Dirençli Gram-Negatif Enterik Çomaklarda Yeni Ne Var? Yeni tedaviler, umutlar...

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2020 Ocak

Hirudoterapi

Ozon

Hiperbarik

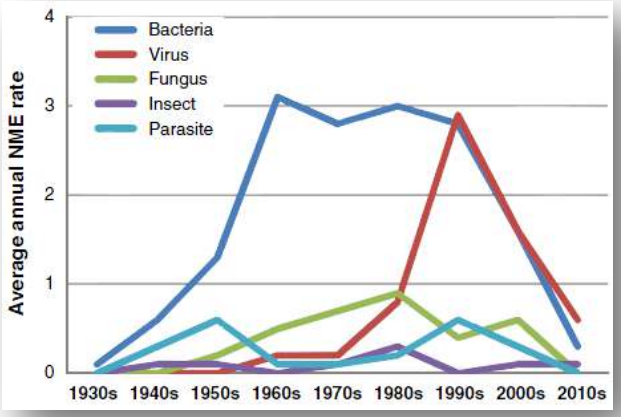
Bitki börtü böcük

The antibiotic era

1950-60s	1970-90s	2000s	2010s
Small spectrum	Broad spectrum	Small spectrum	Small spectrum
Gram positive	Gram negative Gram positive	Gram positive	Gram negative targeted
Natural products	Medicinal chemistry, Semisynthetic products	Target based	Natural products? Alternative approaches?

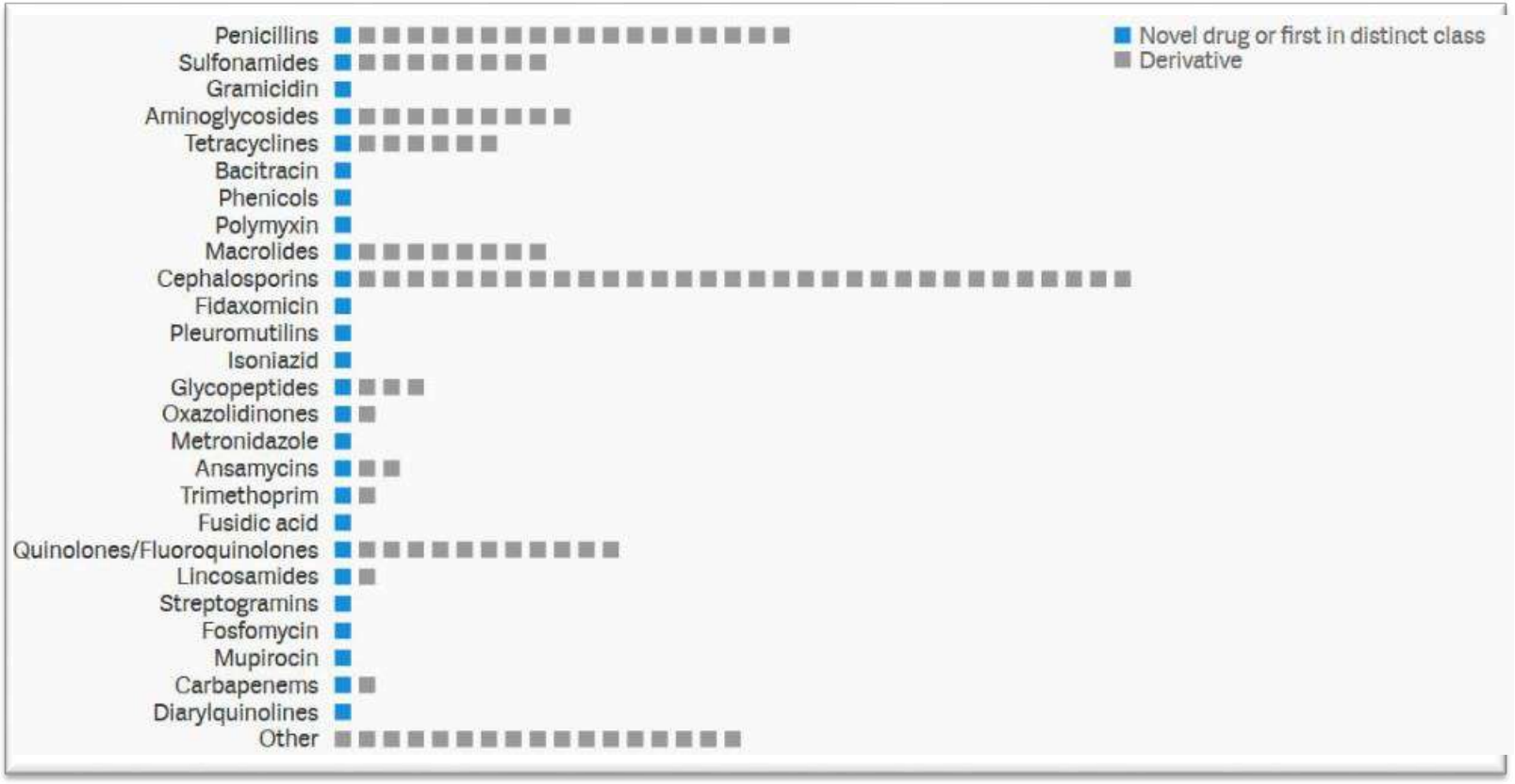
Golden years of pills and profits

Fixing selected resistance problems

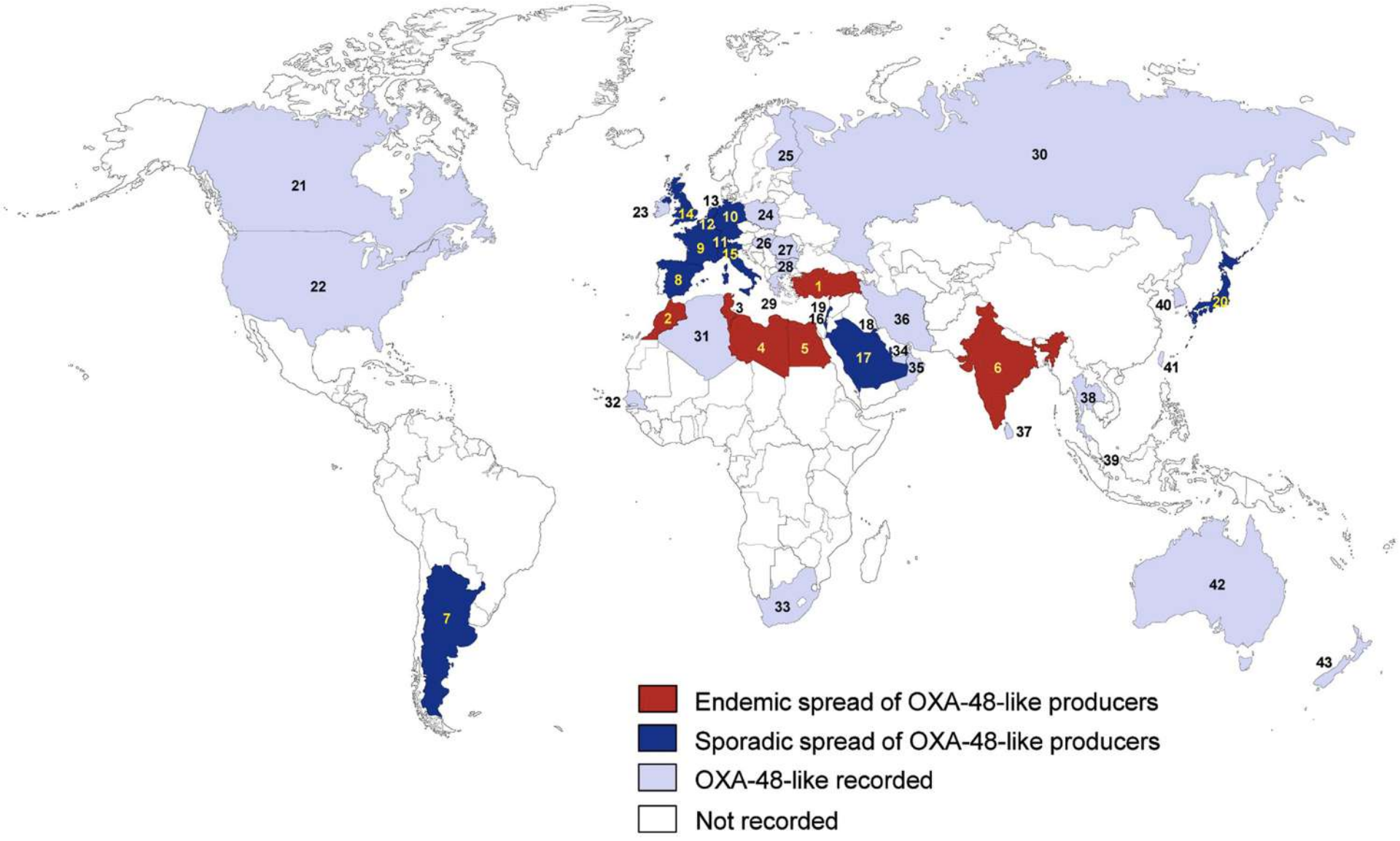


MS Kinch et al: Drug Discovery Today 2014, 19 (9)

