazobactam (n=398)	Levofloxacin (n=402)
Male	105 (26·4%)	103 (25·6%)
White ethnic origin	340 (85·4%)	346 (86·1%)
Age (years)	49·1 (19·7)	48·1 (20·2)
Age ≥65 years	100 (25·1%)	99 (24·6%)
Body-mass index (kg/m²)	25·5 (5·8)	26·1 (5·6)
Baseline creatinine clearance (mL/s per m²)		
Normal (≥1·3)	247 (62·1%)	274 (68·2%)
Mild renal impairment (>0·8 to <1·3)	116 (29·1%)	100 (24·9%)
Moderate renal impairment (≥0·5 to ≤0·8)	31 (7·8%)	27 (6·7%)
Severe renal impairment (<0·5)	3 (0·8%)	1 (0·2%)
Primary diagnosis		
Pyelonephritis	328 (82·4%)	328 (81·6%)
cLUTI	70 (17·6%)	74 (18·4%)
Antibiotics within 14 days before first dose*	14 (3·5%)	6 (1·5%)
Urinary catheter†	11 (2·8%)	10 (2·5%)
Bacteraemia	29 (7·3%)	33 (8·2%)
Diabetes	42 (10·6%)	40 (10·0%)
Hypertension	125 (31·4%)	119 (29·6%)

Data are number (%) or mean (SD). cLUTI=complicated lower-urinary-tract infections. *No antibiotics were permitted within 48 h before baseline urine culture. †Urinary catheter was removed before end of treatment in all but three patients in the ceftolozane-tazobactam group and one patient in the levofloxacin group.

Table 1: **Demographic and clinical baseline characteristics in the microbiological modified intention-to-treat population**

Komplike ÜSİ için FDA onayı: Aralık 2014

Lancet 2015; 385: 1949–56

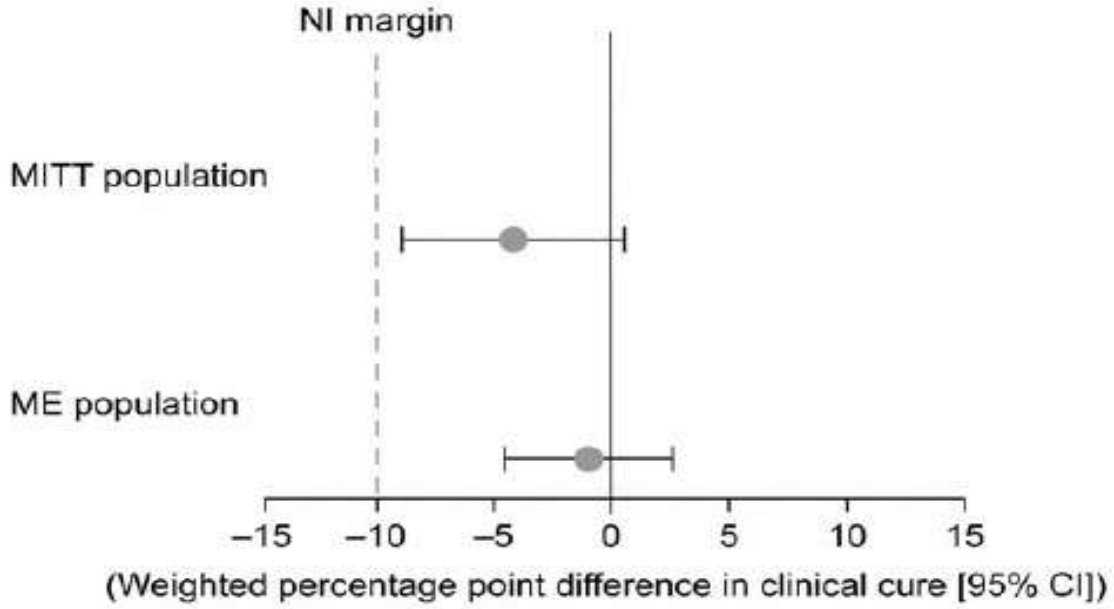
Ceftolozane/Tazobactam Plus Metronidazole for Complicated Intra-abdominal Infections in an Era of Multidrug Resistance: Results From a Randomized, Double-Blind, Phase 3 Trial (ASPECT-cIAI)

Joseph Solomkin,[1] Ellie Hershberger,[2] Benjamin Miller,[2] Myra Popejoy,[2] Ian Friedland,[2,a] Judith Steenbergen,[2]

Seftolozan/TZP (3 x 1.5g) + Metronidazol 3 x 500 mg

Vs

Meropenem (3 x 1g)



	Ceftolozane/ tazobactam plus metronidazole No. (%)	Meropenem No. (%)	Percentage difference (95% CI)
MITT population	n = 389	n = 417	
Cure	323 (83.0)	364 (87.3)	−4.2 (−8.91 to .54)
Failure	32 (8.2)	34 (8.2)	
Indeterminate	34 (8.7)	19 (4.6)	
ME population	n = 275	n = 321	
Cure	259 (94.2)	304 (94.7)	−1.0 (−4.52 to 2.59)
Failure	16 (5.8)	17 (5.3)	

Komplike İAİ için FDA onayı: Aralık 2014

Clinical Infectious Diseases 2015;60(10):1462–71

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,

34 ülke 263 merkez
VİP, vHİP(ventile) 726 hasta

Seftolozan/TZP (3 x 3g)
Vs
Meropenem (3 x 1g)

	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;
19: 1299–311

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,

	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.

Table 3: **Per-pathogen clinical cure at test-of-cure visit in the microbiological intention-to-treat population**

Güvenlilik Popülasyonundaki AO'ların Özeti

AO kategorisi, n (%)	Seftolozan/tazobaktam N=361	Meropenem N=359
≥1 AO	310 (85,9)	299 (83,3)
Şiddetli	143 (39,6)	136 (37,9)
Ciddi	152 (42.1)	129 (35,9)
Çalışmayı bırakmaya yol açan	37 (10,2)	42 (11,7)
Ölüme neden olan	105 (29,1)	101 (28,1)
≥1 TİAE	38 (10,5)	27 (7,5)
Şiddetli	5 (1,4)	3 (0,8)
Ciddi	8 (2.2)	2 (0,6)
Çalışmayı bırakmaya yol açan	4 (1,1)	5 (1,4)
Ölüme neden olan	0	0

HİP/VİP için FDA onayı: Haziran 2019

Seftolozan-Tazobaktam

KISA ÜRÜN BİLGİSİ

▼Bu ilaç ek izlemeye tabidir. Bu üçgen yeni güvenlilik bilgisinin hızlı olarak belirlenmesini sağlayacaktır. Sağlık mesleği mensuplarının şüpheli advers reaksiyonları TÜFAM'a bildirmeleri beklenmektedir. Bakınız Bölüm 4.8 Advers reaksiyonlar nasıl raporlanır.

1. BEŞERİ TIBBI ÜRÜNÜN ADI

ZERBAXA 1 g/0,5 g infüzyonluk çözelti hazırlamak için toz

4.1 Terapötik endikasyonlar

ZERBAXA, yetişkinlerde aşağıdaki enfeksiyonların tedavisinde endikedir (bkz. Bölüm 5.1):

- Komplike intra-abdominal enfeksiyonlar (bkz. Bölüm 4.4),
- Akut piyelonefrit,
- Komplike idrar yolu enfeksiyonları (bkz. Bölüm 4.4),
- Ventilatör ilişkili pnömoni (VİP) dahil hastaneden edinilmiş pnömoni (HEP).

MSD

Seftolozan-Tazobaktam

4.2 Pozoloji ve uygulama şekli

Pozoloji/uygulama sıklığı ve süresi
Kreatinin klerensi >50 mL/dk olan hastalar için önerilen intravenöz doz rejimi, enfeksiyon tipine göre Tablo 1'de gösterilmektedir.

Tablo 1: Kreatinin klerensi >50 mL/dk olan hastalarda enfeksiyon tipine göre intravenöz ZERBAXA dozu

Enfeksiyon Tipi	Doz	Sıklık	İnfüzyon süresi	Tedavi süresi
Komplike intra-abdominal enfeksiyon*	1 g seftolozan/ 0,5 g tazobaktam	8 saatte bir	1 saat	4-14 gün
Komplike idrar yolu enfeksiyonu Akut piyelonefrit	1 g seftolozan/ 0,5 g tazobaktam	8 saatte bir	1 saat	7 gün
Ventilatör ilişkili pnömoni (VİP) dahil hastaneden edinilmiş pnömoni (HEP)**	2 g seftolozan/ 1 g tazobaktam	8 saatte bir	1 saat	8-14 gün

MSD

Seftolozan-Tazobaktam

KISA ÜRÜN BİLGİSİ

▼Bu ilaç ek izlemeye tabidir. Bu üçgen yeni güvenlilik bilgisinin hızlı olarak belirlenmesini sağlayacaktır. Sağlık mesleği mensuplarının şüpheli advers reaksiyonları TÜFAM'a bildirmeleri beklenmektedir. Bakınız Bölüm 4.8 Advers reaksiyonlar nasıl raporlanır.

