İSTANBUL
MEDENİYET ÜNİVERSİTESİ

EKMUD

Gram Negatif Bakterilerde Güncel ve Yeni Tedavi Alternatifleri

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Kasım 2020

GNB Enfeksiyonlarda Mevcut Tedavi Seçenekleri

- Seftazidim
- Sefepim
- Sefoksitin
- Ampisillin/sulbactam
- Co-amoksiclav
- Piperacillin/tazobactam
- Karbapenemler
- Aminoglikozidler
- Fluoroquinolonlar
- Tigecycline
- Fosfomycin
- Trimethoprim/sulfamethoxazole
- Polimiksinler

- Mevcut antibiyotiklerle, özellikle XDR ve PDR suşlarla oluşan enfeksiyonların tedavisinde güçlükler yaşanmakta

MDR-XDR GNB ile oluşan enfeksiyonlarda tedavi seçenekleri

- Karbapenemler veya pip/taz gibi antibiyotiklerin yüksek doz ve /veya uzamış infuzyonla uygulanması
- Kolistin ve fosfomisin gibi eski antibiyotiklerin kullanımı
- Antibiyotiklerin çoklu kullanımı
- Yeni geliştirilen antibiyotikler

Lancet Infect Dis. 2018 Jan;18(1):108-120. doi: 10.1016/S1473-3099(17)30615-1. Epub 2017 Nov 5.

Prolonged versus short-term intravenous infusion of antipseudomonal β-lactams for patients with sepsis: a systematic review and meta-analysis of randomised trials.

Vardakas KZ[1], Voulgaris GL[2], Maliaros A[3], Samonis G[4], Falagas ME[5].

Summary

Background The findings of randomised controlled trials (RCT), observational studies, and meta-analyses vary regarding the effectiveness of prolonged β-lactam infusion. We aimed to identify the effectiveness of prolonged versus short-term infusion of antipseudomonal β-lactams in patients with sepsis.

Methods We did a systematic review and meta-analysis to compare prolonged versus short-term intravenous infusion of antipseudomonal β-lactams in patients with sepsis. Two authors independently searched PubMed, Scopus, and the Cochrane Library of clinical trials until November, 2016, without date or language restrictions. Any RCT comparing mortality or clinical efficacy of prolonged (continuous or ≥3 h) versus short-term (≤60 min) infusion of antipseudomonal β-lactams for the treatment of patients with sepsis was eligible. Studies were excluded if they were not RCTs, the antibiotics in the two arms were not the same, neither mortality nor clinical efficacy was reported, only pharmacokinetic or pharmacodynamic outcomes were reported, or if ten or fewer patients were enrolled or randomised. Data were ext el. The pri PERO da

Sepsisli hastalarda antipseudomonal beta-laktamların uzun süreli (sürekli veya 3 saat ve üzeri) uygulaması kısa süreli (1 saat ve altı) uygulamaya göre azalmış mortalite ile ilişkili

Fir alysis. Ac idence for Acute Physiology and Chronic Health Evaluation (APACHE) II score, severity of sepsis and renal function were enrolled. 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.