Yeni antibiyotikler ve türevleri



QUARTZ, Keith Collins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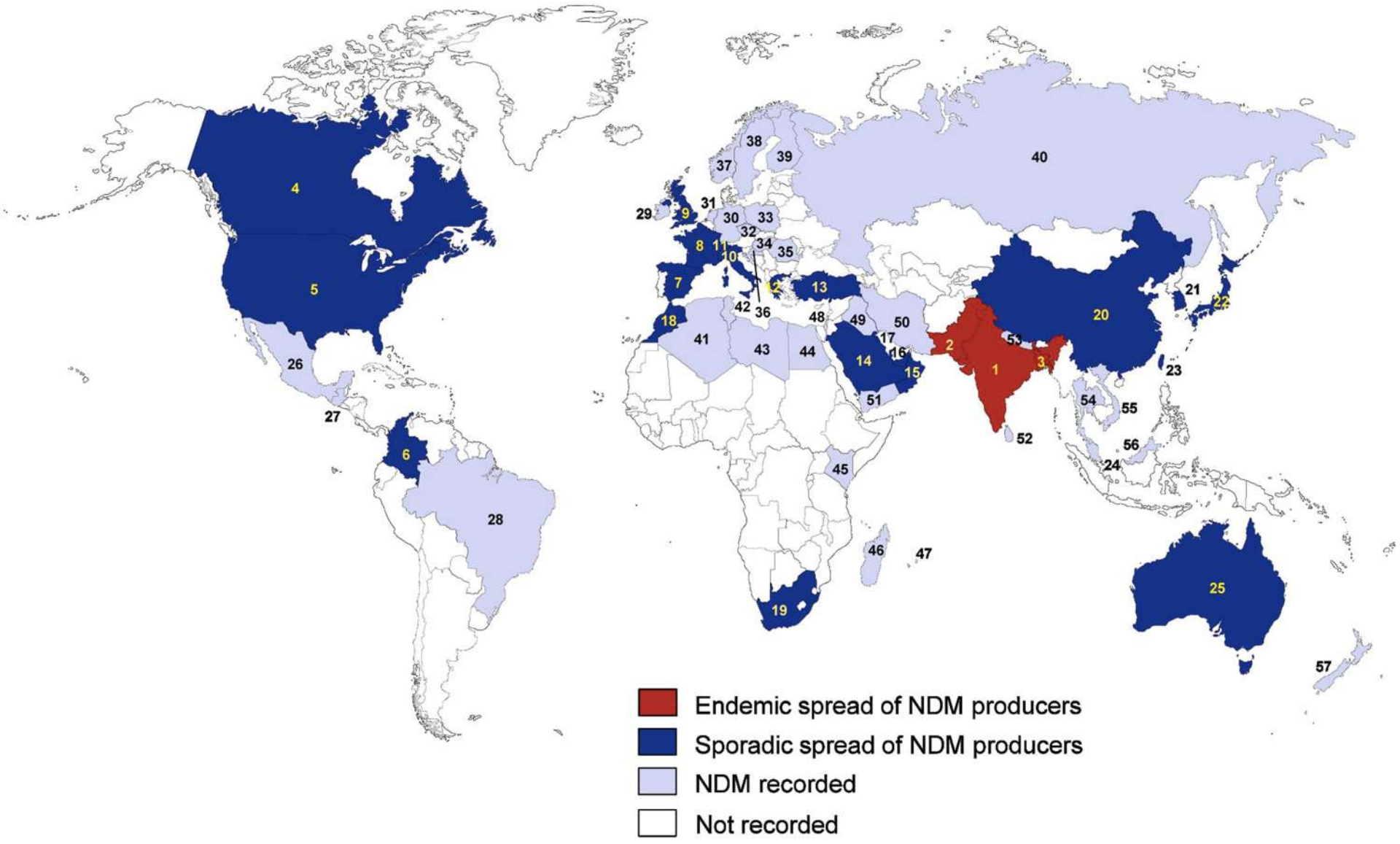
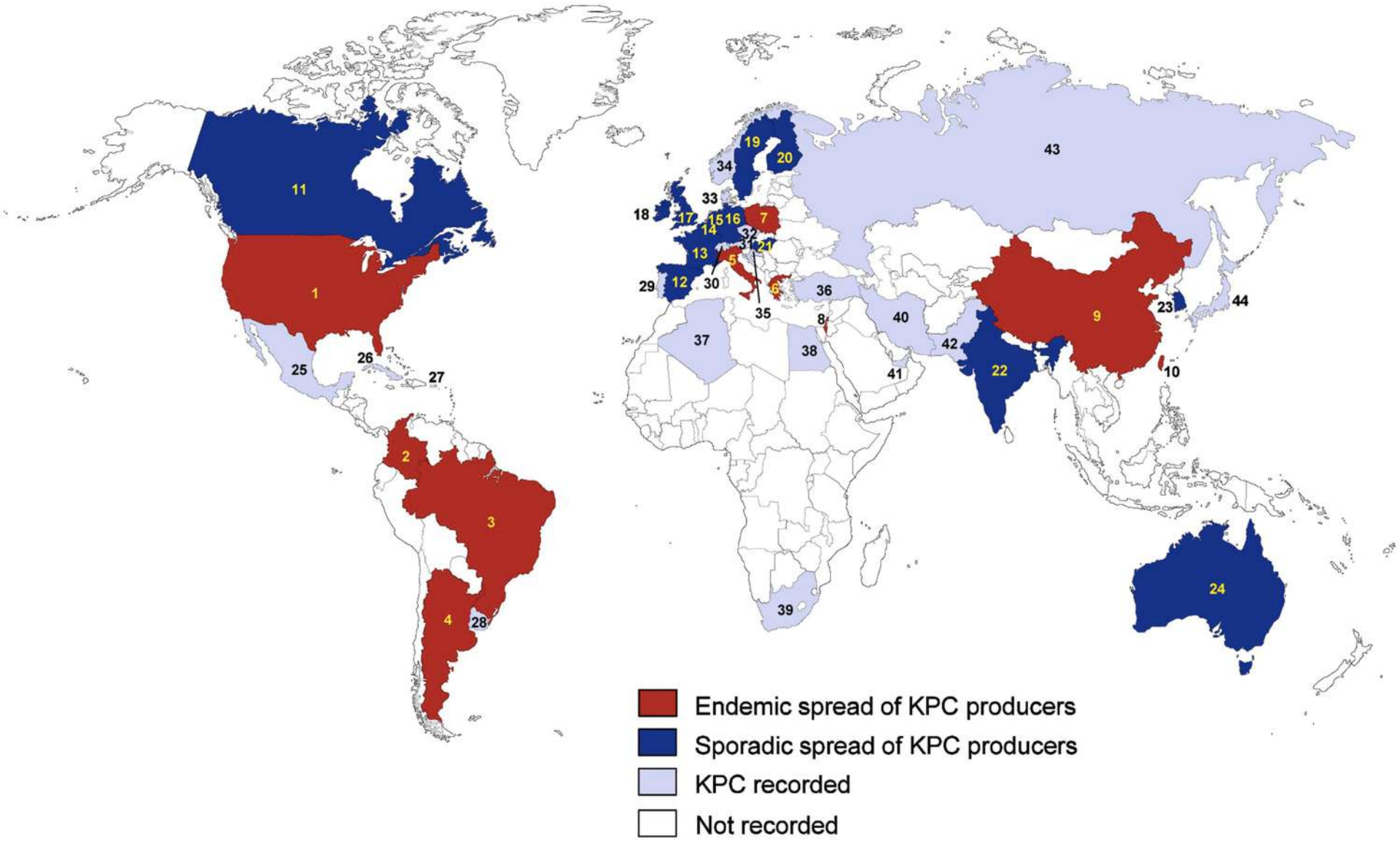
Endemic spread of OXA-48-like producers
Sporadic spread of OXA-48-like producers
OXA-48-like recorded
Not recorded


Endemic spread of NDM producers
Sporadic spread of NDM producers
NDM recorded
Not recorded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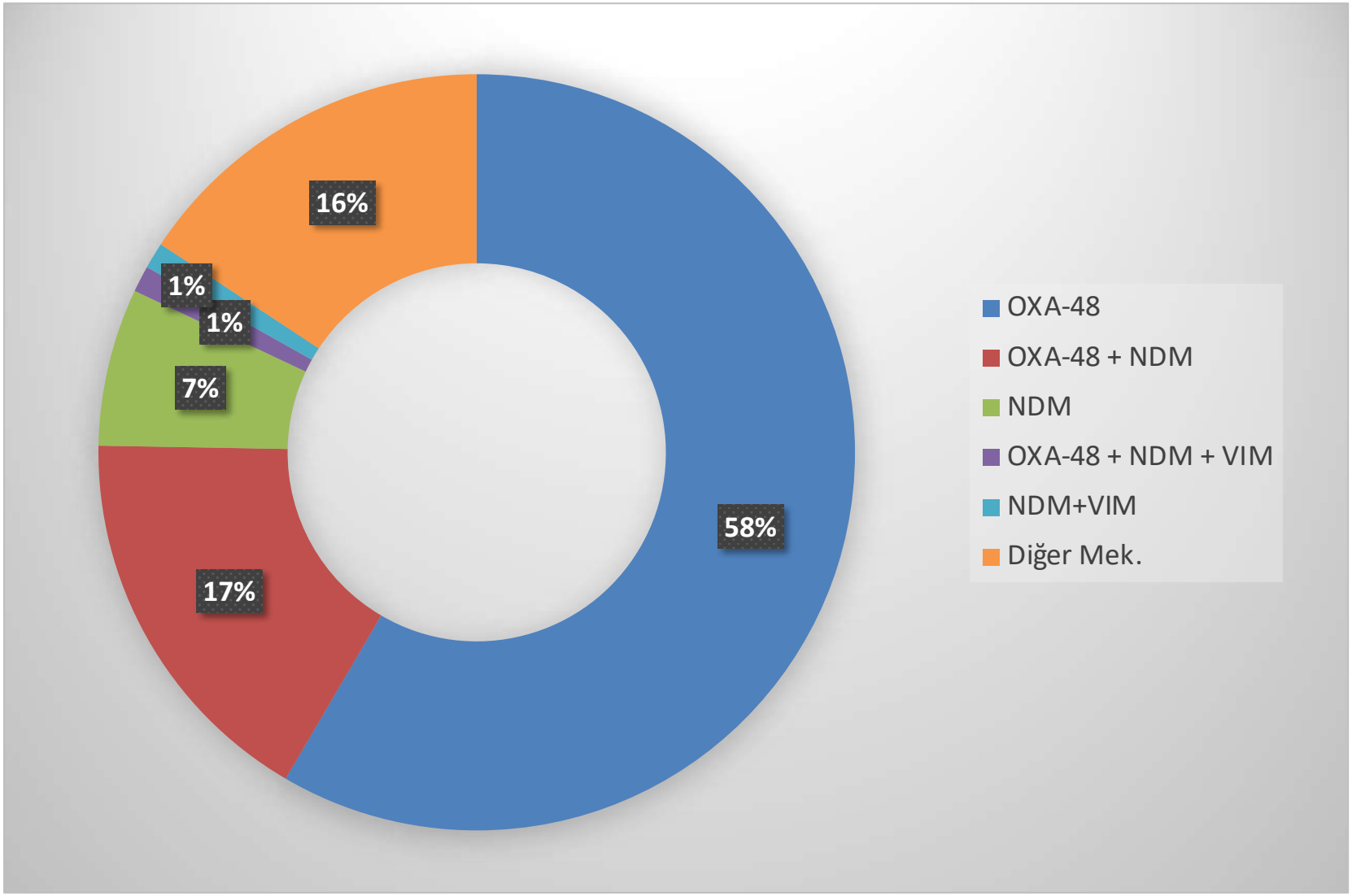
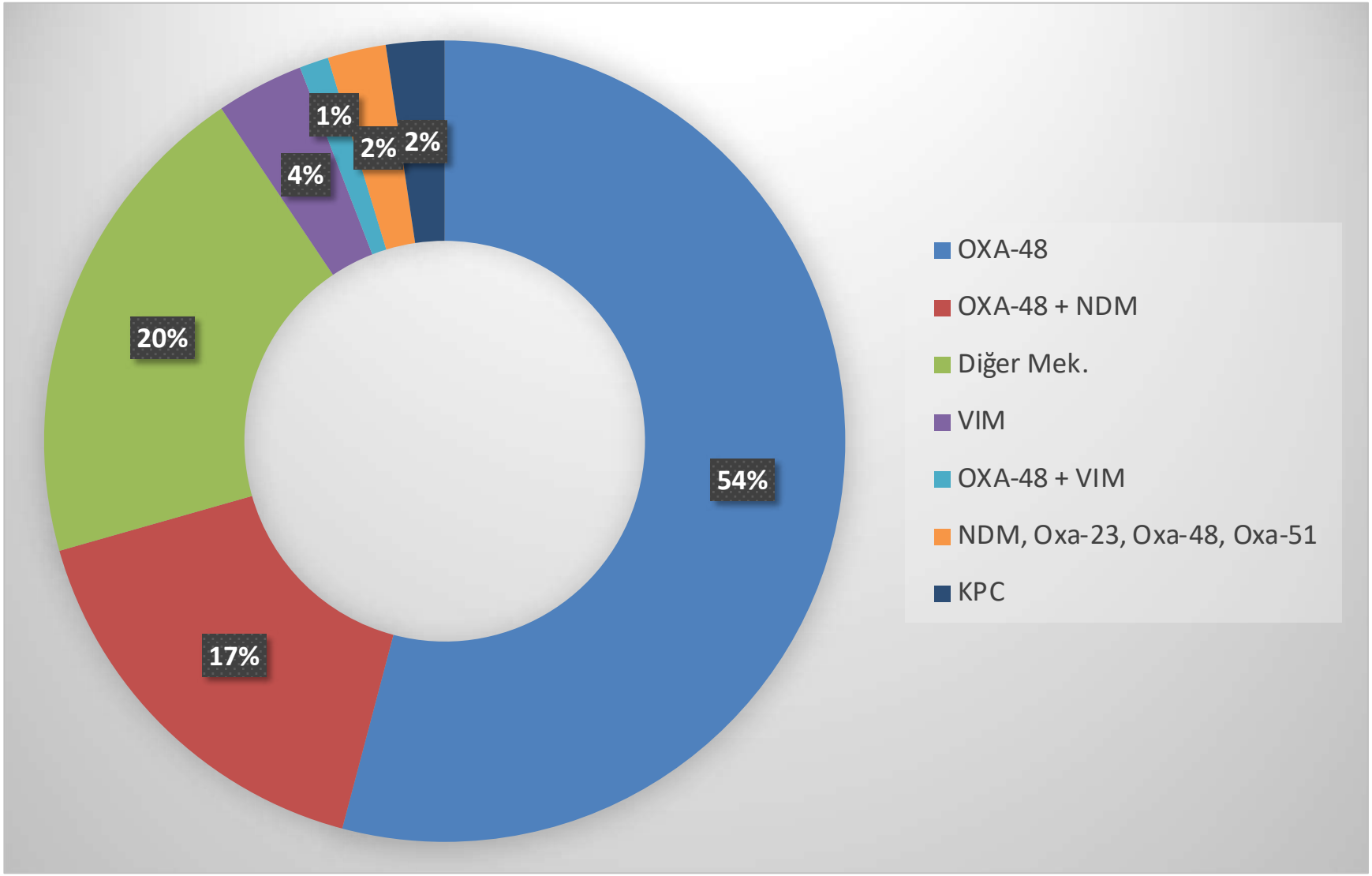
Endemic spread of KPC producers
Sporadic spread of KPC producers
KPC recorded
Not recorded

Medipol Mega Hastanesi



İ.Ü. - Cerrahpaşa



İhtiyaçları anlamak....