1. BEŞERİ TIBBI ÜRÜNÜN ADI

ZERBAXA 1 g/0,5 g infüzyonluk çözelti hazırlamak için toz
Steril

2. KALİTATİF VE KANTİTATİF BİLEŞİM

Etkin madde: Her bir flakon 1 g seftolozana eşdeğer 1.147 mg seftolozan sülfat ve 0,5 g tazobaktama eşdeğer 537 mg tazobaktam sodyum içerir.

10 mL seyreltiyle sulandırıldıktan sonra, flakondaki çözeltinin toplam hacmi 11,4 mL'dir ve 88 mg/mL seftolozan ve 44 mg/mL tazobaktam içerir.

Yardımcı maddeler: Her bir flakon 10 mmol (230 mg) sodyum içerir.

Toz, 10 mL 9 mg/mL (%0,9) enjeksiyonluk sodyum klorür çözeltisi ile sulandırıldığında, flakon 11,5 mmol (265 mg) sodyum içerir.

MSD

Clinical Infectious Diseases
MAJOR ARTICLE

Trends in Hospital-Acquired and Ventilator-Associated Bacterial Pneumonia Trials

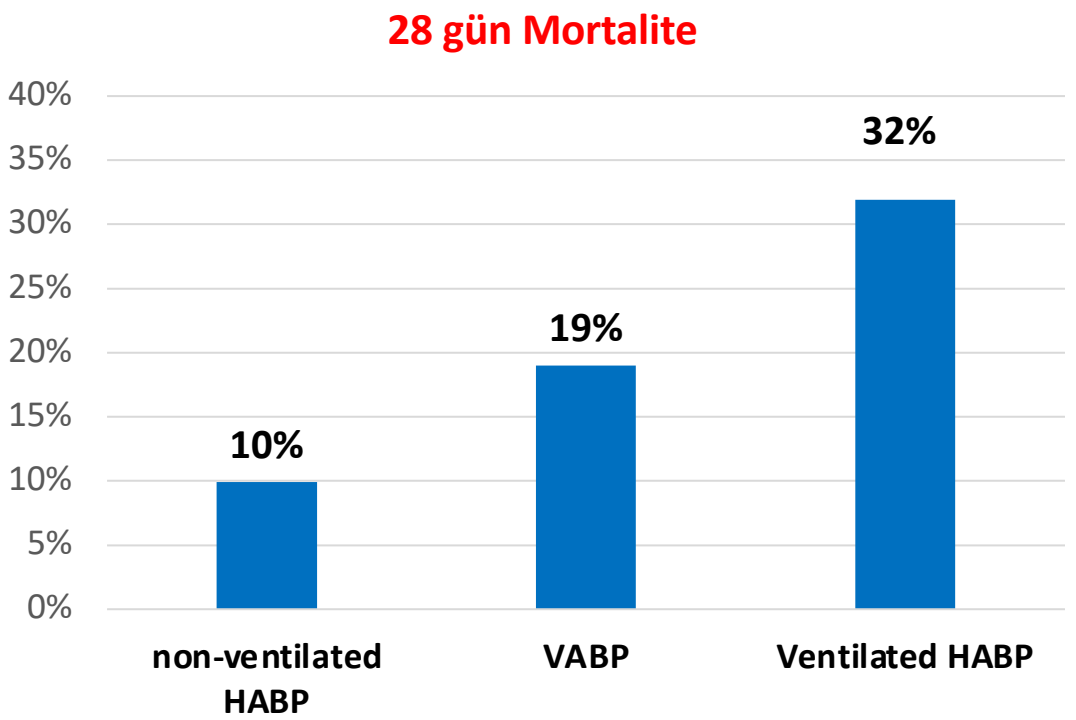
Stephen M. Bart,[1] Daniel Rubin,[2] Peter Kim,[1] John J. Farley,[1] and Sumathi Nambiar[1]

2015 yılından sonra HAP/VAP tedavisi için yapılmış tedavi karşılaştırma çalışmaları

4 RKÇ, 2433 katılımcı

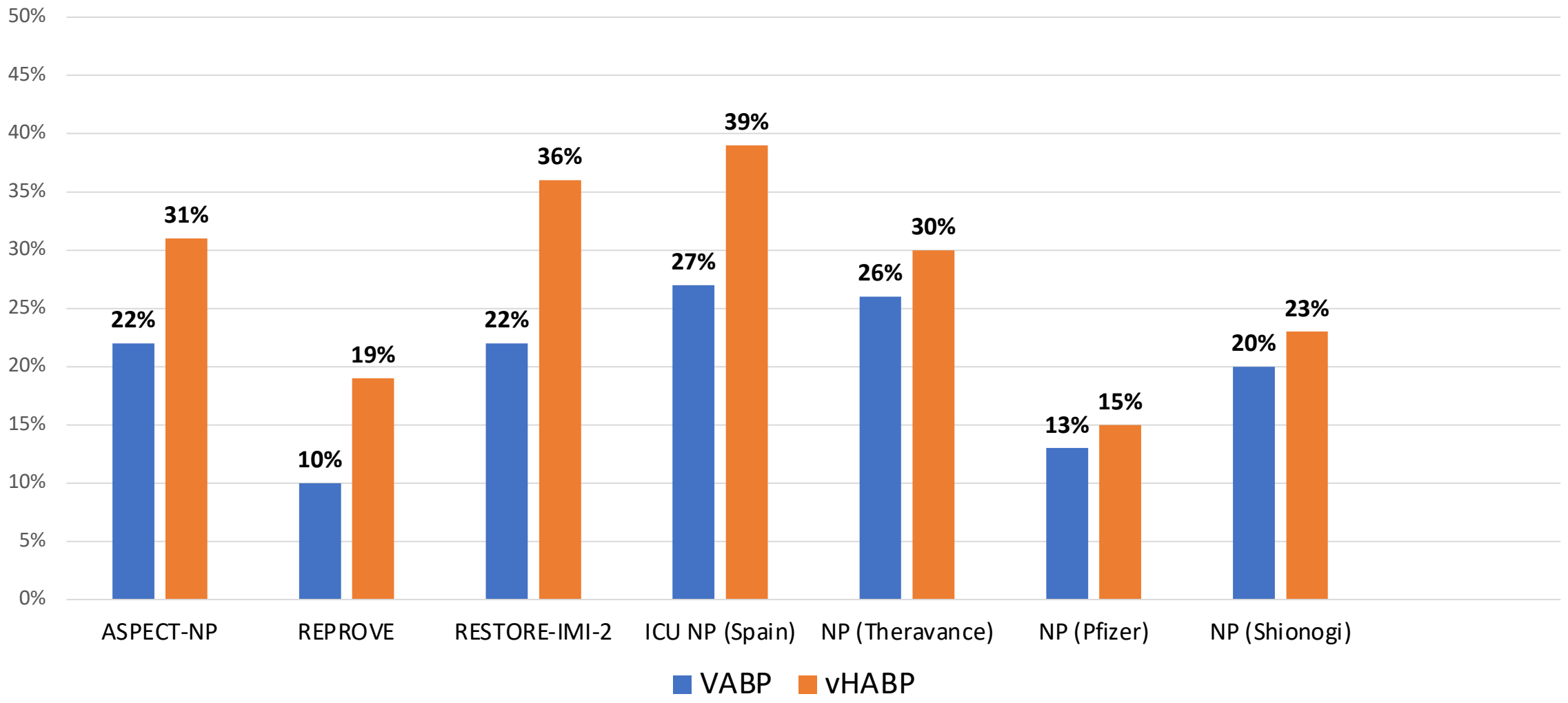
Table 4. Carbapenem Resistance Among Gram-Negative Isolates, by Region

	A. baumannii[a]	Enterobacteriaceae[a]	*P. aeruginosa*[a]
Overall	270/341 (79.2%)	111/1394 (8%)	127/423 (30%)
Asia/Pacific	41/68 (60.3%)	14/257 (5.4%)	37/113 (32.7%)
Eastern Europe	210/242 (86.8%)	89/802 (11.1%)	77/217 (35.5%)
North America	9/10 (90%)	3/65 (4.6%)	7/24 (29.2%)
South America	9/15 (60%)	5/108 (4.6%)	3/29 (10.3%)
Western Europe	1/6 (16.7%)	0/162 (0%)	3/40 (7.5%)



Clin Infect Dis. 2021;73(3):e602–8.