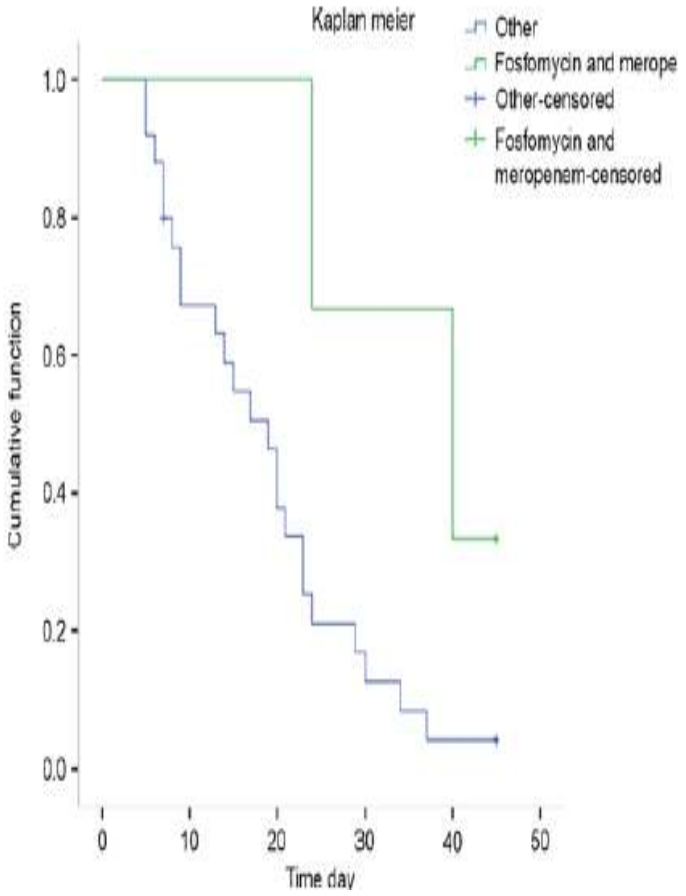
Interpretation Prolonged infusion of antipseudomonal β-lactams for the treatment of patients with sepsis was associated with significantly lower mortality than short-term infusion. Further studies in specific subgroups of patients according to age, sepsis severity, degree of renal dysfunction, and immunocompetence are warranted.

EXPERIMENTAL AND THERAPEUTIC MEDICINE 13: 1003-1010, 2017

Retrospective analysis of fosfomycin combinational therapy for sepsis caused by carbapenem-resistant *Klebsiella pneumoniae*

YUN LIAO[1*], GUANG-HUI HU[2*], YUN-FEI XU[2], JIAN-PING CHE[2], MING LUO[2],

Abstract. The aim of the present study was to compare the efficacy and safety of fosfomycin combinational therapy with other antibiotics for the treatment of infections caused by carbapenem-resistant *Klebsiella pneumoniae* (CRKP). This retrospective cohort study examined 104 cases of sepsis caused by CRKP occurring between January 2012 and November 2014 in Shanghai Tenth People's Hospital. Three categories of patient outcome were assessed: Survival/mortality, duration of intensive care unit stays and duration of medical ventilation. Univariate ordinal analyses were adopted to evaluate the correlations between outcome and treatment. A total of 104 patients with physician-diagnosed CRKP were involved in the study. The overall mortality rate was 25.0%. The majority of the infections (84; 80.8%) were hospital acquired. Critical infections received more than one active antibiotic as therapy. associated with improved survival rate.



- 104 KRKP'nın etken olduğu sepsis (%80 nazokomiyal sepsis)
- Genel mortalite %25
- Fosfomisinli kombinasyon yapılan grupta
  - Tedavi başarısızlığı daha düşük, Mortalite %8.3
  - MV süresi daha kısa

Yeni Onaylanan Antibiyotikler

- Yeni betalaktam ve betalaktam-betalaktamaz inhibitörleri kombinasyonları
  - Seftazidim-avibaktam
  - Seftolozan-tazobaktam
  - Meropenem-vaborbaktam
  - İmipenem/cilastatin-relebactam
  - Cefiderocol

- Florokinolonlar
  - Delafloksasin
- Aminoglikozitler
  - Plazomisin
- Tetrasiklinler
  - Eravasiklin
  - Omadosiklin

Beta-laktamaz İnhitörlerinin Etkinliği

Table 3 Activities of β-lactamase inhibitors against various β-lactamase enzymes

	β-lactamase inhibitor					
	Relebactam	Vaborbactam	Avibactam	Clavulanic acid	Sulbactam	Tazobactam
Class A						
TEM	+	+	+	+	+	+
SHV	+	+	+	+	+	+
CTX-M	+	+	+	+	+	+
KPC	+	+	+	−	−	−
Class B						
MBL	−	−	−	−	−	−
Class C						
AmpC	+	+	+	−	±[a]	−
Class D						
OXA	±	−[b]	±	−	−	−
Reference	[5]	[5]	[5, 24]	[25, 26]	[27]	[27]