Güncel antimikrobiyal direnci karşılayabilmek için temel ihtiyaçlar:

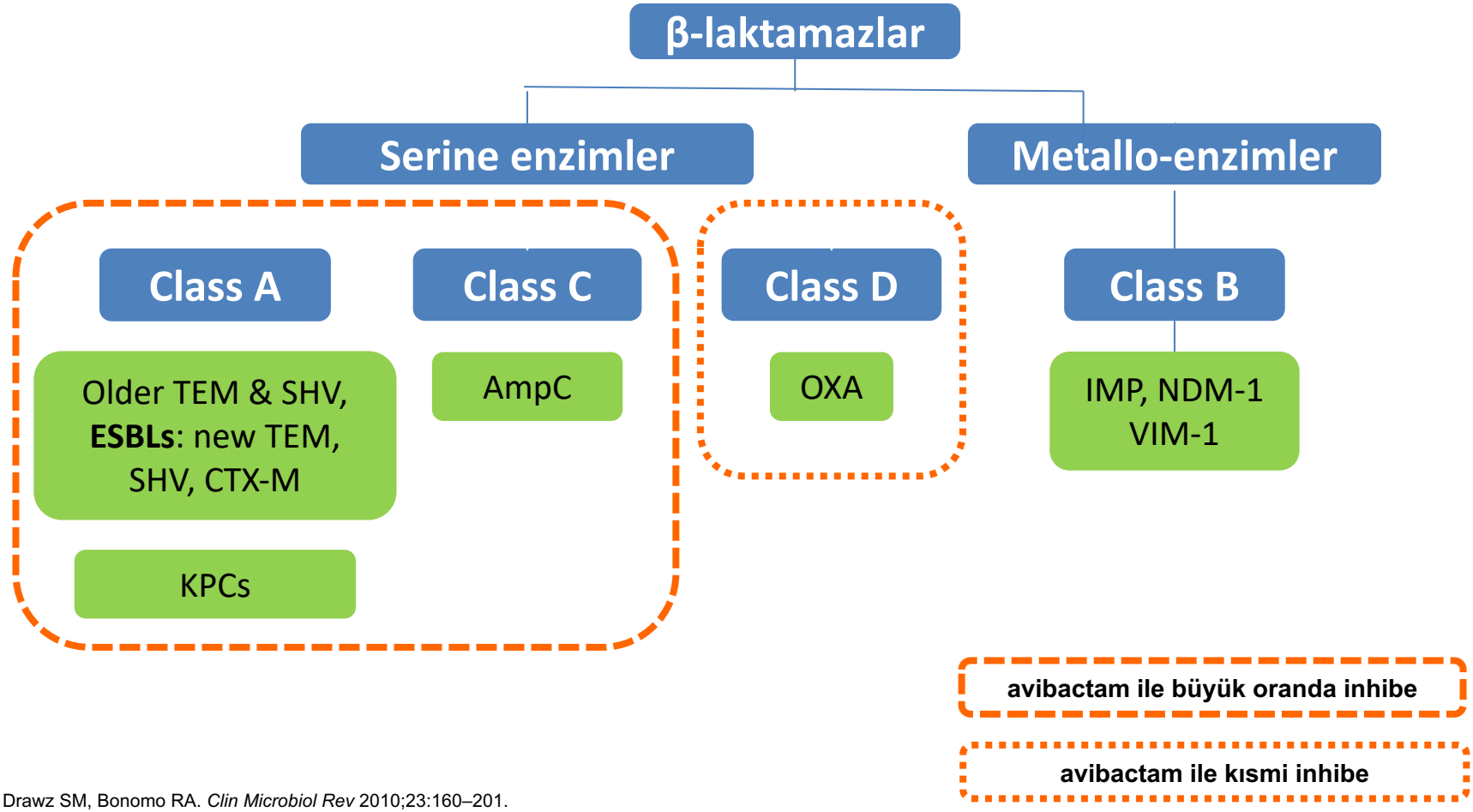
- XDR Gram-negatif bakteriler
  - Klebsiella, Acinetobacter, E. coli, Pseudomonas
  - Kritik hastalarda
- Karbapenem-siz tedaviler, i.v., oral
  - Klebsiella, E. coli, ve diğer Enterobacteriaceae
  - MDR bakterilerle gelişen Üriner sistem enfeksiyonları
  - ESBL yapan bakteri enfeksiyonları

ESKAPE

- Gram-positive: *Enterococcus faecium, Staphylococcus aureus*
- Gram-negative*: Klebsiella pneumoniae, Acinetobacter baumannii, Pseudomonas aeruginosa, Enterobacter species*

CDC – WHO acil eylem planı

- carbapenem-resistant *Acinetobacter baumannii* (CRAB)
- carbapenem-resistant *Pseudomonas aeruginosa* (CRPA)
- carbapenem-resistant Enterobacteriaceae (CRE)
- extended spectrum β-lactamase (ESBL) producing Enterobacteriaceae
- *Clostridioides difficile (C. diff)*
- drug-resistant *N. gonorrhoeae*



- Drawz SM, Bonomo RA. *Clin Microbiol Rev* 2010;23:160–201.

Spectrum of Beta-Lactamase Inhibitors

Spectrum	Beta-lactamase Inhibitor			
	Tazobactam	Avibactam	Vaborbactam	Relebactam
Class A narrow-spectrum				
Class A ESBLs				
Class A carbapenamases (KPC)				
Some class C enzymes				
Some class D enzymes (OXA-48)				
Class B enzymes (MBLs)				

Drug name	Development phase[2]	Company	Drug class	Target	Expected activity against ESKAPE pathogens?[3]	Expected activity against CDC urgent or WHO critical threat pathogen?[4]
Xerava (eravacycline)	**Approved Aug. 27, 2018 (U.S. FDA)**	Tetraphase Pharmaceuticals Inc.	Tetracycline	30S subunit of bacterial ribosome	Yes: *E. faecium, S. aureus, K. pneumoniae, Enterobacter spp.*; Possibly: *A. baumannii*	Yes (ESBL); possibly (CRE, CRAB)
– **Potential indication(s)?[5]** **Complicated intra-abdominal infections**						
Nuzyra (omadacycline)	**Approved Oct. 2, 2018 (U.S. FDA)**	Paratek Pharmaceuticals Inc.	Tetracycline	30S subunit of bacterial ribosome	Yes: *E. faecium, S. aureus, K. pneumoniae, Enterobacter spp.*	No
– **Potential indication(s)?[5]** *Approved for:* **Community-acquired bacterial pneumonia, acute bacterial skin and skin structure infections;** *other potential indications* **complicated urinary tract infections** and **uncomplicated urinary tract infections**						

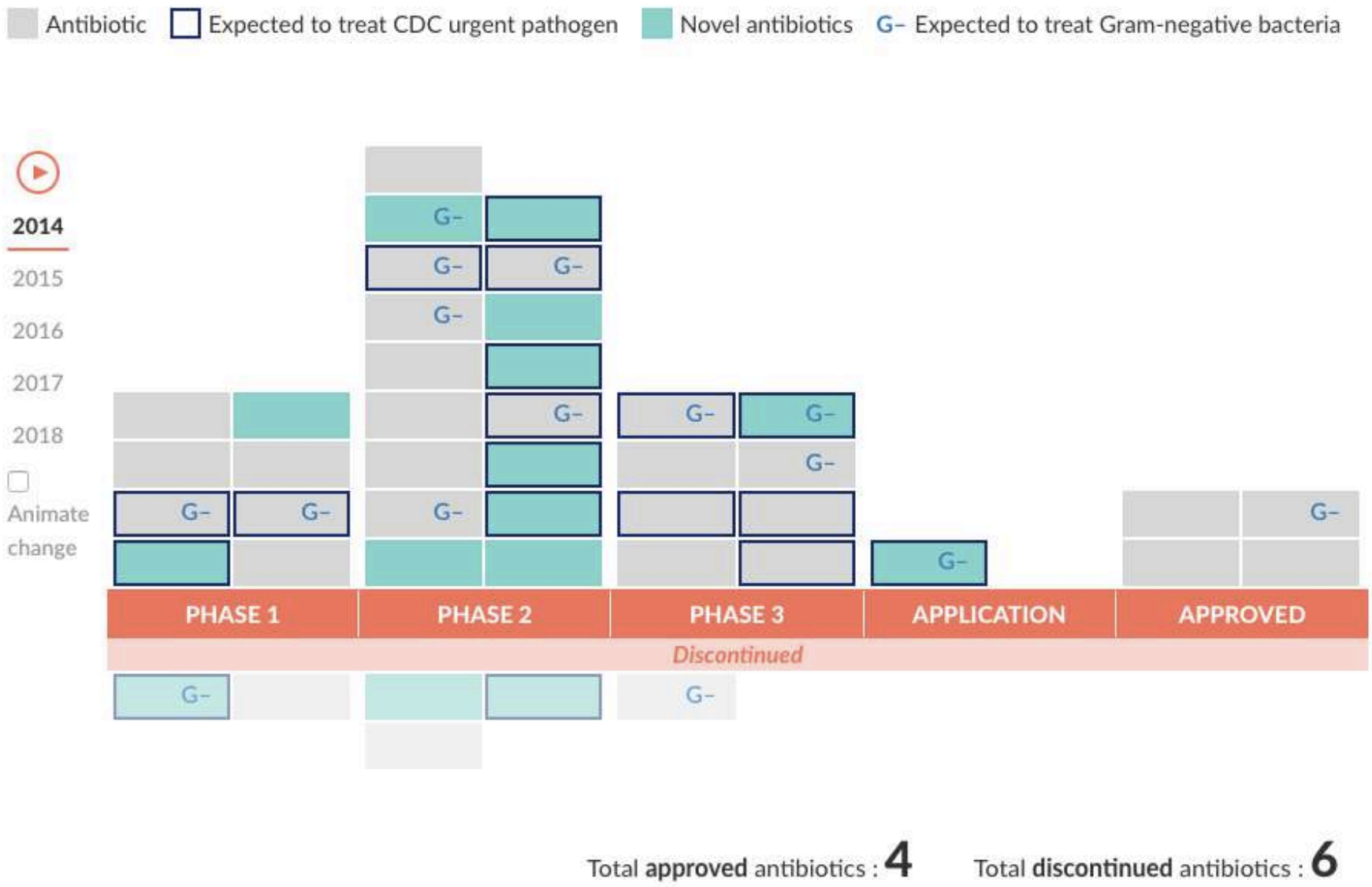
Drug name	Development phase[2]	Company	Drug class	Target	Expected activity against ESKAPE pathogens?[3]	Expected activity against CDC urgent or WHO critical threat pathogen?[4]
Iclaprim	**Complete response letter to new drug application (U.S. FDA)**	Motif Bio PLC	2,4-diaminopyrimidine	Dihydrofolate reductase	Yes: *S. aureus*	No
– **Potential indication(s)?[5]** **Acute bacterial skin and skin structure infections** and **hospital-acquired bacterial pneumonia**[6]						
Imipenem/cilastatin + relebactam (MK-7655A)	**New drug application (U.S. FDA) and marketing authorization application (EMA) submitted**	Merck & Co. Inc.	β-lactam (carbapenem)/dehydropeptidase inhibitor + β-lactamase inhibitor (diazabicyclooctane)	PBP + β-lactamase	Yes: *K. pneumoniae, P. aeruginosa, Enterobacter spp.*	Yes (CRE), possibly (CRPA)
– **Potential indication(s)?[5]** **Complicated urinary tract infections** including pyelonephritis, **complicated intra-abdominal infections,** and **hospital-acquired bacterial pneumonia/ventilator-associated bacterial pneumonia**						