VABP vs. vHABP: 28-day All Cause Mortality Comparison

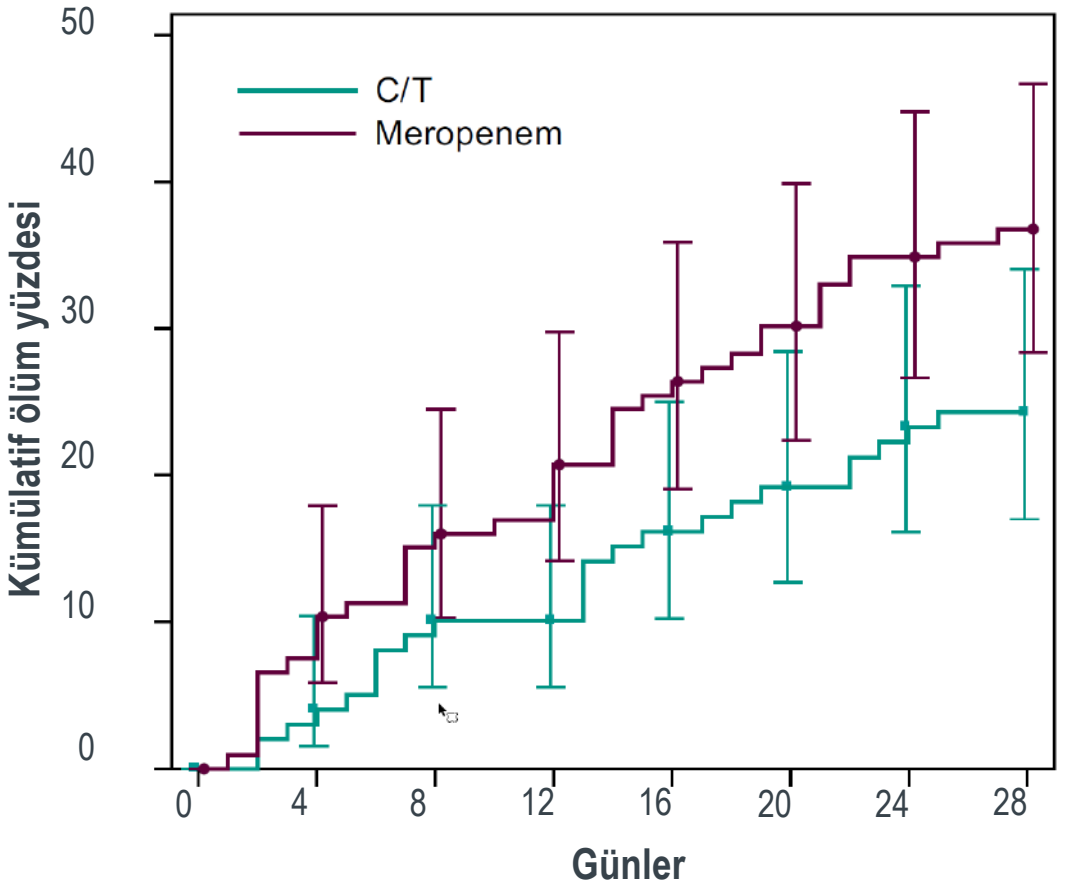


Ceftolozane/tazobactam versus meropenem in patients with ventilated hospital-acquired bacterial pneumonia: subset analysis of the ASPECT-NP randomized, controlled phase 3 trial

Jean-François Timsit[1], Jennifer A. Huntington[2], Richard G. Wunderink[3], Nobuaki Shime[4], Marin H. Kollef[5],

ASPECT-NP Alt grup analizi;

- 99 C/T vs 108 meropenem kullanan hasta
- 28 günlük tüm nedenlere bağlı mortalite
  Tedavi ITT: Meropenem kolunda %37'ye kıyasla C/T'de %24.2 (%95GA: 0.2-24.8)
  Mikrobiyolojik ITT: Meropenem kolunda %36.6'ya kıyasla C/T'de %18.2
- Klinik kür ITT
  Meropenem kolunda %44.4'e kıyasla C/T'de %50.5



Critical Care;2021;25:290

Ceftolozane/tazobactam versus meropenem in patients with ventilated hospital-acquired bacterial pneumonia: subset analysis of the ASPECT-NP randomized, controlled phase 3 trial

Jean-François Timsit[1], Jennifer A. Huntington[2], Richard G. Wunderink[3], Nobuaki Shime[4], Marin H. Kollef[5],

Table 5 Odds ratio estimates (and confidence intervals) for risk of death due to any cause by day 28 associated with the significant factors included into the final logistic regression model, each adjusted for both of the other factors

Patient characteristic	Odds ratio for 28-day ACM (95% CI)
Baseline bacteremia with any pathogen (vs no bacteremia)*	2.7 (1.1, 7.1)
Concomitant vasopressor use (vs no vasopressor use)‡	5.4 (2.6, 11.0)
Meropenem treatment (vs ceftolozane/tazobactam treatment)§	2.3 (1.2, 4.5)

Critical Care;2021;25:290

RESEARCH Open Access

Outcomes in participants with failure of initial antibacterial therapy for hospital-acquired/ventilator-associated bacterial pneumonia prior to enrollment in the randomized, controlled phase 3 ASPECT-NP trial of ceftolozane/tazobactam versus meropenem

Marin H. Kollef[1], Jean-François Timsit[2], Ignacio Martin-Loeches[3,4], Richard G. Wunderink[5],

Table 1 Antibacterial treatments received within 72 h prior to starting study treatment in ASPECT-NP participants[a] who were failing prior antibacterial therapy

Antibacterial treatment, *n* (%)	C/T (*N* = 53)	MEM (*N* = 40)
Piperacillin/tazobactam	16 (30.2)	17 (42.5)
Fluoroquinolones	15 (28.3)	12 (30.0)
Third/fourth-generation cephalosporins	13 (24.5)	16 (40.0)
Cefepime	4 (7.5)	3 (7.5)
Cefotaxime	0	4 (10.0)
Ceftriaxone	9 (17.0)	6 (15.0)
Amoxicillin/clavulanate	6 (11.3)	2 (5.0)
Ampicillin/sulbactam	5 (9.4)	1 (2.5)
Aminoglycosides	7 (13.2)	4 (10.0)
Amikacin	5 (9.4)	4 (10.0)
Macrolides	3 (5.7)	1 (2.5)
Carbapenems	2 (3.8)	3 (7.5)
Cefoperazone/sulbactam	4 (7.5)	3 (7.5)

Table 4 Efficacy outcomes in ASPECT-NP participants who were failing prior antibacterial therapy

Endpoint	C/T *n*/*N* (%)	MEM *n*/*N* (%)	% Difference (95% CI)[a]
28-day all-cause mortality (ITT)[b]	12/53 (22.6)	18/40 (45.0)	22.4 (3.1 to 40.1)
28-day all-cause mortality (mITT)[b]	7/39 (17.9)	11/24 (45.8)	27.9 (4.7 to 49.0)
Clinical cure at TOC (ITT)[b]	26/53 (49.1)	15/40 (37.5)	11.6 (– 8.6 to 30.2)
Clinical cure at TOC (CE)[c]	21/33 (63.6)	9/20 (45.0)	18.6 (– 8.2 to 42.5)
Microbiologic eradication at TOC (mITT)[b,d]	26/39 (66.7)	16/24 (66.7)	0.0 (– 22.0 to 23.7)
Microbiologic eradication at TOC (ME)[b,d]	10/17 (58.8)	4/7 (57.1)	1.7 (– 33.7 to 39.3)

Critical Care (2022) 26:373

International Journal of Antimicrobial Agents 57 (2021) 106278

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Short Communication

Evaluating the emergence of nonsusceptibility among *Pseudomonas aeruginosa* respiratory isolates from a phase-3 clinical trial for treatment of nosocomial pneumonia (ASPECT-NP)

Matthew G. Johnson[a,*], Christopher Bruno[a], Mariana Castanheira[b], Brian Yu[a],

- Başlangıçta duyarlı olan P. aeruginosa suşlarında direnç
- Direnç gelişen suşların moleküler karakterizasyonu
- Direnç mekanizması