− no inhibitory activity, + inhibitory activity, *MBL* metallo-β-lactamase

[a]Enterobacteriaceae resist inhibition by sulbactam, although *Klebsiella* spp., *Salmonella* spp., and *Proteus* spp. normally do not harbor chromosomal bla_{AmpC} genes

[b]Limited data available

Zhanel GG. Drugs. 2018 Jan;78(1)

Seftazidim-Avibaktam

- 3. kuşak sefalosporin olan seftazidimin, yeni bir geliştirilen bir non betalaktam beta laktamaz inhibitörü olan avibaktam ile kombinasyonu
- Avibaktam sınıf A, C ve kısmen de D beta laktamazlara karşı etkili (*Acinetobacter* tarafından üretilen sınıf D'ye etkisiz),
- ESBL üreten GNB ve karbapenem dirençli Enterobacteriaceae'ya etkili
- 2015 FDA onayı
  - Komplike intraabdominal enfeksiyonlar (metranidazol ile kombine edilerek)
  - Komplike üriner sistem enfeksiyonları

Falcone, M., & Paterson, D. 2016. *JAC*, *71*(10)

Seftazidim-Avibaktam

- 2.5 g (2 g/0.5 g) IV her 8 saatte, infüzyon süresi >2 saat
- Tedavi süresi 5-14 gün
- Orta ve ciddi renal yetmezlikte doz ayarı gerektirir
- Genellikle iyi tolere edilir
- En sık yan etkiler
  - Baş ağrısı, gastrointestinal rahasızlıklar, infüzyon bölgesinde reaksiyon

Falcone, M., & Paterson, D. 2016. *JAC*, *71*(10)

Clinical Infectious Diseases

MAJOR ARTICLE

Colistin Versus Ceftazidime-Avibactam in the Treatment of Infections Due to Carbapenem-Resistant Enterobacteriaceae

David van Duin,[1] Judith J. Lok,[2] Michelle Earley,[2] Eric Cober,[3] Sandra S. Richter,[4] Federico Perez,[5,6] Robert A. Salata,[6] Robert C. Kalayjian,[7] Richard R. Watkins,[8,9] Yohei Doi,[10] Keith S. Kaye,[11] Vance G. Fowler Jr,[12,13] David L. Paterson,[14] Robert A. Bonomo,[5,6,15,16] and Scott Evans[2],

Methods. Patients initially treated with either ceftazidime-avibactam or colistin for CRE infections were selected from the Consortium on Resistance Against Carbapenems in *Klebsiella* and other Enterobacteriaceae (CRACKLE), a prospective, multicenter, observational study. Efficacy, safety, and benefit-risk analyses were performed using intent-to-treat analyses with partial credit and the desirability of outcome ranking approaches. The ordinal efficacy outcome was based on disposition at day 30 after starting treatment (home vs not home but not observed to die in the hospital vs hospital death). All analyses were adjusted for confounding using inverse probability of treatment weighting (IPTW).

Results. Thirty-eight patients were treated first with ceftazidime-avibactam and 99 with colistin. Most patients received additional anti-CRE agents as part of their treatment. Bloodstream (n = 63; 46%) and respiratory (n = 30; 22%) infections were most common. In patients treated with ceftazidime-avibactam versus colistin, IPTW-adjusted all-cause hospital mortality 30 days after starting treatment was 9% versus 32%, respectively (difference, 23%; 95% bootstrap confidence interval, 9%–35%; $P = .001$). In an analysis of disposition at 30 days, patients treated with ceftazidime-avibactam, compared with those treated within colistin, had an IPTW-adjusted probability of a better outcome of 64% (95% confidence interval, 57%-71%). Partial credit analyses indicated uniform superiority of ceftazidime-avibactam to colistin.

Conclusions. Ceftazidime-avibactam may be a reasonable alternative to colistin in the treatment of *K. pneumoniae* carbapenemase–producing CRE infections. These findings require confirmation in a randomized controlled trial.