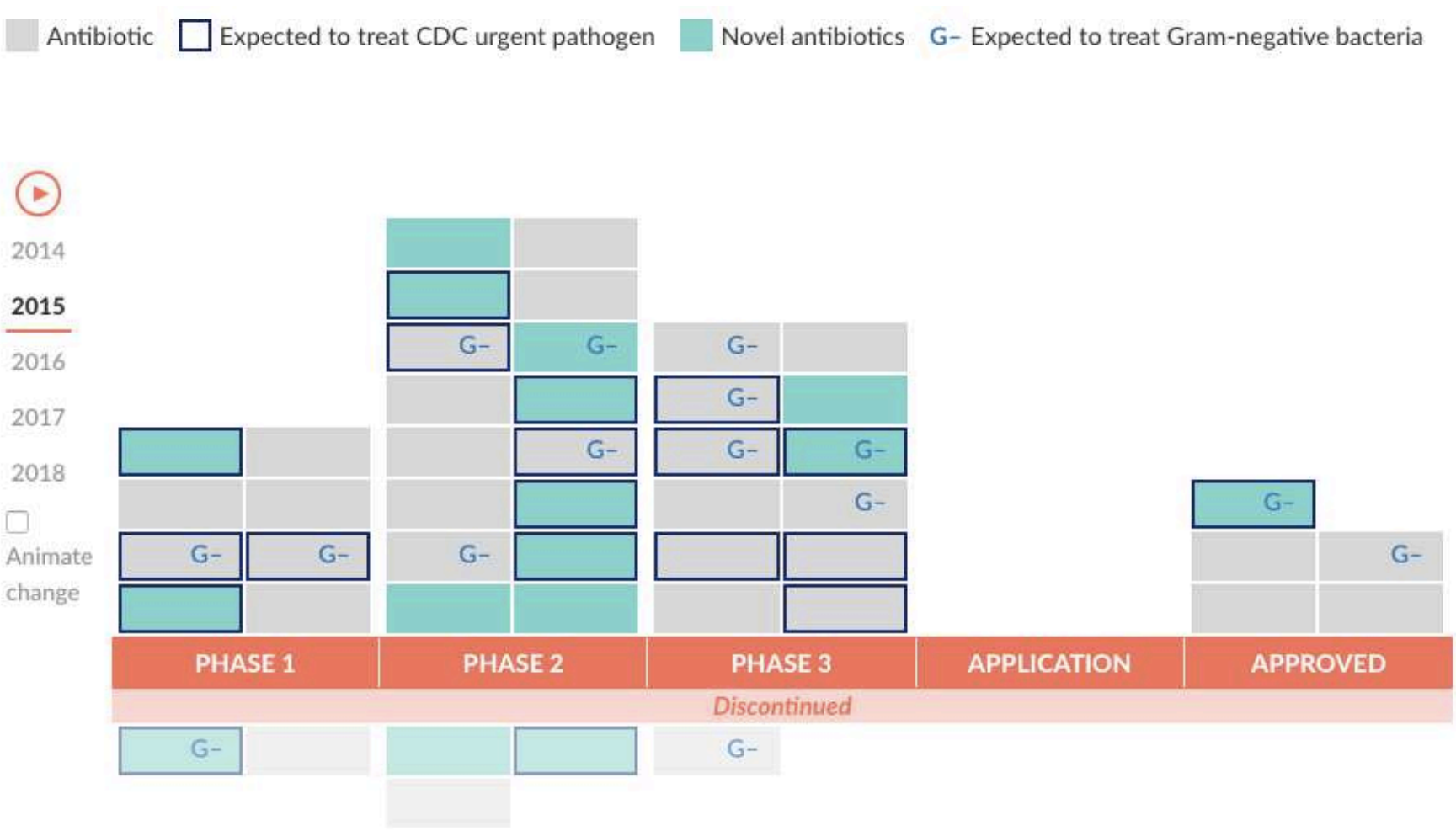
Drug name	Development phase[2]	Company	Drug class	Target	Expected activity against ESKAPE pathogens?[3]	Expected activity against CDC urgent or WHO critical threat pathogen?[4]
Lefamulin (BC-3781)	**New drug application (U.S. FDA) and marketing authorization application (EMA) submitted**	Nabriva Therapeutics PLC	Pleuromutilin[10]	50S ribosomal subunit at the peptidyl transferase center	Yes: *S. aureus*	Possibly *(N. gonorrhoeae)*
– **Potential indication(s)?[5]** **Acute bacterial skin and skin structure infections,[6] community-acquired bacterial pneumonia,** hospital-acquired bacterial pneumonia/ventilator-associated bacterial pneumonia,[6] cervicitis,[6] and urethritis[6]						
Cefiderocol (S-649266)	**New drug application (U.S. FDA) and marketing authorization application (EMA) submitted**	Shionogi & Co. Ltd.	Siderophore-β-lactam (cephalosporin)	PBP	Yes: *K. pneumoniae, A. baumannii, P. aeruginosa, Enterobacter spp.*	Yes (CRE, CRAB, and CRPA)
– **Potential indication(s)?[5]** **Complicated urinary tract infections,** hospital-acquired bacterial pneumonia/ventilator-associated bacterial pneumonia, bloodstream infections, and sepsis						

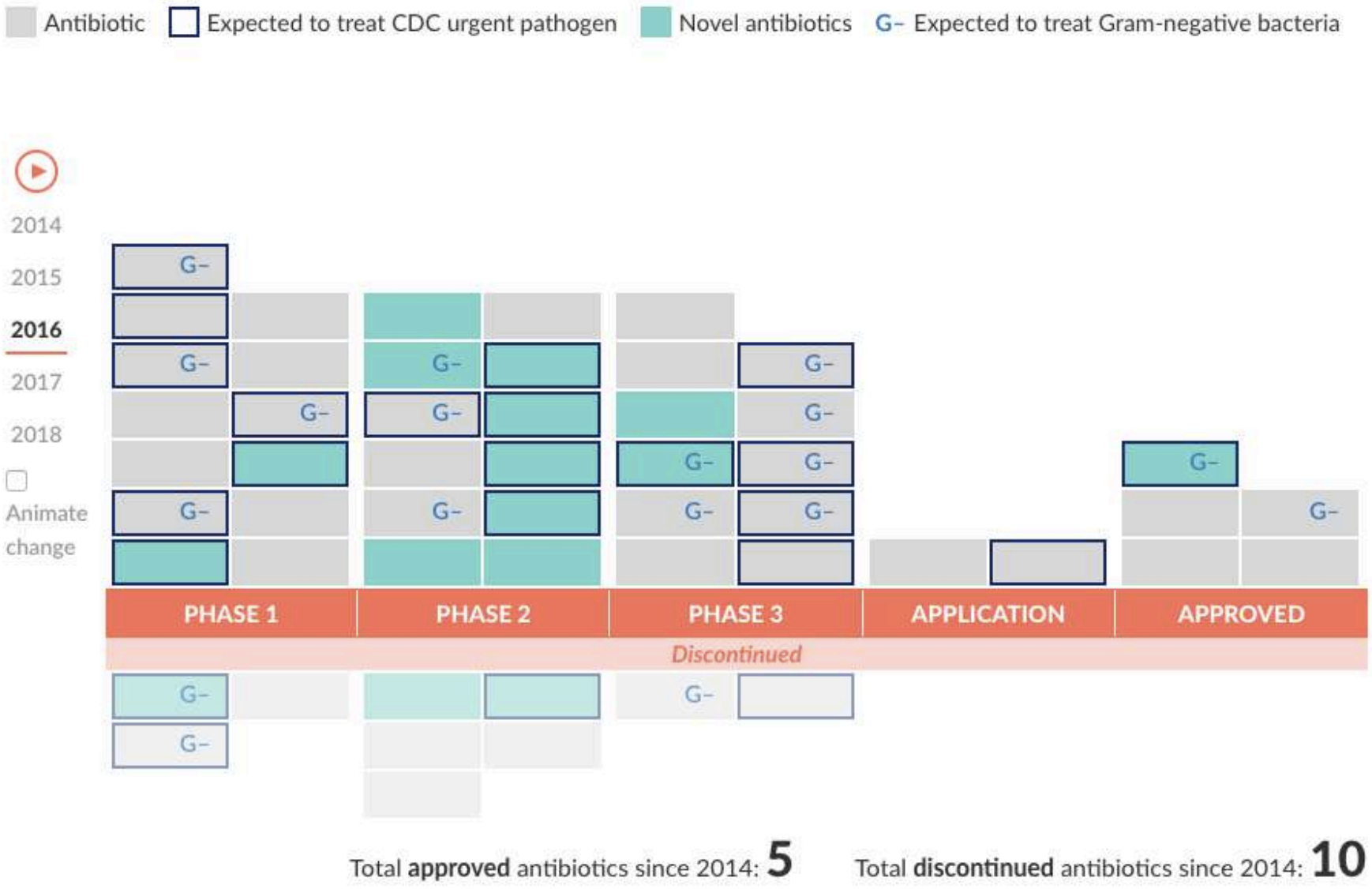
Drug name	Development phase[2]	Company	Drug class	Target	Expected activity against ESKAPE pathogens?[3]	Expected activity against CDC urgent or WHO critical threat pathogen?[4]
Cefepime + taniborbactam (VNRX-5133)	**Phase 3**	VenatoRx Pharmaceuticals Inc.	β-lactam (cephalosporin) + β-lactamase inhibitor (cyclic boronate)	PBP + β-lactamase	Yes: *K. pneumoniae, P. aeruginosa, Enterobacter spp.*	Yes (CRE), possibly (CRPA)
– **Potential indication(s)?[5]**						
Complicated urinary tract infections[6]						