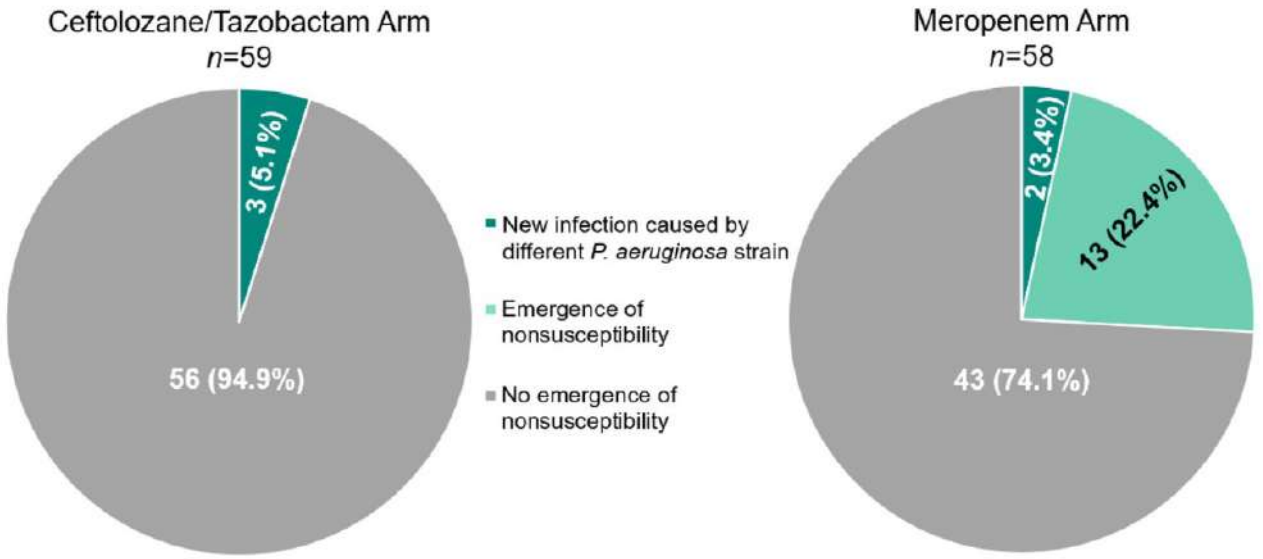


Figure 1. Comparison of rates of emergence of nonsusceptibility in baseline susceptible *Pseudomonas aeruginosa* isolates in ASPECT-NP.

- C/T kolunda 3/59 (%5.1) suş dirençli: Hepsi yeni suş
- 13/58 (%22.4) suş MEM'e direnç geliştirmiş
- MEM'e direnç gelişen suşların tamamı C/T duyarlı
- Direnç gelişimi klinik sonuçları etkilememiş

Johnson ve ark. Int J Antimicrob Agents. Mar 2021;57(3):106278

ASPECT-NP Alt Analizi: Duyarsızlığın Oluşması Meropenem Tedavi Kolundaki P. aeruginosa İzolatlarda Moleküler Direnç Mekanizmaları

Table 2
Emergence of nonsusceptibility among participants with baseline susceptible *Pseudomonas aeruginosa* isolates in the meropenem treatment arm from ASPECT-NP[a].

Participant ID	Treatment	Day 28 ACM	CR at TOC	Visit type	MIC (μg/mL)[b]							MLST	Resistance mechanism(s)[d,e]
					Ceftolozane/ tazobactam[c]	Piperacillin/ tazobactam[c]	Cefepime	Levofloxacin	Ceftazidime	Imipenem	Meropenem		
2016	MEM	Died	Failure	Screen	0.5	8	2	0.25	2	**1**	**0.5**	235	PDC-35, OXA-488, PA5542-like
				Day 14	0.5	8	2	0.25	1	**8**	**4**		PDC-35, OXA-488, PA5542-like, MexXY moderate expression, OprD loss
1265	MEM	Alive	Cure	Screen	0.5	16	4	2	4	**0.25**	**1**	319	PDC-46, OXA-488-like, PA5542-like
				Day 10	0.5	16	4	2	2	**4**	**4**		PDC-46, OXA-488-like, PA5542-like, OprD loss
1183	MEM	Alive	Cure	Screen	1	8	8	1	2	8	**0.25**	1751	PDC-5, OXA-395-like, PA5542-like, AmpC elevated expression
				Day 8	1	16	8	2	4	16	**16**		PDC-5, OXA-395-like, PA5542-like, OprD loss
2138	MEM	Died	Failure	Screen	0.5	**4**	2	0.5	**2**	**1**	**0.25**	446	PDC-16, OXA-395-like, PA5542-like
				Day 8	1	**16**	8	2	**8**	**16**	**16**		PDC-16, OXA-395-like, PA5542-like, OprD loss
1022	MEM	Alive	Cure	Screen	2	128	16	2	32	**2**	**2**	155	PDC-5, OXA-396, PA5542-like, MexCD-OprJ elevated expression
				Day 2	2	128	16	2	32	**8**	**8**		PDC-5, OXA-396, PA5542-like, MexXY moderate expression, OprD decrease
1245	MEM	Alive	Cure	Screen	4	256	32	1	64	**2**	**2**	1050	PDC-31, OXA-486, PA5542-like, AmpC elevated expression, OprD decrease
				Day 8	4	≥256	32	1	64	**16**	**8**		PDC-31, OXA-486, PA5542-like, OprD loss
2189	MEM	Alive	Cure	Screen	0.5	2	0.5	1	1	**2**	**<0.064**	1248	PDC-16, OXA-395, PA5542-like
				Day 8	1	4	2	0.25	1	**8**	**4**		PDC-16, OXA-395, PA5542-like, OprD loss
2065	MEM	Alive	Failure	Screen	0.5	8	2	1	2	**1**	**0.125**	386	PDC-8, OXA-494, PA5542-like
				Day 8	0.5	32	2	0.5	2	**8**	**4**		PDC-8, OXA-494, PA5542-like AmpC elevated expression; MexCD-OprJ elevated expression; MexAB-OprM moderate expression
4047	MEM	Alive	Failure	Screen	1	8	8	1	8	4	**1**	2099	PDC-3, OXA-395, PA5542-like
				Day 8	1	32	8	4	8	16	**8**		PDC-3, OXA-395, PA5542-like, OprD decrease
2174	MEM	Alive	Cure	Screen	1	**4**	2	0.5	2	**2**	**0.25**	641	PDC-8, OXA-50, PA5542-like
				Day 8	1	**8**	8	2	4	**16**	**8**		PDC-8, OXA-50, PA5542-like, OprD loss
1278	MEM	Alive	Cure	Screen	1	**4**	4	1	2	**1**	**0.5**	235	PDC-35, OXA-488, PA5542-like
				Day 8	1	**8**	**4**	1	2	**16**	**4**		PDC-35, OXA-488, PA5542-like, MexXY moderate expression, OprD loss
				Day 22	1	**16**	**32**	2	4	**8**	0.5		PDC-35, OXA-488, PA5542-like, MexXY moderate expression
3012	MEM	Alive	Cure	Screen	1	**4**	2	1	2	**1**	**0.125**	2021	PDC-8, OXA-486-like, PA5542-like
				Day 8	1	**8**	4	1	2	**16**	**4**		PDC-8, OXA-486-like, PA5542-like, OprD loss
1117	MEM	Alive	Cure	Screen	0.5	4	2	0.5	2	**2**	**0.125**	641	PDC-5, OXA-50, PA5542-like
				Day 8	0.5	8	2	1	2	**16**	**4**		PDC-5, OXA-50, PA5542-like, OprD loss

RESEARCH Open Access

Ceftolozane/tazobactam probability of target attainment and outcomes in participants with augmented renal clearance from the randomized phase 3 ASPECT-NP trial

Andrew F. Shorr[1], Christopher J. Bruno[2*], Zufei Zhang[2], Erin Jensen[2], Wei Gao[2], Hwa-Ping Feng[2],