- **CRE tedavisinde seftazidim avibaktam bazlı tedavi ve kolisitin bazlı tedavi**
- **30 günlük mortalite seftazidim avibaktam %9, kolisitin %32**

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Review

Evaluation of the efficacy and safety of ceftazidime/avibactam in the treatment of Gram-negative bacterial infections: a systematic review and meta-analysis

Han Zhong[a,1], Xian-Yuan Zhao[b,1], Zai-Li Zhang[a], Zhi-Chun Gu[a], Chi Zhang[a], Yuan Gao[b,*], Min Cui[a,*]

- GNB enfeksiyonların tedavisinde CAZ/AVI – karbapenem
  - Klinik yanıt ve bakteriyel eradikasyon benzer
  - Mortalite ve yan etki arasında fark yok
- Subgrup analizinde karbapenem dirençli Enterobacteriaceae enfeksiyonlarında CAZ-AVI daha iyi klinik yanıt ve azalmış mortalite

0.96–1.02; $I^2 = 0\%$) and non-inferior bacterial eradication (RR = 1.04, 95% CI 0.93–1.17; $I^2 = 79.1\%$) to carbapenems. No significant difference was detected between groups regarding mortality and adverse events. Moreover, subgroup analyses demonstrated that CAZ-AVI improved the clinical response (RR = 1.61, 95% CI 1.13–2.29) with reduced mortality (RR = 0.29, 95% CI 0.13–0.63) in patients infected by carbapenem-resistant Enterobacteriaceae versus comparators. Likewise, CAZ-AVI improved the clinical cure rate of bloodstream infections (RR = 2.11, 95% CI 1.54–2.88). An improved ability of CAZ-AVI in microbiological eradication was also detected in patients with complicated urinary tract infections (RR = 1.13, 95% CI 1.05–1.21). CAZ-AVI exhibited comparable efficacy and safety with carbapenems. Therefore, this agent might be a potential powerful agent for patients with serious Gram-negative bacterial infections.

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International Journal of Antimicrobial Agents

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Efficacy of ceftazidime/avibactam in monotherapy or combination therapy against carbapenem-resistant Gram-negative bacteria: A meta-analysis

Lorenzo Onorato[a,1], Giovanni Di Caprio[b,1], Simona Signoriello[c], Nicola Coppola[a,b,*]

Clinicians may use ceftazidime/avibactam in combination with other active agents to treat infections due to carbapenem-resistant organisms, although no conclusive data support this practice. This meta-

- CRE ve CRPA enfeksiyonlarında CAZ/AVI'ın kombine ve monoterapide kullanımı
- Mortalite oranları ve mikrobiyolojik kür oranları benzer bulunmuş

as full papers and indexed up to February 2019 comparing the efficacy, in terms of mortality and microbiological cure rates, of ceftazidime/avibactam monotherapy or combination therapy with other active agents for infections due to CRE or CRPa. The relative risk (RR) of mortality and microbiological eradication was estimated based on pooled data from all eligible studies. Eleven studies were included in the meta-analysis accounting for 396 subjects, of whom 202 received combination therapy. The mortality rate was 38.1% for combination therapy and 30.9% for monotherapy (RR = 1.18, 95% CI 0.88–1.58; $P = 0.259$). Similarly, no difference was found between the two groups when analysing the rate of microbiological cure (64.9% for combination therapy vs. 63.4% for monotherapy; RR = 1.04, 95% CI 0.85–1.28, $P = 0.705$). Moreover, no difference was observed for both outcomes when patients infected with *P. aeruginosa* were excluded from the analysis. This meta-analysis suggests that use of ceftazidime/avibactam in monotherapy or combination therapy for infections due to CRE or CRPa could show a similar effect on mortality and microbiological cure rates. Studies on larger samples are needed to address this important issue.