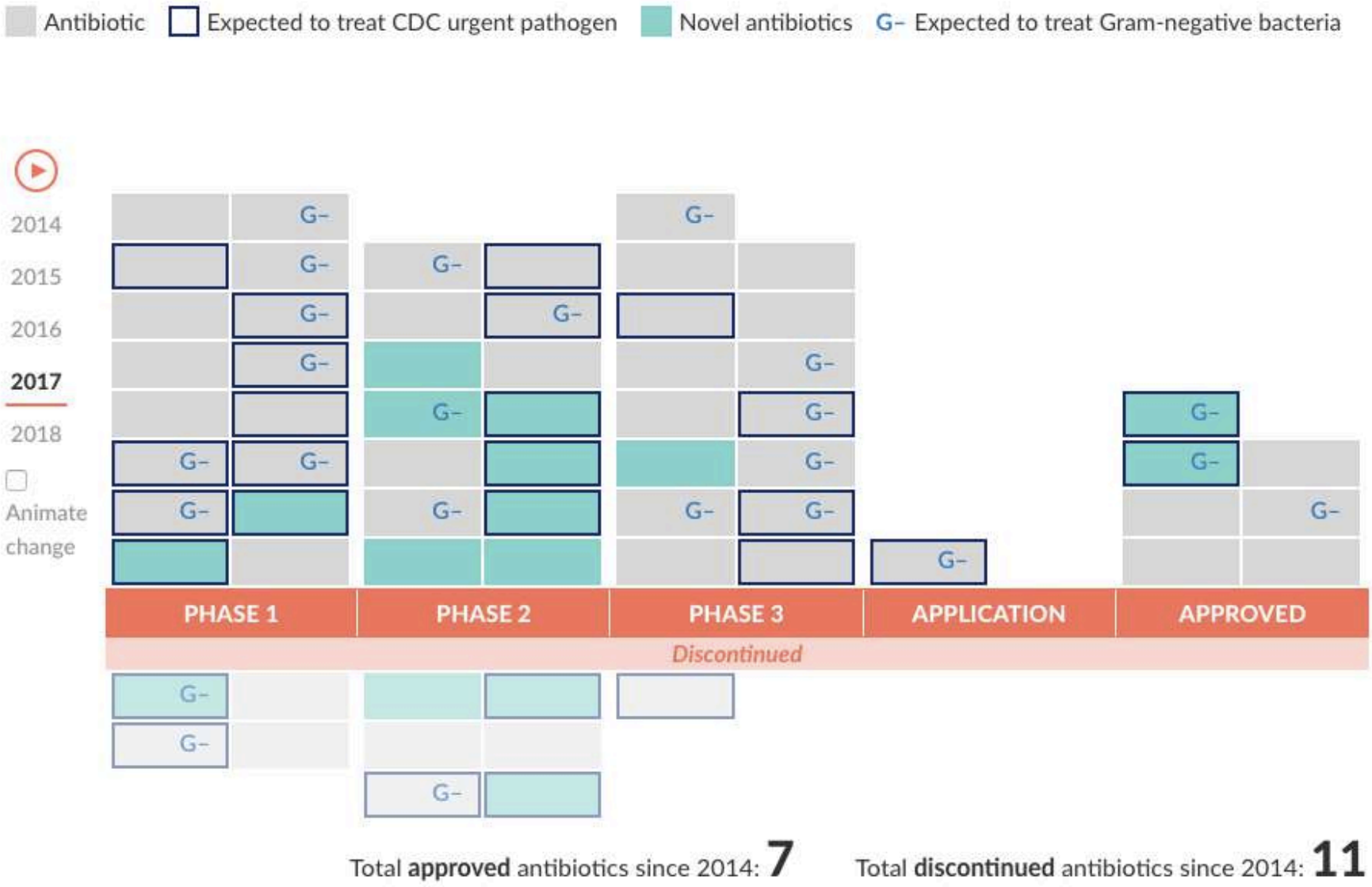
Drug name	Development phase[2]	Company	Drug class	Target	Expected activity against ESKAPE pathogens?[3]	Expected activity against CDC urgent or WHO critical threat pathogen?[4]
Sulopenem/sulopenem-etzadroxil[14]	**Phase 3**	Iterum Therapeutics plc	β-lactam (carbapenem)	PBP	Yes: *K. pneumoniae, Enterobacter spp.*	Yes (*N. gonorrhoeae*, ESBL)
– **Potential indication(s)?[5]** **Complicated urinary tract infections, uncomplicated urinary tract infections, complicated intra-abdominal infections, community-acquired pneumonia,[6] acute bacterial prostatitis,[6] gonococcal urethritis,[6] and pelivic inflammatory disease[6]**						
Murepavadin (POL7080)	**Phase 3**	Polyphor AG	Antimicrobial peptide mimetic[10]	LptD[11]	Yes: *P. aeruginosa*	Yes (CRPA)
– **Potential indication(s)?[5]** **Hospital-acquired bacterial pneumonia/ventilator-associated bacterial pneumonia, acute bacterial skin and skin structure infection,[6] bloodstream infection,[6]** and **complicated intra-abdominal infection[6]**						
Tebipenem-Pivoxil (SPR994[14]/SPR859)[7]	**Phase 3**	Spero Therapeutics Inc.	β-lactam (carbapenem)	PBP	Yes: *K. pneumoniae, P. aeruginosa*	Yes (ESBL)
– **Potential indication(s)?[5]** **Community-acquired bacterial pneumonia,[6] complicated urinary tract infections, diabetic foot infection,[6]** and acute pyelonephritis						

Drug name	Development phase[2]	Company	Drug class	Target	Expected activity against ESKAPE pathogens?[3]	Expected activity against CDC urgent or WHO critical threat pathogen?[4]
Cefepime + AAI101	**Phase 3**	Allecra Therapeutics GmbH	β-lactam (cephalosporin) + β-lactamase inhibitor (β-lactam)	PBP + β-lactamase	Yes: *K. pneumoniae, Enterobacter spp.*	Yes (ESBL), possibly (CRE)
− **Potential indication(s)?[5]**						
Complicated urinary tract infections including pyelonephritis, **complicated intra-abdominal infections,**[6] and **hospital-acquired bacterial pneumonia**[6]**/ventilator-associated bacterial pneumonia**[6]						
Ceftobiprole[7]	**Phase 3**	Basilea Pharmaceutica International Ltd.	β-lactam (cephalosporin)	PBP	Yes: *S. aureus, K. pneumoniae, Enterobacter spp.*	No
+ **Potential indication(s)?[5]**						
Sulbactam-durlobactam (SUL-DUR) (ETX2514SUL)	**Phase 3**	Entasis Therapeutics Inc.	β-lactam (sulbactam) + β-lactamase inhibitor (diazabicyclooctane)	PBP + β-lactamase	Yes: *A. baumannii*	Yes (CRAB)
− **Potential indication(s)?[5]**						
Complicated urinary tract infection including acute pyelonephritis, and **hospital-acquired bacterial pneumonia/ventilator-associated bacterial pneumonia**						


Antibiotic
Expected to treat CDC urgent pathogen
Novel antibiotics
G– Expected to treat Gram-negative bacteria
2014
2015
2016
2017
2018
Animate change
PHASE 1
PHASE 2
PHASE 3
APPLICATION
APPROVED
Discontinued
Total approved antibiotics : 4
Total discontinued antibiotics : 6


Antibiotic
Expected to treat CDC urgent pathogen
Novel antibiotics
G– Expected to treat Gram-negative bacteria
2014
2015
2016
2017
2018
Animate change
PHASE 1
PHASE 2
PHASE 3
APPLICATION
APPROVED
Discontinued
Total approved antibiotics since 2014: 5
Total discontinued antibiotics since 2014: 6


Antibiotic
Expected to treat CDC urgent pathogen
Novel antibiotics
G– Expected to treat Gram-negative bacteria
2014
2015
2016
2017
2018
Animate change
G–
PHASE 1
PHASE 2
PHASE 3
APPLICATION
APPROVED
Discontinued
Total approved antibiotics since 2014: 5
Total discontinued antibiotics since 2014: 10


Antibiotic
Expected to treat CDC urgent pathogen
Novel antibiotics
G– Expected to treat Gram-negative bacteria
2014
2015
2016
2017
2018
Animate change
PHASE 1
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PHASE 3
APPLICATION
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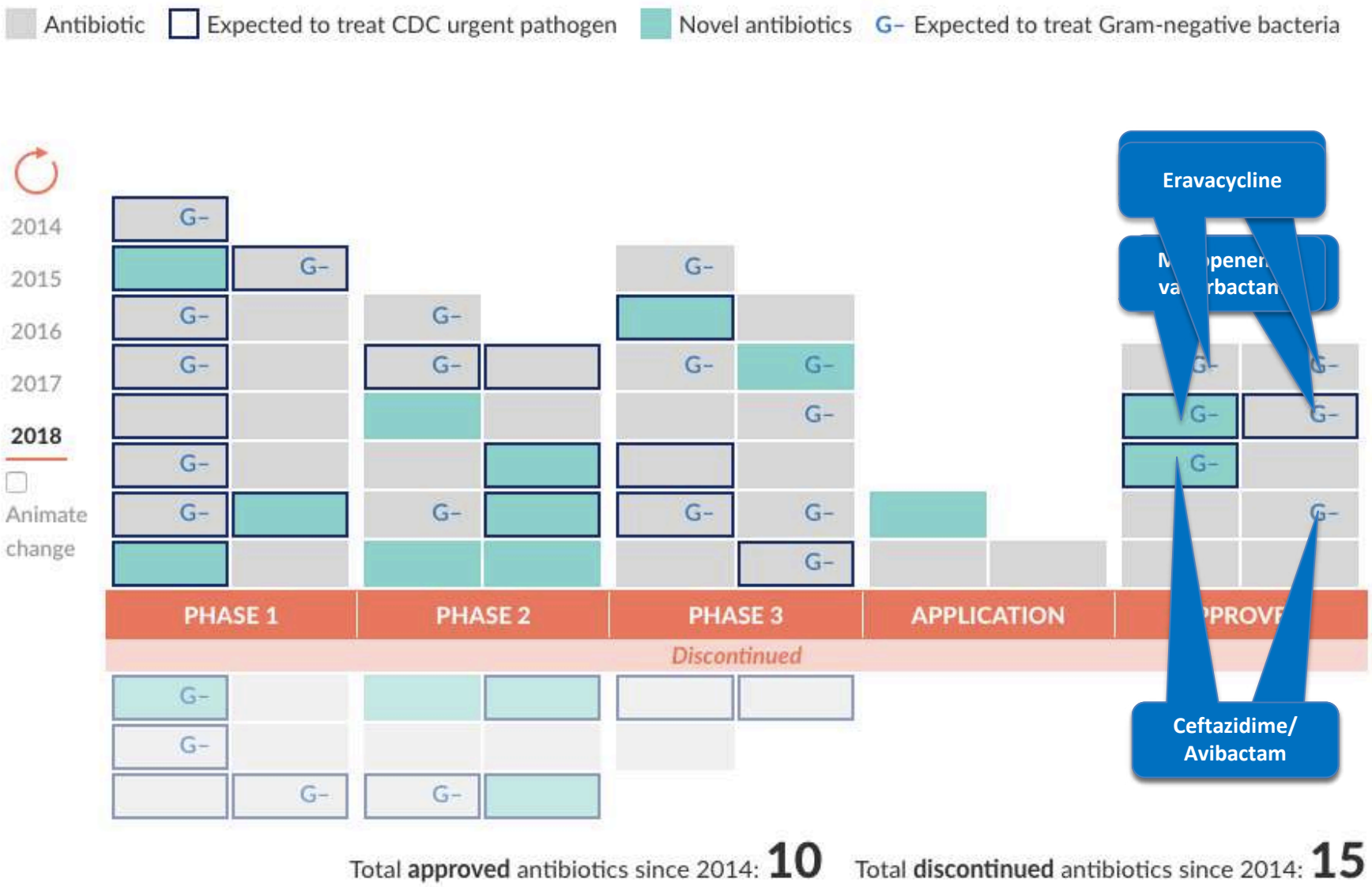
Discontinued
Total approved antibiotics since 2014: 7
Total discontinued antibiotics since 2014: 11


Antibiotic
Expected to treat CDC urgent pathogen
Novel antibiotics
G– Expected to treat Gram-negative bacteria
2014
2015
2016
2017
2018
Animate change
PHASE 1
PHASE 2
PHASE 3
APPLICATION
Discontinued
Eravacycline
Ceftazidime/ Avibactam
Total approved antibiotics since 2014: 10
Total discontinued antibiotics since 2014: 15

There are only **42 antibiotics** in clinical development.*

Name (synonym)	Phase	Antibiotic class	Route of Administration (Developer)	Expected activity against priority pathogens				Innovativeness			
				CRAB	CRPA	CRE	OPP	C	T	MoA	NCR
Delafloxacin[a]	NDA[1]	Fluoroquinolone	IV & oral (Melinta)	■	■	■	□	✖	✖	✖	✖
Vaborbactam + meropenem (Carbavance)	NDA	Boronate BLI + carbapenem	IV (The Medicines Co)	■	■	□	[b]	✓	✖	✖	/

Vaborbactam: Class A β-laktamazlara etkili, MBL ve OXA etkinliği zayıf

Relebactam: Class A ve C β-laktamazları inhibe eder

C, yeni kimyasal sınıf MoA, yeni etki mekanizması T, yeni hedef NCR, çapraz direnç yok

active, possibly active, not or insufficiently active.