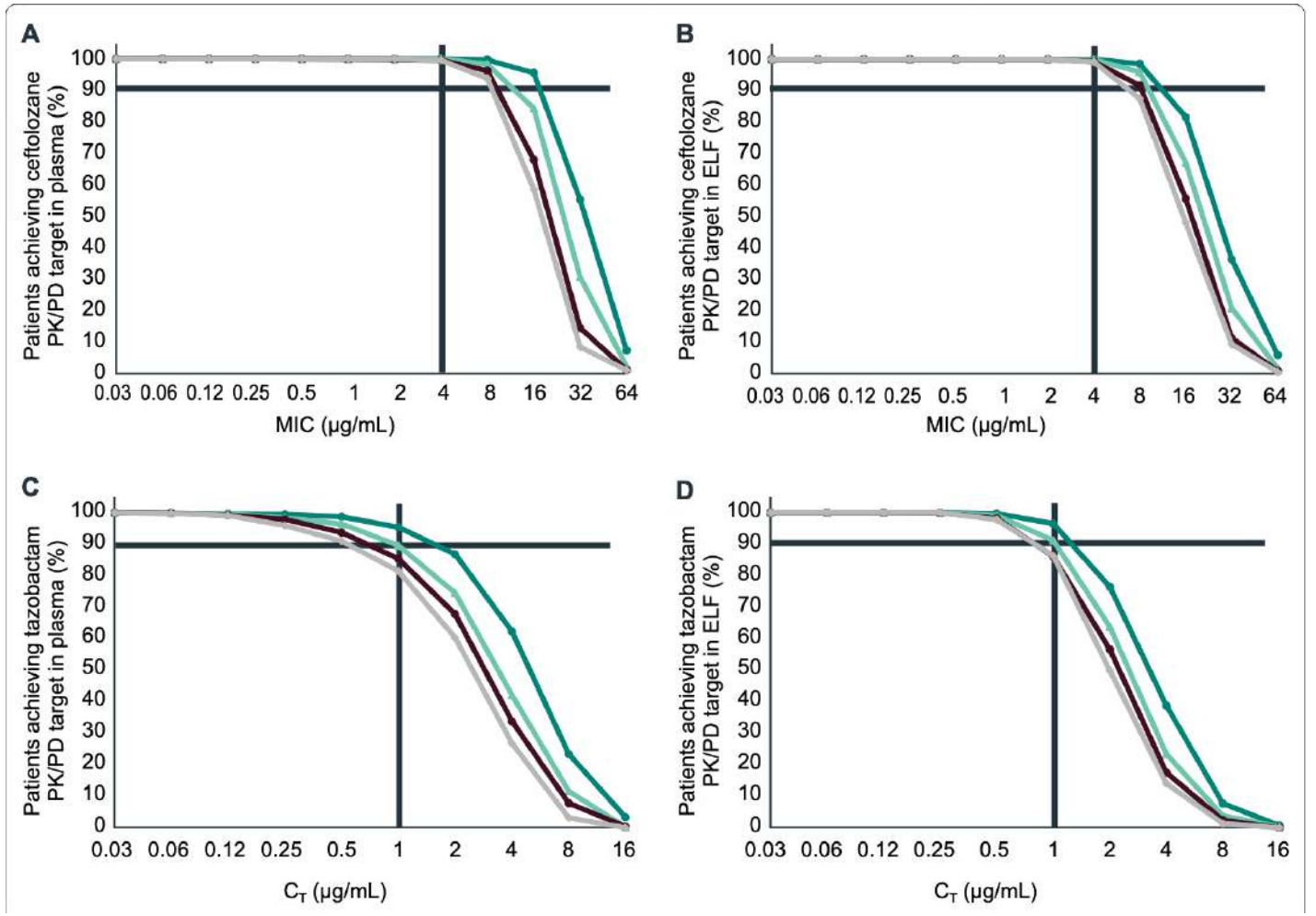
- Artmış renal klirensi olan hastalarda;

Hem seftolozan hem tazobaktam için
Hedef PK/PD indeksler tutturulmuştur.

- C: %50 ƒT/MİK (4 µg/ml)
- TZP: %35 ƒT/Eşik konsantrasyon (1 µg/ml)

- Farklı renal klirense sahip hastalarda klinik sonuçlar birbirine benzer

Sonuç:
Pnömonide 3 x 3g ideal doz!



Crit Care (2021) 25:354

Klirense göre doz ayarlamak önemli !

Tablo 2: Kreatinin klerensi ≤50 mL/dk olan hastalarda ZERBAXA'nın önerilen intravenöz doz rejimleri

Tahmini CrCL (mL/dak)*	Komplike intra-abdominal enfeksiyonlar, komplike idrar yolu enfeksiyonları ve akut piyelonefrit**	Ventilatör ilişkili pnömoni (VİP) dahil hastaneden edinilmiş pnömoni (HEP) **
30 - 50	500 mg seftolozan/250 mg tazobaktam intravenöz yoldan 8 saatte bir	1 g seftolozan/0,5 g tazobaktam intravenöz yoldan 8 saatte bir
15 - 29	250 mg seftolozan/125 mg tazobaktam intravenöz yoldan 8 saatte bir	500 mg seftolozan/250 mg tazobaktam intravenöz yoldan 8 saatte bir
Son evre böbrek hastalığı, hemodiyaliz	500 mg seftolozan/250 mg tazobaktamın tek bir yükleme dozu, 8 saat sonrasından itibaren tedavinin geri kalanı boyunca 8 saatte bir 100 mg seftolozan / 50 mg tazobaktam idame dozu (hemodiyaliz günlerinde doz, hemodiyalizin tamamlanmasını takiben mümkün olan en kısa zamanda uygulanmalıdır).	1,5 g seftolozan/0,75 g tazobaktamın tek bir yükleme dozu, 8 saat sonrasından itibaren tedavinin geri kalanı boyunca 8 saatte bir 300 mg seftolozan/150 mg tazobaktam idame dozu (hemodiyaliz günlerinde doz, hemodiyalizin tamamlanmasını takiben mümkün olan en kısa zamanda uygulanmalıdır).

MSD

J Antimicrob Chemother 2022; 77: 1166–1177
https://doi.org/10.1093/jac/dkab494 Advance Access publication 12 January 2022

Journal of Antimicrobial Chemotherapy

Clinical and microbiological outcomes, by causative pathogen, in the ASPECT-NP randomized, controlled, Phase 3 trial comparing ceftolozane/tazobactam and meropenem for treatment of hospital-acquired/ventilator-associated bacterial pneumonia

Table 1. Most common ($n \geq 10$) baseline LRT isolates (pooled across both treatment arms) in the mITT population ($N = 511$), with summary MIC values and susceptibility to both study drugs

Pathogen	Statistic	Ceftolozane/tazobactam	Meropenem
Gram-negative pathogens (overall)	*N1*	699	697
	MIC range	< 0.064 to ≥256	< 0.064 to ≥256
	MIC_{50}	0.5	< 0.064
	MIC_{90}	16	1
	Susceptible, *n*/*N1* (%)	608/699 (87.0)	650/697 (93.3)
	Intermediate, *n*/*N1* (%)	17/699 (2.4)	5/697 (0.7)
	Resistant, *n*/*N1* (%)	74/699 (10.6)	42/697 (6.0)
P. aeruginosa	*N1*	127	127
	MIC range	0.125 to ≥256	< 0.064 to 128
	MIC_{50}	1	0.5
	MIC_{90}	2	8
	Susceptible, *n*/*N1* (%)	123/127 (96.9)	106/127 (83.5)
	Intermediate, *n*/*N1* (%)	0/127	5/127 (3.9)
	Resistant, *n*/*N1* (%)	4/127 (3.1)	16/127 (12.6)
AmpC-overexpressing *P. aeruginosa*	*N1*	15	15
	MIC range	1–8	0.25–32
	MIC_{50}	2	8
	MIC_{90}	4	32
	Susceptible, *n*/*N1* (%)	15/15 (100)	6/15 (40)
	Intermediate, *n*/*N1* (%)	0/15	1/15 (6.7)
	Resistant, *n*/*N1* (%)	0/15	8/15 (53.3)
Enterobacterales (overall)	*N1*	456	457
	MIC range	< 0.064 to ≥256	< 0.064 to 16
	MIC_{50}	0.5	< 0.064
	MIC_{90}	16	0.125
	Susceptible, *n*/*N1* (%)	381/456 (83.6)	456/457 (99.8)
	Intermediate, *n*/*N1* (%)	17/456 (3.7)	0/457
	Resistant, *n*/*N* (%)	58/456 (12.7)	1/457 (0.2)

- mITT (mikrobiyolojik ITT) 511 hasta
- 264 C/T, 247 MEM

J Antimicrob Chemother 2022; **77**: 1166–1177
https://doi.org/10.1093/jac/dkab494 Advance Access publication 12 January 2022