Seftolozan-Tazobaktam

- Seftolozan yeni bir sefalosporin olup sefem çekirdeğinin 3. pozisyonundaki yan zincirin modifikasyonu ile seftazidimden farklıdır
- Artmış antipsödomonal aktiviteye sahiptir.
- ESBL-üreten *E. coli, K. pneumoniae,* ve diğer *Enterobacteriaceae* etkili
- AmpC etkili, KPC veya MBLs e karşı etkisiz
- Komplike intraabdominal (metranidazol ile kombine edilerek) ve komplike üriner sistem enfeksiyonlarının tedavisinde 2014 FDA onayı

Zhanel, George G. 2014. *Drugs* 74.1

- 1.5 g IV her 8 saatte, infüzyon süresi 1 saat,
- Tedavi süresi 4-14 gün
- Orta ve ciddi renal yetmezlikte doz ayarı gerektirir
- Gastrointestinal rahasızlıklar, baş ağrısı, pireksi en sık yan etkiler

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Salvage Therapy with Ceftolozane-Tazobactam for Multidrug-Resistant *Pseudomonas aeruginosa* Infections

Juan José Castón,[a,b] Álvaro De la Torre,[c] Isabel Ruiz-Camps,[d] María Luisa Sorlí,[e] Vicente Torres,[f] Julián Torre-Cisneros[a,b,g]

ABSTRACT Infections caused by multidrug-resistant *Pseudomonas aeruginosa* (MDRPA) present a major problem for therapeutic management. We report here our experience with 12 patients with a severe MDRPA infection (6 of which were pneumonia) who received salvage therapy with ceftolozane-tazobactam after inappropriate empirical treatment and/or suboptimal targeted treatment. Although 10 of the 12 patients (83.3%) experienced septic shock, only 3 patients (25%) died during the follow-up period. Microbiological cure in 7 patients (58.3%) was observed.

- Retrospektif, çok merkezli
- 10/12 septik şok, 1 sepsis, 1 ciddi sepsis
- Tüm hastalar meropenem, siprofloksasin ve pip-taz dirençli
- 8 hasta kolistin hassas
- Başlangıç empirik tedaviden median 7. günde hedefe yönelik tedaviye (Çogunlukla kolistin) geçilmiş.
- Tedavi yanıtsızlığı gelişmesi üzerine median 12. günde seftolozan-tazobaktam'a geçilmiş.
- 8/12 Klinik kür,

Meropenem-Vaborbaktam

- Vaborbactam siklik boranik asit bazlı bir betalaktamaz inhibitörü
- Serin beta laktamazlara karşı geniş inhibitör aktivite göstermektedir. Ambler sınıf A ve C'ye etkili
- Komplike üriner sistem enfeksiyonlarının tedavisi 2017 FDA onayı
- 4 g (meropenem 2g/vaborbactam 2g) IV her 8 saatte, infuzyon süresi >3 saat

JAMA | Original Investigation

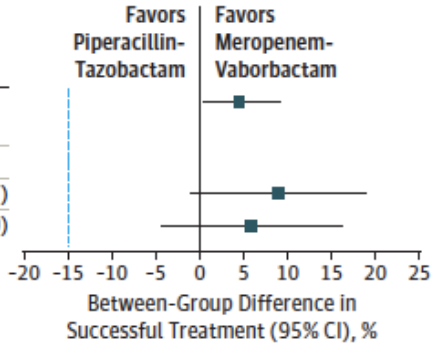
Effect of Meropenem-Vaborbactam vs Piperacillin-Tazobactam on Clinical Cure or Improvement and Microbial Eradication in Complicated Urinary Tract Infection

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;