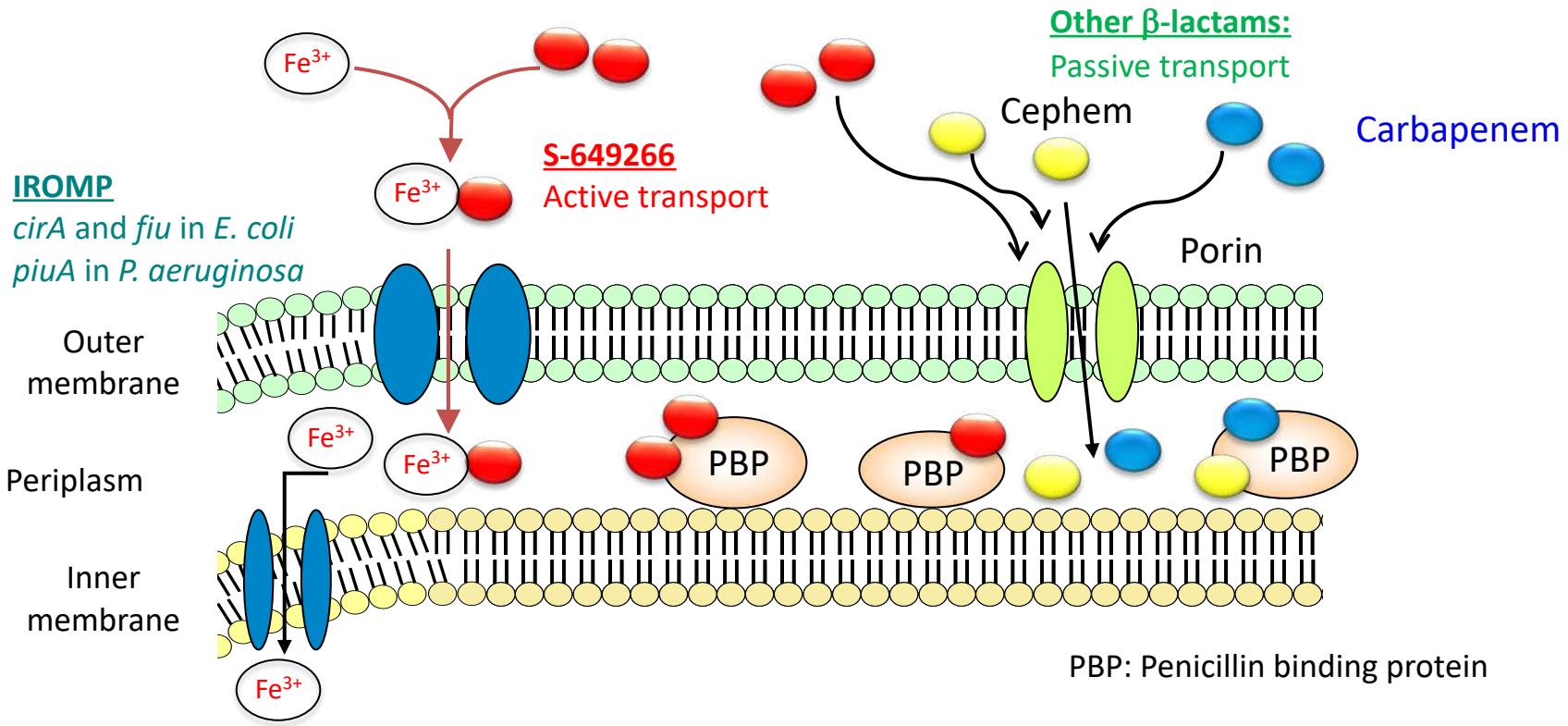
Name (synonym)	Phase	Antibiotic class	Route of Administration (Developer)	Expected activity against priority pathogens				Innovativeness			
				CRAB	CRPA	CRE	OPP	C	T	MoA	NCR
Cefiderocol	3	Siderophore-cephalosporin	IV (Shionogi)	active	active	active		✖	✖	✖	/
Relebactam + imipenem/ cilastatin	3	DBO-BLI + carbapenem/ degradation inhibitor	IV (Merck & Co)	not or insufficiently active	possibly active	active	[b]	✖	✖	✖	✖

Relebactam: Class A ve C β-laktamazları inhibe eder, diğerlerine etki zayıf

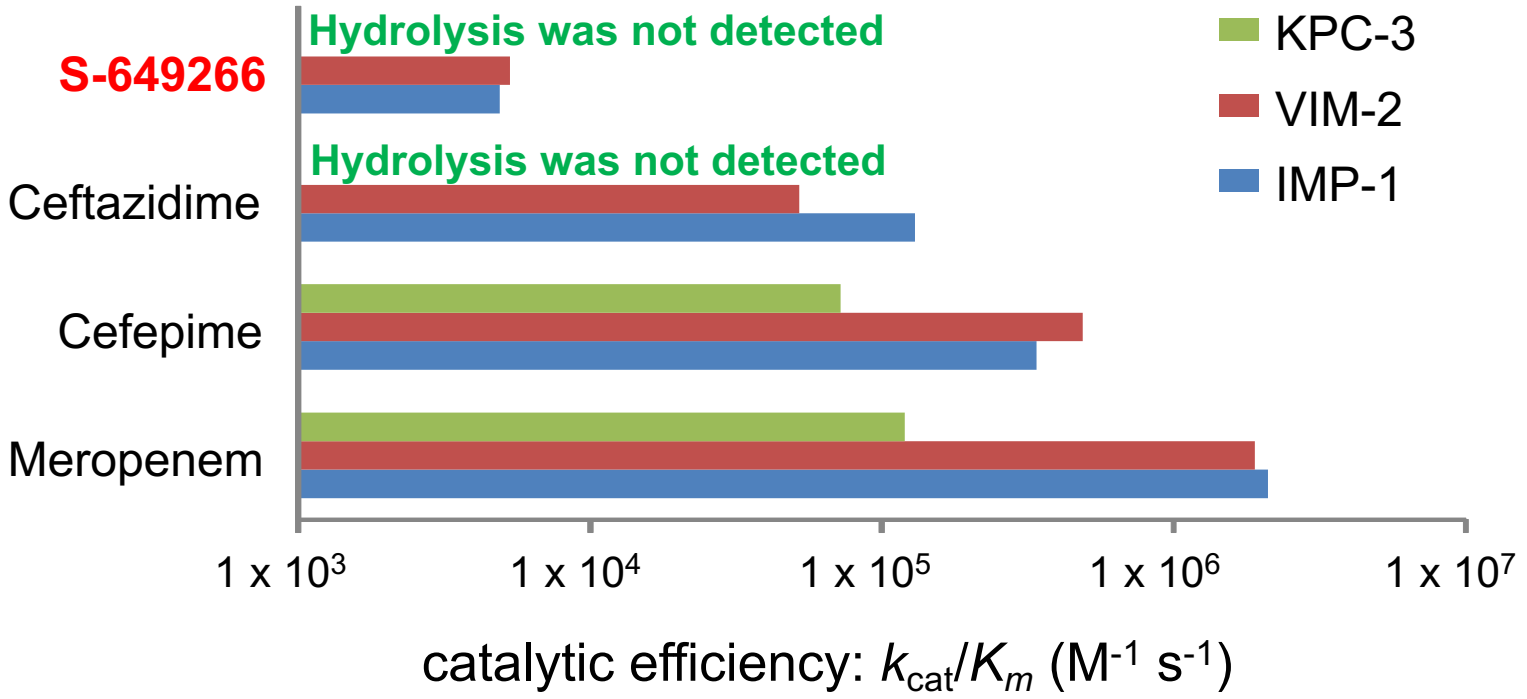
active, possibly active, not or insufficiently active.

Etki Mekanizması

- Fe-regülasyonlu Dış Membran Proteinleri (IROMP) ortamdaki demir eksildiğinde indüklenir
- S-649266 IROMP dan aktif transport ile içeri alınır
- apotransferrin eklenmiş Mueller-Hinton Broth da potent in vitro etkinlik



Karbapenemazlara karşı yüksek stabilite



- Karbapenemazlara karşı yüksek stabilite
  - KPC, OXA gibi Serine-tip karbapenemaz
  - IMP, VIM ve NDM gibi Metallo-tip karbapenemaz
- CTX-M gibi ESBL karşı yüksek stabilite

- Plazomicin: NDM üretenlerde sık bulunan 16S rRNA methylases ilacı parçalar
- Omadacycline: eravacycline ve tigecycline kıyasla daha iyi farmakokinetiği var, linear; plasma protein bağlanma: 20–30%
- Iclaprim: Yeni Dihydrofolate reductase inhibitörü, non-inferiority çalışmaları başarısız

Name (synonym)	Phase	Antibiotic class	Route of Administration (Developer)	Expected activity against priority pathogens				Innovativeness			
				CRAB	CRPA	CRE	OPP	C	T	MoA	NCR
LYS-228	1	Monobactam	IV (Novartis)	■	■	■		✖	✖	✖	✖
GSK-3342830	1	Siderophore-cephalosporin	IV (GlaxoSmithKline)	■	■	■		✖	✖	✖	/
AIC-499 + unknown BLI	1	β-lactam+BLI	IV (AiCuris)	■	■	■		✖	✖	✖	✖
Zidebactam + Cefepime	1	DBO-BLI/ PBP2 binder + cephalosporin	IV (Wockhardt)	■	■	■		✖	✖	✖	✖

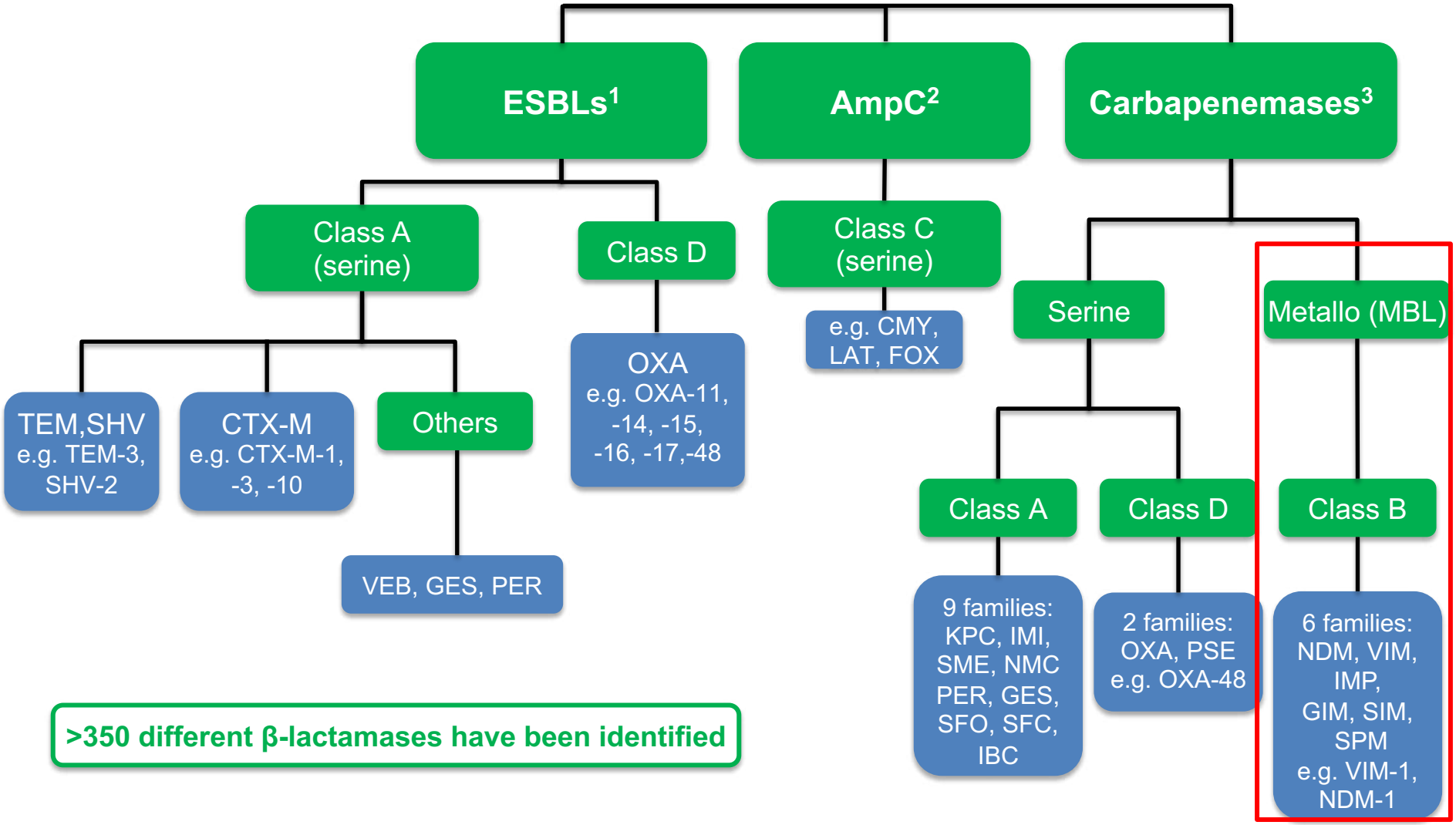
■ active, ■ possibly active, ■ not or insufficiently active.