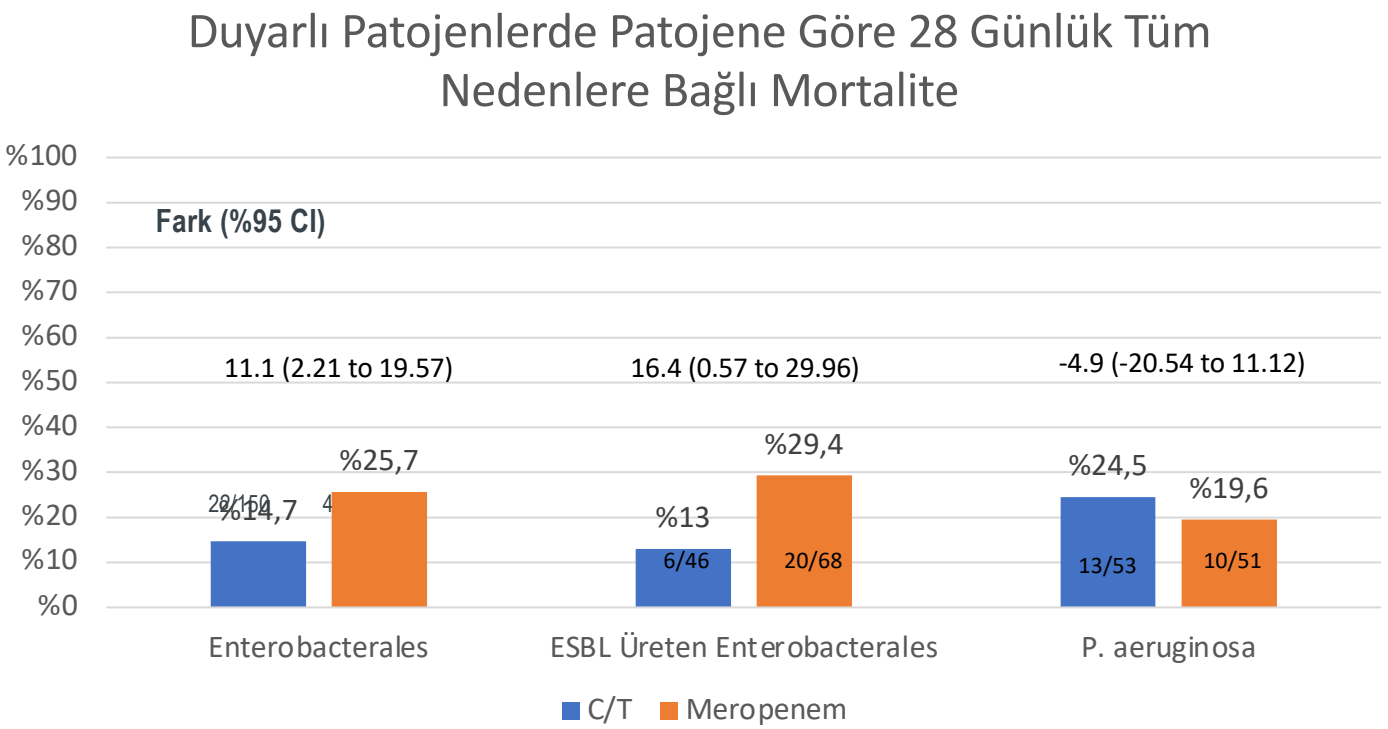
Journal of Antimicrobial Chemotherapy

Clinical and microbiological outcomes, by causative pathogen, in the ASPECT-NP randomized, controlled, Phase 3 trial comparing ceftolozane/tazobactam and meropenem for treatment of hospital-acquired/ventilator-associated bacterial pneumonia

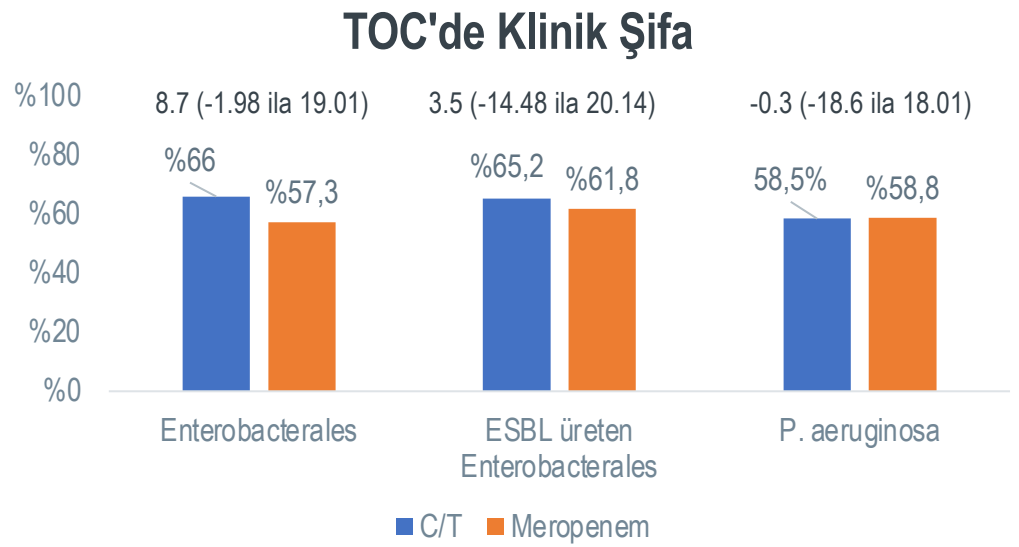
Table 3. Per-pathogen 28 day ACM, clinical cure and microbiological eradication rates for key baseline LRT pathogens in participants in the mITT population with all pathogens susceptible to study treatment

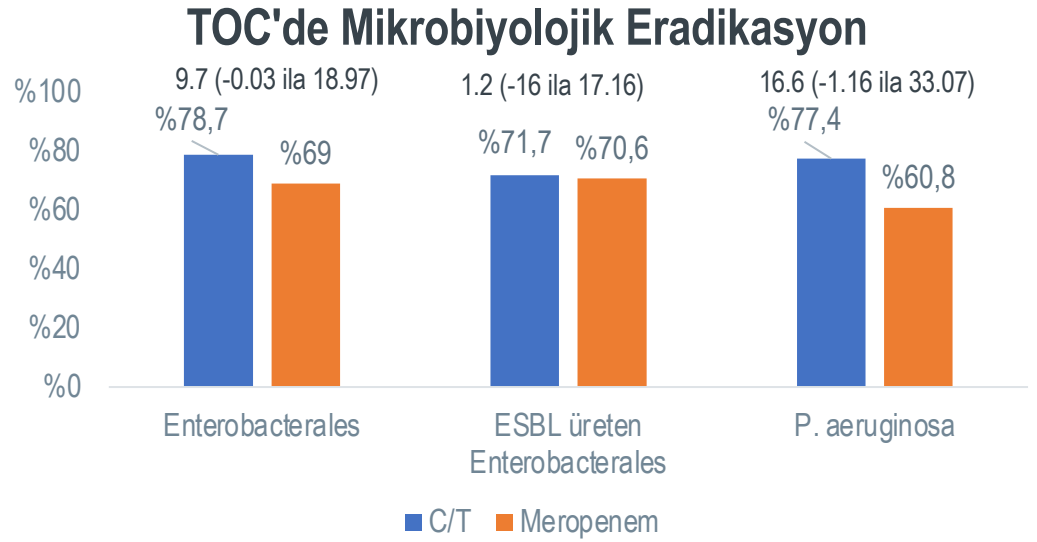
	Ceftolozane/tazobactam *n/N* (%)	Meropenem *n/N* (%)	% Difference (95% CI)[a]
28-day ACM			
Enterobacterales	22/150 (14.7)	44/171 (25.7)	11.1 (2.21–19.57)
ESBL-producing Enterobacterales	6/46 (13.0)	20/68 (29.4)	16.4 (0.57–29.96)
P. aeruginosa	13/53 (24.5)	10/51 (19.6)	−4.9 (−20.54 to 11.12)
Clinical cure at TOC			
Enterobacterales	99/150 (66.0)	98/171 (57.3)	8.7 (−1.98 to 19.01)
ESBL-producing Enterobacterales	30/46 (65.2)	42/68 (61.8)	3.5 (−14.48 to 20.14)
P. aeruginosa	31/53 (58.5)	30/51 (58.8)	−0.3 (−18.60 to 18.01)
Microbiological eradication at TOC			
Enterobacterales	118/150 (78.7)	118/171 (69.0)	9.7 (−0.03 to 18.97)
ESBL-producing Enterobacterales	33/46 (71.7)	48/68 (70.6)	1.2 (−16.00 to 17.16)
P. aeruginosa	41/53 (77.4)	31/51 (60.8)	16.6 (−1.16 to 33.07)

Çalışma Tedavisine Duyarlı Tüm Patojenlerle Klinik ve Mikrobiyolojik Şifa, 28 Günlük ACM



ACM, tüm nedenlere bağlı mortalite; TOC, şifa testi





Martin-Loeches ve ark. J Antimicrob Chemother. Mar 31 2022;77(4):1166-1177.