A Primary end points

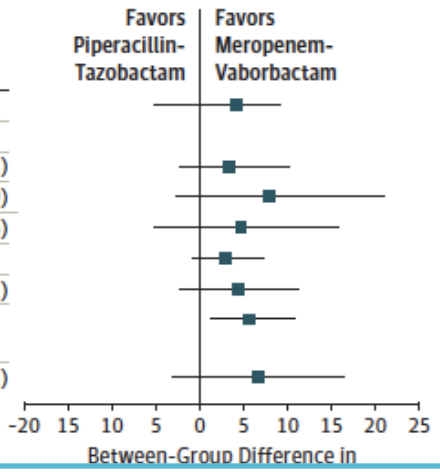
	No. of Patients Successfully Treated/Total No. (%)		Between-Group Difference (95% CI), %
	Meropenem-Vaborbactam	Piperacillin-Tazobactam	
FDA primary: overall success at end of intravenous treatment (microbiologic MITT analysis)[a,b]	189/192 (98.4)	171/182 (94.0)	4.5 (0.7 to 9.1)
EMA primary: microbial 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)



Faz 3 çalışması komplike İYE'de MER- VAB ve PİP-TAZ

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)



Sefiderokol

- Bir siderofora bağlı sefalosporin
- Gram-negatif bakterilerin dış zarından alımını kolaylaştırmak için bakteriyel demir taşıma mekanizmasını kullanır
- Siderofor benzeri özelliği nedeniyle periplazmik boşluğa daha fazla giriyor.
- ESBL ve AmpC dahil-betalaktamazlara karşı doğal olarak daha stabildir.
- Şu anda en geniş Gram negatif spektruma sahip ajan
- Komplike üriner sistem enfeksiyonları, HABP/VABP FDA onayı 2020
- Ancak mevcut antibiyotik sınıflarıyla önemli ölçüde çapraz direnç sergilemektedir.

Frampton J E. *Drugs*, 2013, 73.10

Table 3. Expected activity of β-lactams and β-lactam/BLI combinations against common β-lactamases

	CRE				CRAB	CRPA
	A	A	D	B		
	ESBL (CTX-M)	KPC (KPC-2,-3)	OXA (OXA-48)	MBL (NDM)		
Vaborbactam + meropenem	●	●	●	–	–	–
Relebactam + imipenem/cilastatin	●	●	●	–	–	?
Cefiderocol	●	●	●	●	●	●

Table 1. Antibiotics that gained market authorization between July 2017 and September 2019

Name (trade name)	Market authorization holder	Approved by (date)	Antibiotic class	Route of administration	Indication/s	WHO EML & AWaRe	Expected activity against priority pathogens				Innovation			
							CRAB	CRPA	CRE	OPP	NCR	CC	T	M
Delafloxacin (Baxdela)	Melinta	FDA (6/2017 ABSSSI, 10/2019 CAP) MAA	Fluoroquinolone	iv & oral	ABSSSI, CAP	AWaRe: Watch	○	○	○	●	-	-	-	
Vaborbactam + meropenem (Vabomere)	Melinta	FDA (8/2017) EMA (11/2018)	Boronate BLI + carbapenem	iv	cUTI	WHO EML & AWaRe: Reserve	○	○	●[1]	/	?	✓	-	
Plazomicin (Zemdri)	Achaogen	FDA (8/2018)	Aminoglycoside	iv	cUTI	WHO EML & AWaRe: Reserve	○	○	●	/	-	-	-	
Eravacycline (Xerava)	Tetraphase	FDA (8/2018) EMA (9/2018)	Tetracycline	iv	cIAI	AWaRe: Reserve	?	○	●	/	-	-	-	
Omadacycline (Nuzyra)	Paratek	FDA (10/2018)	Tetracycline	iv & oral	CAP (iv), ABSSSI (iv, oral)	AWaRe: Reserve	○	○	○	●	-	-	-	
Relebactam + imipenem/ cilastatin (Recarbrio)	MSD	FDA (7/2019)	DBO-BLI + carbapenem/ degradation inhibitor	iv	cUTI, cIAI (HABP/VABP)		○	?	●[1]	/	-	-	-	
Lefamulin	Nabriva	FDA (8/2019)	Pleuromutilin	iv & oral	CAP		/	/	/	●	?	✓[2]	-	
Pretomanid (PA-824)	TB Alliance	FDA (8/2019)	Nitroimidazole	oral	XDR TB		/	/	/	●[3]	-	-	-	

Pathogen activity: ● active; ? possibly active; ○ not or insufficiently active; / activity not assessed, as the antibiotic is focused and developed for only either Gram-positive cocci or Gram-negative rods. The only agents assessed against OPP were those that are not active against critical priority pathogens. OPP includes the high- and medium-priority pathogens.