Name (synonym)	Phase	Antibiotic class	Route of Administration (Developer)	Expected activity against priority pathogens				Innovativeness			
				CRAB	CRPA	CRE	OPP	C	T	MoA	NCR
Nacubactam + unknown antibiotic	1	DBO-BLI/ PBP2 binder + unknown antibiotic	IV (Roche)	■	■	■		✖	✖	✖	✖
AAI101 + cefepime or piperacillin	1	β-lactam BLI + cephalosporin or penicillin	IV (Allecra)	■	■	■		✖	✖	✖	✖
VNRX-5133 + unknown antibiotic	1	Boronate-BLI + unknown class	IV (VenatoRX)	■	■	■		✓	✓	/	✖
ETX2514 + sulbactam	1	DBO-BLI /PBP2 binder + β-lactam-BLI/PBP1,3 binder	IV (Entasis)	■	■	■		✖	✖	✖	✖
SPR-741 + unknown antibiotic	1	Polymixin + unknown class	IV (Spero)	■	■	■		✖	✖	/	/
TP-271	1	Tetracycline	IV & oral (Tetraphase)	■	■	■	■	✖	✖	✖	✖
TP-6076	1	Tetracycline	IV (Tetraphase)	■	■	■		✖	✖	✖	✖
KBP-7072	1	Tetracycline	IV & oral (KBP BioSciences)	■	■	■	■	✖	✖	✖	✖
TNP-2092	1	Rifamycin-quinolone hybrid	Oral (Tennor)	■	■	■	■	✖	✖	✖	✖
Alalevonadifloxacin	1[f]	Fluoroquinolone	Oral (Wockhardt)	■	■	■	■	✖	✖	✖	✖

Yepyeni kombinasyonlar

Name (synonym)	Phase	Antibiotic class	Route of Administration (Developer)	Expected activity against priority pathogens			
				CRAB	CRPA	CRE	OPP
Aztreonam + avibactamt	2	Monobactam + DBO-BLI	iv (Pfizer)				
Cefepime + tazobactam	1	Cephalosporin + β-lactam BLI	iv (Wockhardt)			[a]	
C-Scape	1	β-lactam + BLI	oral (Achaogen)				
ARB-002+colistin	1	Unknown (approved) potentiator + polymyxin	iv (Helperby)			[a]	

β-laktamaz ailesi



Antibiotic	Enterobacteriaceae (e.g. E. coli, Klebsiella spp.)					*Pseudomonas* spp.		*Acinetobacter* spp.
	ESBL	AmpC	KPC	OXA-48	NDM	Efflux	AmpC	
Ceftolozane-tazobactam								
Ceftazidime-avibactam								
Meropenem-vaborbactam								
Imipenem-relebactam								
Aztreonam-avibactam								
Eravacycline								
Plazomicin								
Cefiderocol								

ESBL – Extended spectrum beta-lactamase

AmpC – Ambler class C beta-lactamase (the Amp probably stands for Ampicillin)

KPC - Klebsiella pneumoniae carbapenemase

OXA - Oxacillin carbapenemase number 48

NDM - New Delhi metallo-beta-lactamase

Avibaktam daha geniş bir betalaktamaz inhibisyonu sağlar

		Clavulanic acid	Tazobactam	Avibactam
Class A	TEM, SHV	✓	✓	✓
	CTX-M	✗	✓	✓
	KPC	✗	✗	✓
Class B	IMP, VIM, NDM1	✗	✗	✗
Class C	Chromosomal Enterobacteriaceae AmpC	✗	✗	✓
	Chromosomal *Pseudomonas* AmpC	✗	✗	✓
Class D	Carbapenemase-type OXA 48	✗	✗	✓

Lagacé-Wiens P, et al. Core Evid 2014;9:13–25.

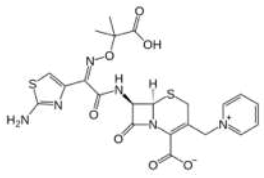
Yeni BL/BLI ile karşılaştırma

	Ceftazidime - avibactam	Ceftolozane-tazobactam	Meropenem-vaborbactam	Imipenem-relebactam
ESBL	✓	✓	✓	✓
• SHV/TEM	✓	±	✓	✓
• CTX-M	✓	±	✓	✓
CRE	✓	✗	✓	✓
• KPC	✓	✗	✓	✓
• MBL	✗	✗	✗	✗
• OXA-48	✓	✗	✗	✗
P. aeruginosa	✓	✓	✓	✓
• Ceftazidime-resistant	✓	✓	±	✓
• Carbapenem-resistant	✓	±	✗	✓

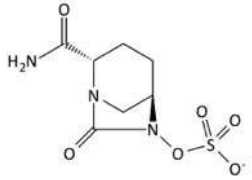
https://www.cdc.gov/drugresistance/threat-report-2013/index.html. [Accessed October 2018]; Bush K. Int J Antimicrob Agents 2015;46:483–93; Zavicefta Summary of Product Characteristics; Lagacé- Wiens P, et al. Core Evid. 2014;9:1; Wright H, et al. Clin Microbiol Infect 2017;23:704; 6. Lomovskaya

Seftazidim/Avibaktam

3.-kuşak sefalosporin+ yeni β-laktamaz inhibitörü …



Ceftazidime
3.-kuşak sefalosporin



Avibactam
İlk -β-laktam olmayan β-laktamaz inhibitörü (Class A, C ve bazı D) geniş spektrumlu

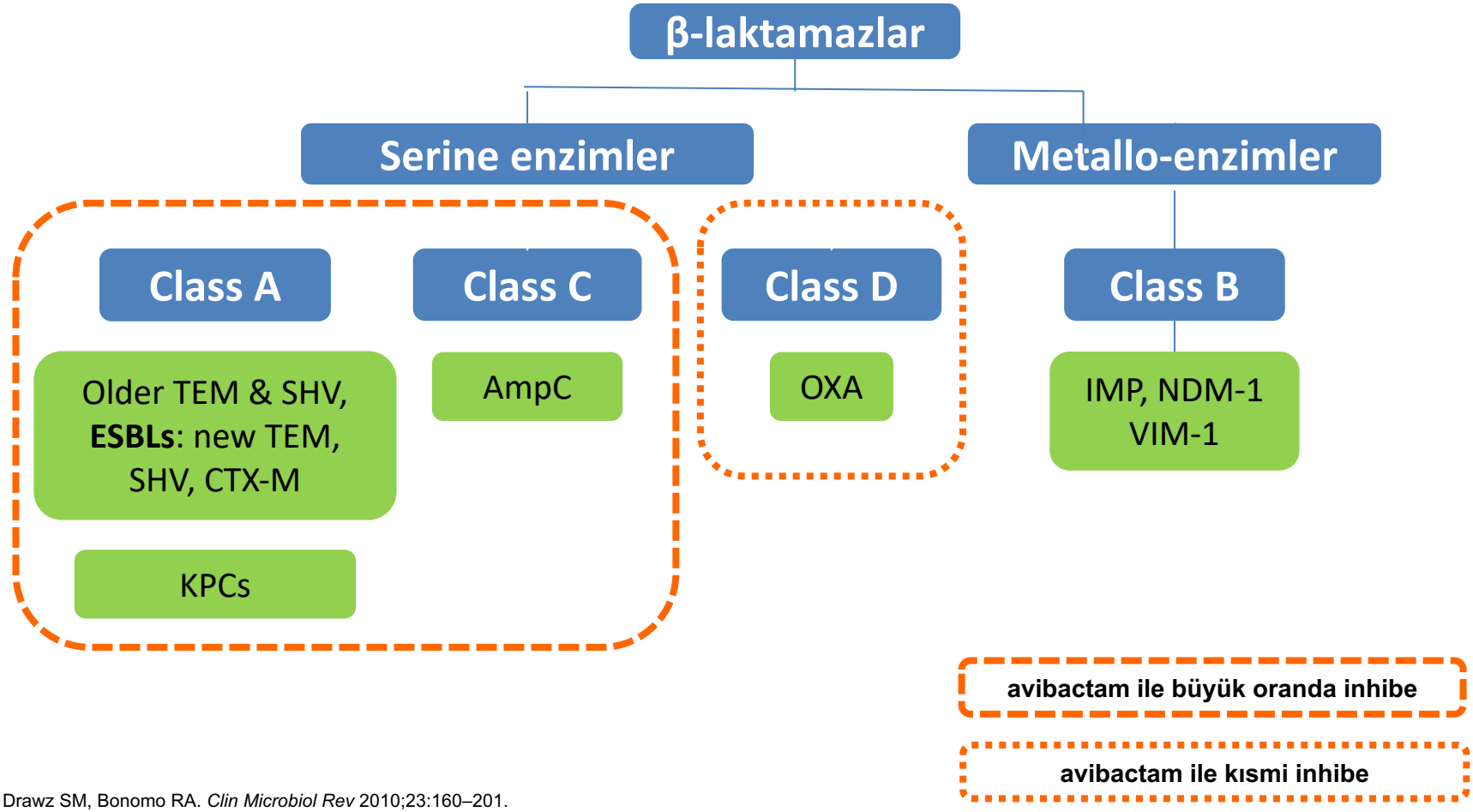
… onaylı 4 endikasyon

- komplike intra-abdominal enfeksiyon **(cIAI)**
- komplike üriner sistem enfeksiyonu **(cUTI)**
- Hastaneden kazanılmış pnömoni **(HAP)**
- Kısıtlı tedavi imkanı olan diğer aerobik GNÇ enfeksiyonları

özellikli endikasyon

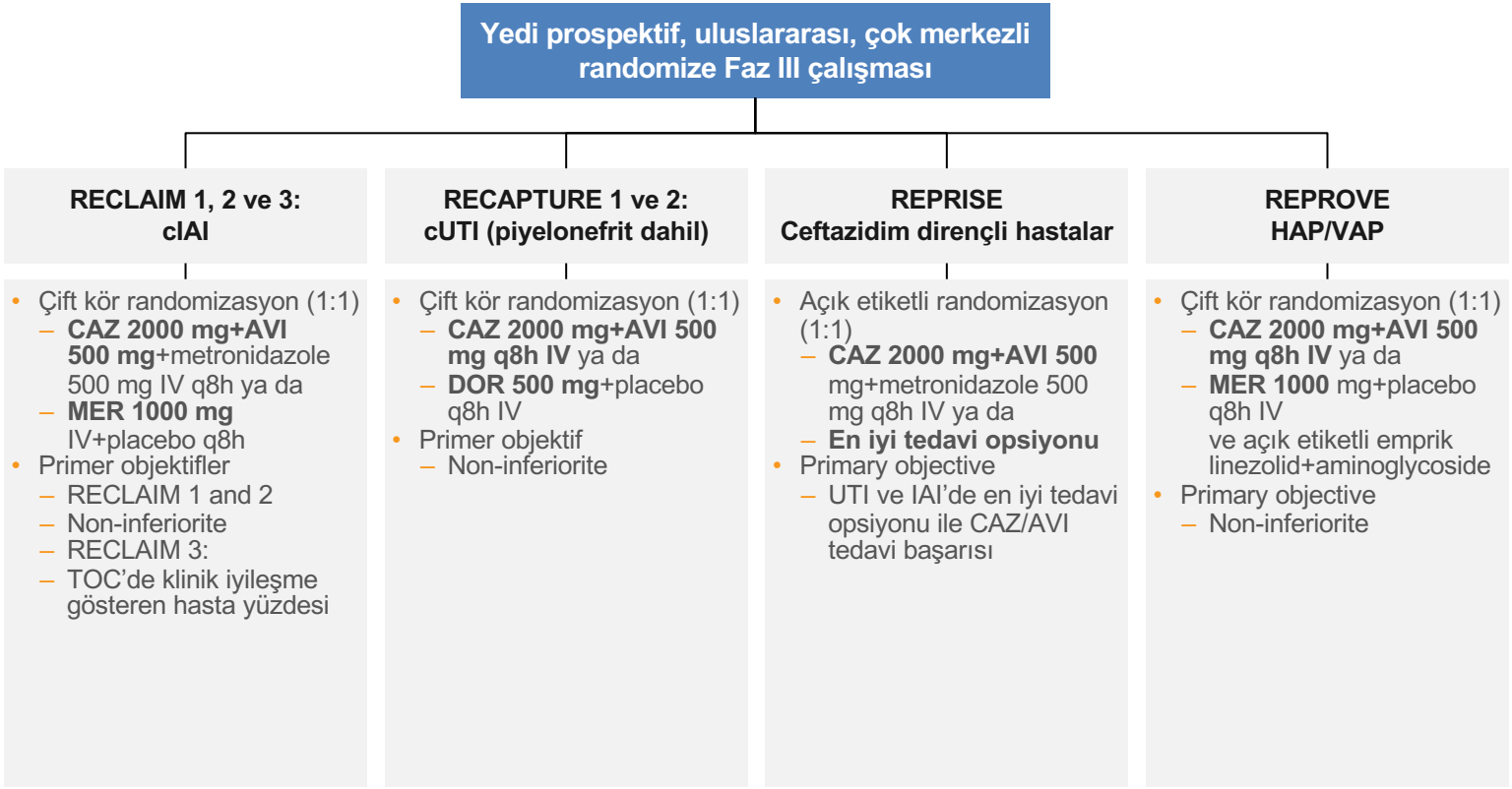
FDA approval 2015
EMA approval 2016
T. C. Sağlık Bakanlığı Ekim 2019