ESBLüreten Enterobacterales enfeksiyonlarında Seftolozan/Tazobaktam kullanalım mı?

Stewart *et al. Trials* (2021) 22:301
https://doi.org/10.1186/s13063-021-05206-8

Trials

STUDY PROTOCOL Open Access

Ceftolozane-tazobactam versus meropenem for definitive treatment of bloodstream infection due to extended-spectrum beta-lactamase (ESBL) and AmpC-producing Enterobacterales ("MERINO-3"): study protocol for a multicentre, open-label randomised non-inferiority trial

Adam G. Stewart[1,2*], Patrick N. A. Harris[1,3], Mark D. Chatfield[1], Roberta Littleford[1] and David L. Paterson[1,2]

Methods: This study will use a multicentre, parallel group open-label non-inferiority trial design comparing ceftolozane-tazobactam and meropenem in adult patients with bloodstream infection caused by ESBL or AmpC-producing Enterobacterales. Trial recruitment will occur in up to 40 sites in six countries (Australia, Singapore, Italy, Spain, Saudi Arabia and Lebanon). The sample size is determined by a predefined quantity of ceftolozane-tazobactam to be supplied by Merck, Sharpe and Dohme (MSD). We anticipate that a trial with 600 patients contributing to the primary outcome analysis would have 80% power to declare non-inferiority with a 5% non-inferiority margin, assuming a 30-day mortality of 5% in both randomised groups. Once randomised, definitive treatment will be for a minimum of 5 days and a maximum of 14 days with the total duration determined by

Clinical Infectious Diseases

MAJOR ARTICLE

Ceftolozane/Tazobactam vs Polymyxin or Aminoglycoside-based Regimens for the Treatment of Drug-resistant *Pseudomonas aeruginosa*

Jason M. Pogue,[1] Keith S. Kaye,[2] Michael P. Veve,[3] Twisha S. Patel,[4] Anthony T. Gerlach,[5] Susan L. Davis,[6] Laura A Puzniak,[7] Tom M. File,[8] Shannon Olson,[9]

Combination therapy	15	72	<.001
Aminoglycoside	0	2	
Polymyxin	0	2	
Ciprofloxacin	3	6	
Meropenem	0	36	
Cefepime	0	8	
Ceftazidime	0	2	
Piperacillin/Tazobactam	0	9	
Aztreonam	0	2	
Inhaled colistin	9	1	
Inhaled aminoglycoside	3	4	
In vitro activity of combination agent			
Susceptible	15	24	
Intermediate	0	17	

- Retrospektif, çok merkezli (ABD 6 merkez), gözlemsel kohort çalışması (2010-2018)
- 200 hasta; %69 YBÜ, %63 MVİ, %42 sepsis/septik şok
- MDR/XDR P. aeruginosa %52 VİP, %7 bakteremik
- 100 hasta Ceftolozan/Tazobaktam (%85 monoterapi)
- 100 hasta AGA/Plymxn (%28 monoterapi)

Clinical Infectious Diseases 2020;71(2):304–10

Clinical Infectious Diseases
MAJOR ARTICLE

Ceftolozane/Tazobactam vs Polymyxin or Aminoglycoside-based Regimens for the Treatment of Drug-resistant *Pseudomonas aeruginosa*

Jason M. Pogue,[1] Keith S. Kaye,[2] Michael P. Veve,[3] Twisha S. Patel,[4] Anthony T. Gerlach,[5] Susan L. Davis,[6] Laura A Puzniak,[7] Tom M. File,[8] Shannon Olson,[9]

Outcome	Ceftolozane/ Tazobactam (N = 100)	Polymyxin/Aminoglycoside (N = 100)	*P* Value	Odds Ratio (95% CI)	Adjusted Odds Ratio[a] (95% CI)
Clinical cure	81	61	.002	2.72 (1.43–5.17)	2.63 (1.31–5.30)
In-hospital mortality	20	25	.40	0.75 (0.38–1.46)	0.62 (.30–1.28)
Acute kidney injury	6	34	<.001	0.12 (0.05–0.31)	0.08 (.03–.22)

C/T
Klinik yanıt için NNT: 5

AGA/Plymxn
Nefrotoksite için NNH:4

Clinical Infectious Diseases 2020;71(2):304–10

Open Forum Infectious Diseases
MAJOR ARTICLE

Ceftolozane-Tazobactam for the Treatment of Multidrug-Resistant *Pseudomonas aeruginosa* Infections: A Multicenter Study

Jason C. Gallagher,[1] Michael J. Satlin,[2] Abdulrahman Elabor,[3] Nidhi Saraiya,[4] Erin K. McCreary,[5] Esther Molnar,[3] Claudine El-Beyrouty,[6] Bruce M. Jones,[7]

- Retrospektif, çok merkezli (ABD 20 merkez), gözlemsel kohort çalışması (2015-2018)
- 205 hasta; %59 Pnömoni (HAP, VAP), %14 ÜSİ
- MDR/XDR P. aeruginosa , %12 bakteremik

Overall Outcomes	Results, n (%)
Mortality	39 (19.0)
Clinical success	151 (73.7)
Microbiological cure	145 (70.7)

Outcomes by infection type

Type (n)[a]	Microbiological Cure, n (%)	Clinical Success, n (%)	Mortality, n (%)
Bloodstream, primary[b] (6)	6 (100)	6 (100)	0 (0)
Bone/joint (16)	13 (81.3)	13 (81.3)	0 (0)
Intra-abdominal (20)	18 (90.0)	15 (75.0)	2 (10.0)
Pneumonia (121)	69 (57.0)	80 (66.1)	31 (25.6)
VAP (58)	31 (53.4)	29 (50.0)	22 (37.9)
Non-VAP (63)	38 (60.3)	51 (81.0)	9 (14.2)
Wound (26)	21 (80.8)	21 (80.8)	4 (15.4)
UTI (28)	25 (89.3)	25 (89.3)	4 (14.3)

Drug tested, %Susceptible (n/N Tested)							
AMK	ATM	FEP/CAZ	GEN	MEM/IPM	TZP	TOB	CST
78.6% (125 of 159)	7.2% (10 of 139)	14.4% (21 of 177)	57.7% (94 of 163)	3.4% (6 of 179)	5.8% (10 of 173)	74.3% (104 of 140)	91.9% (57 of 62)
Ceftolozane-tazobactam (n/N tested, % susceptible)					125 of 139 (89.9%)		