Innovation assessment: ✓ criterion fulfilled; ? inconclusive data or no agreement among the advisory group; - criterion not fulfilled.

Abbreviations: ABSSSI, acute bacterial skin and skin structure infections; CC, new chemical class; DHFR, dihydrofolate reductase; iv, intravenous; EML, essential medicines list; MoA, new mode of action; NCR, no cross-resistance to other antibiotic classes; NDA, New Drug Application (FDA); MAA, marketing authorisation application (EMA); PBP, penicillin-binding protein; T, new target.

CRAB: CR *A. Baumannii*, CRPA: CR *P. Aeruginosa,* CRE: *Enterobacteriaceae*

CRE (Karbapenem dirençli *Enterobacteriaceae*)	• Seftazidim-avibaktam • Meropenem-vaborbaktam • İmipenem/cilastatin-relebactam • Sefiderokol
CRPA (Karbapenem dirençli *P. Aeruginosa)*	• Seftolozan-tazobaktam • Sefiderokol • İmipenem/cilastatin-relebactam • Seftazidim-avibaktam
CRAB (Karbapenem dirençli *A. Baumanni*i)	• Sefiderokol • Polimiksinler

Bassetti M et al. 2019 Front. Med

Ufuktaki Antibiyotikler

- DSÖ 2019 verilerine göre geliştirilmekte olan 50 antibiyotik mevcut
- % 40'ından fazlası DSÖ öncelikli patojenlerini hedefleyen β-laktam ve β-laktamaz inhibitörü (BLI) kombinasyonları
- Faz 3 e kadar gelen ilaçların ortalama %60'ı onaylanmakta