DOI: 10.1093/ofid/ofy280

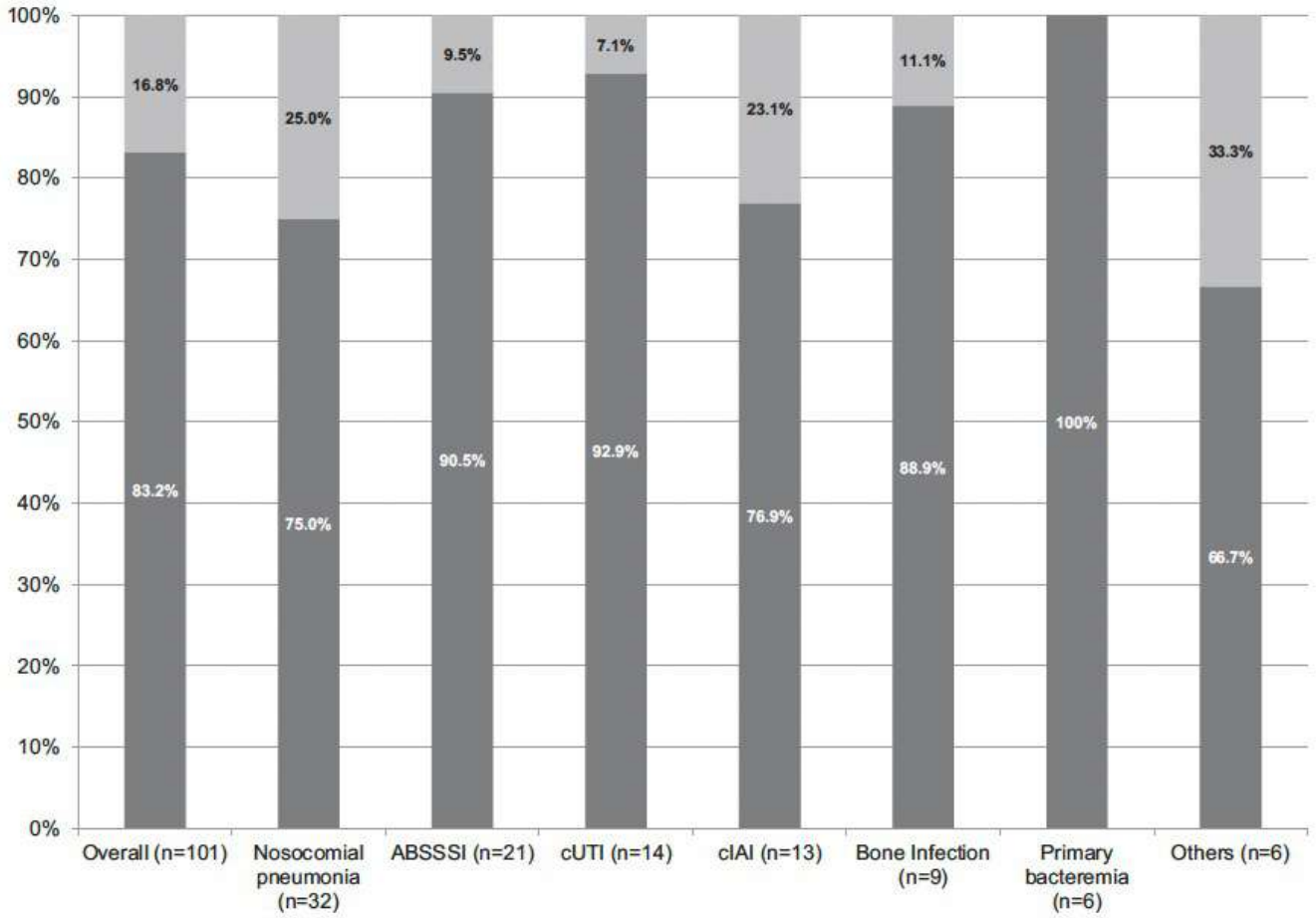
International Journal of Antimicrobial Agents
Volume 53, Issue 4, April 2019, Pages 408-415

Ceftolozane/tazobactam for the treatment of serious *Pseudomonas aeruginosa* infections: a multicentre nationwide clinical experience

Matteo Bassetti [a], Nadia Castaldo [a], Annamaria Cattelan [b], Cristina Mussini [c], Elda Righi [a],

- Retrospektif, çok merkezli (İtalya 22 merkez), gözlemsel kohort çalışması (2016-2018)
- 101 hasta; %32 Pnömoni (HAP, VAP), %21 DYDİ, %14 ÜSİ MDR/XDR P. aeruginosa , %38 sepsis, septik şok

Antimicrobial agent	*n* (%) non-susceptible
Amikacin	48 (47.5)
Cefepime	61 (60.4)
Ceftazidime	70 (69.3)
Ciprofloxacin	74 (73.1)
Colistin	2 (2.0)
Doripenem	76 (75.2)
Gentamicin	51 (50.5)
Fosfomycin	90 (89.1)
Levofloxacin	78 (77.2)
Meropenem	78 (77.2)
Piperacillin/tazobactam	78 (77.2)
Imipenem/cilastatin	76 (75.2)
Tobramycin	58 (57.4)



Clinical Infectious Diseases
IDSA GUIDELINES

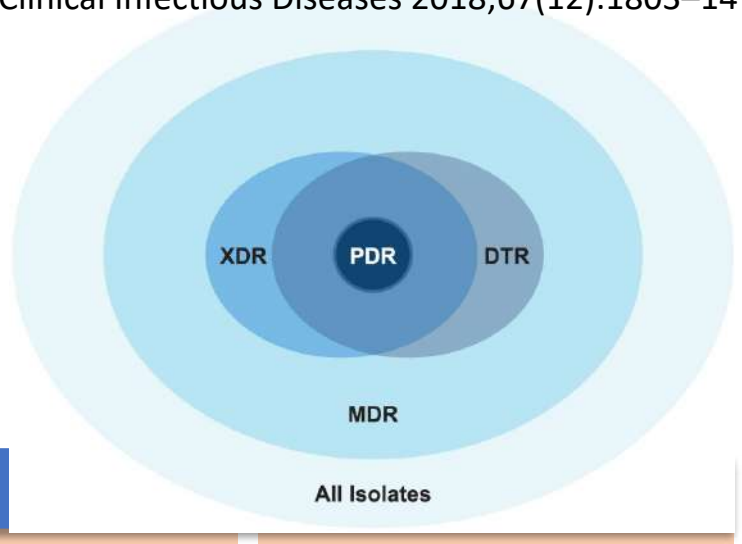
Infectious Diseases Society of America 2022 Guidance on the Treatment of Extended-Spectrum β-lactamase Producing Enterobacterales (ESBL-E), Carbapenem-Resistant Enterobacterales (CRE), and *Pseudomonas aeruginosa* with Difficult-to-Treat Resistance (DTR-*P. aeruginosa*)

Pranita D. Tamma,[1] Samuel L. Aitken,[2] Robert A. Bonomo,[3] Amy J. Mathers,[4] David van Duin,[5] and Cornelius J. Clancy[6]

2022;75(2):187–212

Schematic Relationship of DTR with CDC-defined Co-resistance Phenotypes

Clinical Infectious Diseases 2018;67(12):1803–14



	DTR-*P. aeruginosa*			
	Komplike olmayan sistit	**Piyelonefrit ve komplike UTI**	**İdrar Yolu Dışında**	**Direnç**: tüm yeni ß-laktamlarla ilgilidir, seftolozan-tazobaktam ve seftazidim-avibaktam ile en yüksektir
Öneri	Seftolozan-tazobaktam, seftazidim-avibaktam, imipenem-silastatin-relebaktam, sefiderokol veya tek doz aminoglikozit	Seftolozan-tazobaktam, seftazidim-avibaktam, imipenem-silastatin-relebaktam ve sefiderokol	Seftolozan-tazobaktam, seftazidim-avibaktam ve imipenem-silastatin-relebaktam monoterapisi	Bir hasta yakın zamanda bu ajanlarla tedavi gördüyse ve enfeksiyon belirtileri gösteriyorsa, duyarlılık oluşana kadar farklı bir yeni ß-laktam ajanı düşünün
Ek	Bir ajanın diğerinden daha iyi olduğunu söylemek için yeterli veri yoktur	Bir ajanın diğerinden daha iyi olduğunu söylemek için yeterli veri yoktur	Tedavi kararında yönlendirme sağlaması için her zaman antibiyotik duyarlılık testi çalışılması önerilir	Bu ajanlar arasında çapraz direnç, benzer direnç mekanizmaları nedeniyle yüksektir

Guidelines

European Society of Clinical Microbiology and Infectious Diseases (ESCMID) guidelines for the treatment of infections caused by multidrug-resistant Gram-negative bacilli (endorsed by European society of intensive care medicine)

Mical Paul [1, 2, §], Elena Carrara [3, §], Pilar Retamar [4, 5], Thomas Tängdén [6], Roni Bitterman [1, 2],

Clin Microbiol Infect. Apr 2022;28(4):521-547

Table 2

Potential *in vitro* activity of antibiotics against target carbapenem-resistant Gram-negative bacteria and approved indications

	CRAB	ESBLs	CRPA non-MBL	CRE non-CP	CRE-KPC	CRE-OXA-48	CRE-MBL	Current clinical indications/approval
New antibiotics								
Ceftolozane-tazobactam	No	Yes	Yes	No	No	No	No	FDA and EMA approved for cUTI, cIAI, HAP and VAP

Recommendation	Strength of recommendation	Level of evidence
Among all patients with 3GCephRE infections the new BLBLI are reserved antibiotics for extensively resistant bacteria and therefore, we consider it good clinical practice to avoid their use for infections caused by 3GCephRE, due to antibiotic stewardship considerations.	Good practice statement	Expert opinion
Recommendations on the choice of antibiotic treatment for CRPA		
In patients with severe infections due to difficult to treat CRPA, we suggest therapy with ceftolozane-tazobactam if active *in vitro*. Insufficient evidence is available for imipenem-relebactam, cefiderocol and ceftazidime-avibactam at this time.	Conditional	Very low
In patients with non-severe or low-risk CRPA infections, under the consideration of antibiotic stewardship, we consider it good clinical practice to use the old antibiotics, chosen from among the *in vitro* active antibiotics on an individual basis and according to the source of infection.	Good practice statement	Expert opinion

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