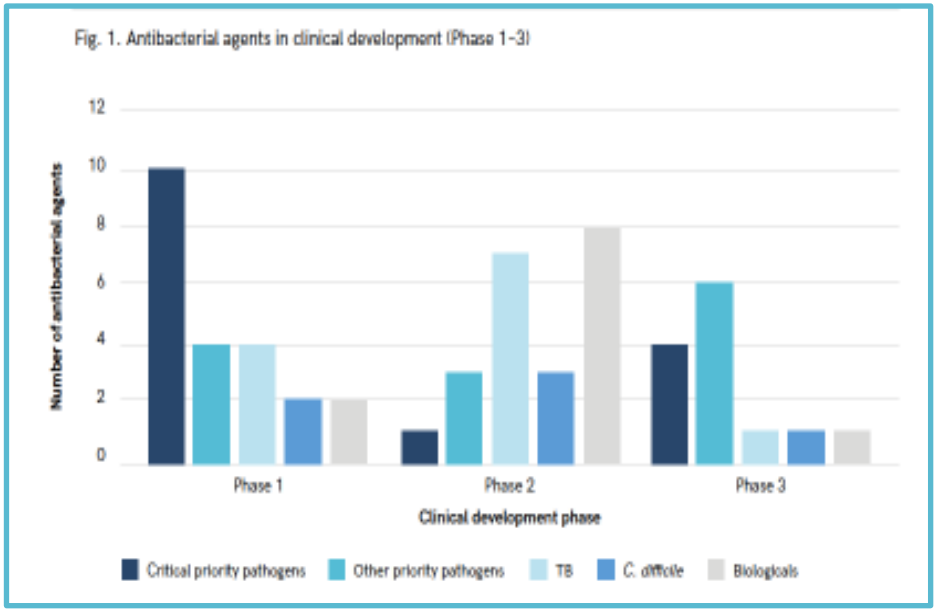


Table 2. Antibiotics that are being developed against WHO priority pathogens

Name (synonym)	Phase	Antibiotic class	Route of administration (developer)	Expected activity against priority pathogens				Innovation			
				CRAB	CRPA	CRE	OPP	NCR	CC	T	MoA
Sulopenem, Sulopenem etzadroxil/ probenecid	3	Penem	iv (Iterum) oral (Iterum)	○	○	○[3]	/	-	-	-	-
Durlobactam (ETX-2514) + sulbactam	3	DBO-BLI/PBP2 binder + β-lactam-BLI/PBP1,3 binder	iv (Entasis)	●	○	○	/	-	-	-	-
Taniborbactam (VNRX-5133) + cefepime	3	Boronate-BLI + cephalosporin	iv (VenatoRx)	○	?	●	/	?	✓	-	-
Enmetazobactam (AAI-101) + cefepime	3	β-lactam BLI + cephalosporin	iv (Allecra)	○	○	○[4]	/	-	-	-	-
Zoliflodacin	3	Topoisomerase inhibitor (spiropyrimidenetrione)	oral (Entasis/GARDP)	/	/	/	●	✓	✓	-	✓
Gepotidacin	3	Topoisomerase inhibitor (triazaacenaphthylene)	iv & oral (GSK)	/	/	/	●	?	✓	-	✓
Levonadifloxacin Alalevonadifloxacin	3[5]	Fluoroquinolone	iv oral (Wockhardt)	○	○	○	?	-	-	-	-
Cefilavancin (TD-1792)	3[6]	Glycopeptide-cephalosporin conjugate	iv (Theravance/R Pharm)	/	/	/	●	-	-	-	-
Solithromycin	3[7]	Macrolide	iv & oral (Melinta/Fujifilm Toyama Chemical)	/	/	/	●	-	-	-	-

Name (synonym)	Phase	Antibiotic class	Route of administration (developer)	Expected activity against priority pathogens				Innovation			
				CRAB	CRPA	CRE	OPP	NCR	CC	T	MoA
Contezolid Contezolid acefosamil	2/3[8]	Oxazolidinone	oral (MicuRx) iv & oral (MicuRx)	/	/	/	●	–	–	–	–
Afabicin (Debio-1450)	2	FabI inhibitor	iv & oral (Debiopharm)	/	/	/	●	✓	✓	✓	✓
BOS-228 (LYS-228)	2	Monobactam	iv (Boston Pharmaceuticals)	○	○	●	/	–	–	–	–
Nafithromycin (WCK-4873)	2	Macrolide	oral (Wockhardt)	/	/	/	●	–	–	–	–
TNP-2092	2	Rifamycin-quinolizinone hybrid	iv & oral (TenNor)	/	/	/	?	–	–	–	–
Benapenem	2[9]	Carbapenem	iv (Sichuan Pharmaceutical)	○	○	○	/	–	–	–	–

Table 3. Expected activity of β-lactams and β-lactam/BLI combinations against commor

	CRE			
	A	A	D	B
	ESBL (CTX-M)	KPC (KPC-2,-3)	OXA (OXA-48)	MBL (NDM)
Sulopenem	●	–	–	–
Durlobactam (ETX-2514) + sulbactam	–	–	–	–
Taniborbactam (VNRX-5133) + cefepime	●	●	●	●
Enmetazobactam (AAI-101) + cefepime	●	?	–	–
BOS-288	●	●	●	●
Zidebactam + cefepime	●	●	●	?
Nacubactam + meropenem	●	●	●	?
ETX-0282 + cefpodoxime	●	●	●	–
VNRX-7145 + ceftibuten	●	●	●	–
ARX-1796 (oral avibactam prodrug)	●	●	●	–

Pathogen activity: ● active; ? possibly active; – not or insufficiently active or activity not assessed.

Sonuç

- Dirençli Gram negatif bakteri enfeksiyonlarının tedavisinde yeni antibiyotikler umut vaadetmektedir.
- Ancak metallobetalaktamaz üreten bakteriler için gelecekte de tedavi seçenekleri sınırlı
- Yeni antibiyotikler akılcı kullanılmadığı sürece direnç kaçınılmaz olacaktır.