Ceftazidime/Avibactam etkinliği



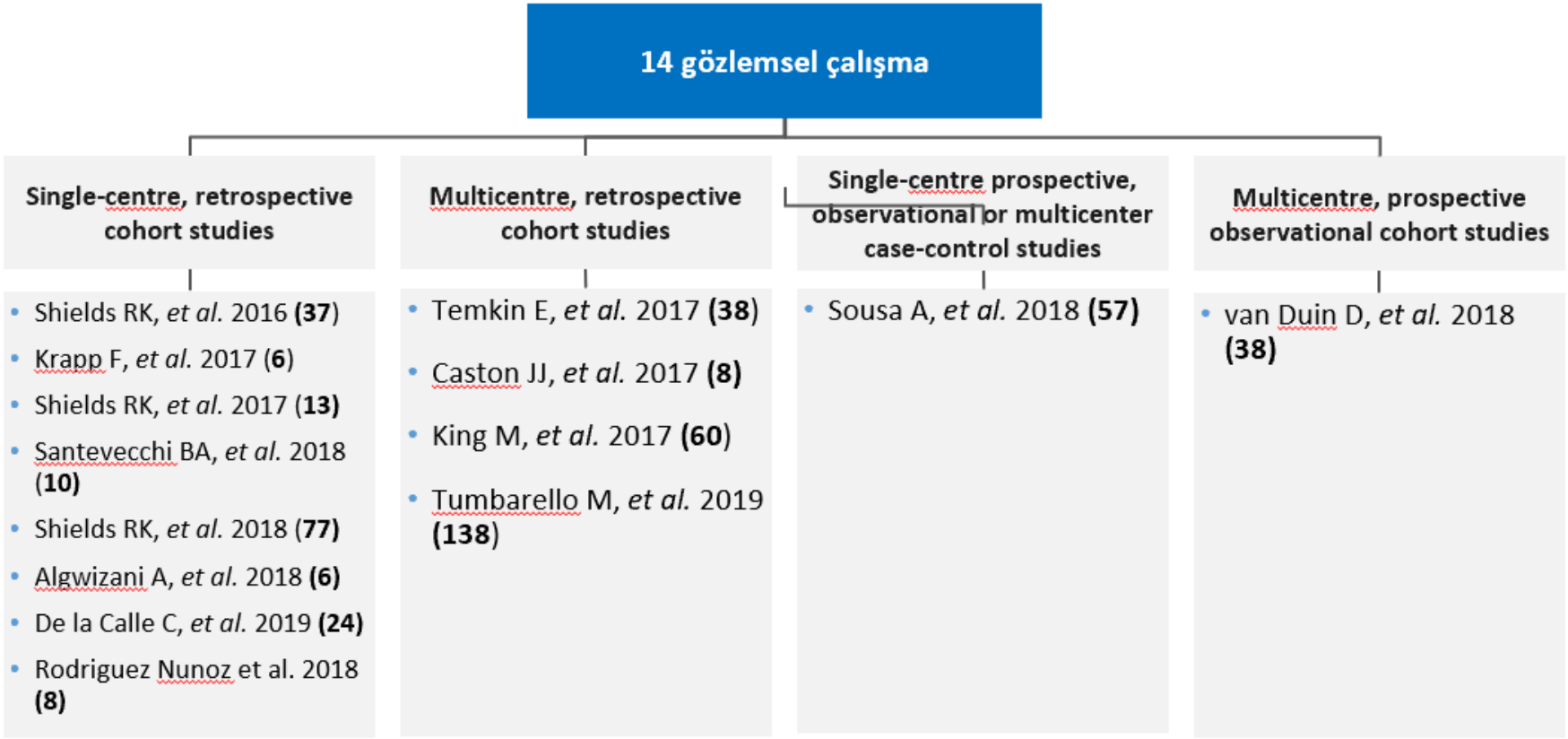
- Drawz SM, Bonomo RA. *Clin Microbiol Rev* 2010;23:160–201.

Seftazidim–avibaktam Faz III Çalışmaları



- AVI, vaibactam; CAZ, ceftazidime; CE, clinically evaluable; cIAI, complicated intra-abdominal infection; cMMIT, clinically modified intent-to-treat; cUTI, complicated urinary tract infection; HAP, hospital-acquired pneumonia; IV, intravenous; MER, meropenem; mMIITT, microbiological modified intent-to-treat ; TOC, test of cure; VAP, ventilator-associated pneumonia.

Ceftazidime–avibactam: gerçek yaşam çalışmaları



Study	Shields R et al. (2016)	Temkin et al (2017)	King M.et al (2017)	Shields R et al. (2017)
Sample Size	**37**	**38**	**60**	**109**
Organisms	**Carbapenem resistant** ***Enterobacteriaceae (CRE)*** ***KPC***	**Carbapenem-resistant** ***Enterobacteriaceae*** **(CRE) or** ***Pseudomonas aeruginosa*** **(CRPa) - KPC**	**Carbapenem resistant** ***Enterobacteriaceae (CRE)*** ***KPC***	**Carbapenem resistant** ***Enterobacteriaceae bacteremia (CRE)*** ***KPC***
Characteristics	• Median **charlson co-mobridity index-4** • **Median APACHE II score -34** • **30% patients were transplant recipients**	**60.5%life-threatening** infections Median duration of Caz–Avi treatment was 16 days **65.8% patients received combination therapy with CAZ-AVI**	• **38% had bacteremia** • **59% acute** illness patients in **ICU** • **38%** requiring **mechanical ventilation** • **25%** of subjects had received a **solid-organ transplant**	• Median **Charlson co-mobridity index-4** • Median **APACHE II score -18,** • **Primary bacteremia in 26%** • **50% bacteremic pts were in ICU**
Outcomes	• 30 day **survival** rate was **76%** • 90 day survival rate was **62%**	**73.7% experienced clinical and/or microbiological cure** • Microbiological cure was associated with improved survival	**The overall in-hospital mortality rate in this study was 32%** (19/60)	**Clinical success: 85% (11/13)** **75% (6/8) for monotherapy** **100% (5/5) for combo therapy (genta)**
Author's Conclusion	Ceftazidime/avibactam can be a **frontline therapy**, in severe bacteremic *CP-Klebsiella pneumoniae*	Ceftazidime–avibactam shows **promising** clinical results for infections for which treatment options are limited	CAZ-AVI is an **option for patients with CRE infections**, including those who are acutely ill or post transplant patients	In multivariate analysis, treatment with **ceftazidime– avibactam was independently associated with clinical success**

Seftazidim/Avibaktam OXA-48 + CTXM-15 etkililiği

De La Calle 2018, İspanya

En geniş OXA-48 üreten bakteri enfeksiyonu çalışması

Tek merkez, retrospektif, 90 gün takip

24 hasta - **%95.8 K. pneumoniae** - **OXA 48 CPE** enfeksiyonu (hemen hepsinde **+ ESBL** var (tamamı **CTX-M15**);

- %30 cIAI, %25 cUTI, %21 solunum yolu enf, %16 SSTI, 1 menenjit
- **%62.5 başlangıç tdv**, **%37.5 kurtarma tdv**-
- **%58.3 mono**, **%41.4 kombine** (amikasin, kolistin, tigesiklin)
- **30. gün Klinik kür %62.5**
- **30. gün mortalite %8.3**, **90. gün mortalite 20.8** (enfeksiyona bağlı mortalite %12.5)
- 90. gün rekürrens %35

De La Calle C. 2019 Int J Antimicr Agents 53(2019);520-524

OXA-48 CPE *kurtarma tedavisinde* Ceftazidime–avibactam

Sousa A. 2018, İspanya

- Ceftazidim-avibaktam ile tedavi edilen ve prospektif olarak toplanan 57 erişkin hastanın gözlemsel değerlendirilmesi
- En sık enfeksiyon kaynakları; intra-abdominal (28%), solunum (26%) ve uriner (25%)
- %54 hastada ağır enfeksiyon: sepsis/septik şok
- %81 hasta ceftazidime–avibactam'ı monoterapi olarak kullanmıştır ve medyan ilaç kullanma süresi 13 gün
- Ceftazidime–avibactam OXA-48 üreten Enterobactericeae kaynaklı ağır enfeksiyonların tedavisinde ümit verici sonuçlar vermiştir.
- Seftazidime–avibactam'a direnç gelişimi gözlenmemiştir.

Sousa A, et al. J Antimicrob Chemother. 2018 Aug 7. doi: 10.1093/jac/dky295. [Epub ahead of print].

Table 3. Comparison of patients receiving monotherapy versus combination treatment with ceftazidime/avibactam

Variable	Monotherapy ($n = 46$)	Combination ($n = 11$)	*P* value
Age, years median (IQR)	69 (30–82)	58 (33–78)	0.21
Male sex, *n* (%)	35 (76)	9 (82)	0.68
Charlson index >2, *n* (%)	27 (59)	6 (55)	0.80
Hospital-acquired, *n* (%)	39 (85)	10 (91)	0.59
INCREMENT-CPE score >7, *n* (%)	19 (41)	4 (36)	0.76
Vasopressor use, *n* (%)	16 (35)	4 (36)	0.42
APACHE-II score, median (IQR)	20 (8–40)	23 (9–45)	0.13
CAZ/AVI started owing to previous treatment failure, *n* (%)	22 (48)	7 (64)	0.34
Source of infection, *n* (%)			
pulmonary	9 (20)	6 (54)	0.02
urinary	13 (28)	1 (9)	0.18
intra-abdominal	10 (22)	4 (36)	0.31
Source control procedure, *n* (%)	7 (15)	2 (18)	0.18
Time to start of treatment with CAZ/AVI, days, median (IQR)	2 (0–15)	4 (2–17)	0.11
14 day mortality, *n* (%)	7 (15)	1 (9)	0.42
30 day mortality, *n* (%)	10 (22)	3 (27)	0.69
90 day recurrence, *n* (%)	4 (9)	2 (18)	0.35
Clinical cure, *n* (%)	37 (80)	7 (64)	0.44
Microbiological cure, *n* (%)	31 (67)	6 (54)	0.58

Ceftazidime–avibactam vs Kolistin

137 hasta

- **Karbapenem-dirençli Enterobactericeae (CRE) enfeksiyonu olan «137 hasta»**
  - 38 hasta ilk seçenek olarak ceftazidime–avibactam aldı
  - 99 hasta ilk seçenek olarak kolistin aldı

- **Hastaların başlangıç karakteristikleri benzer**
  - Median Charlson comorbidity score 3 (IQR: 1–5)
  - Median Pitt Bacteremia score 4 (IQR: 2–6)

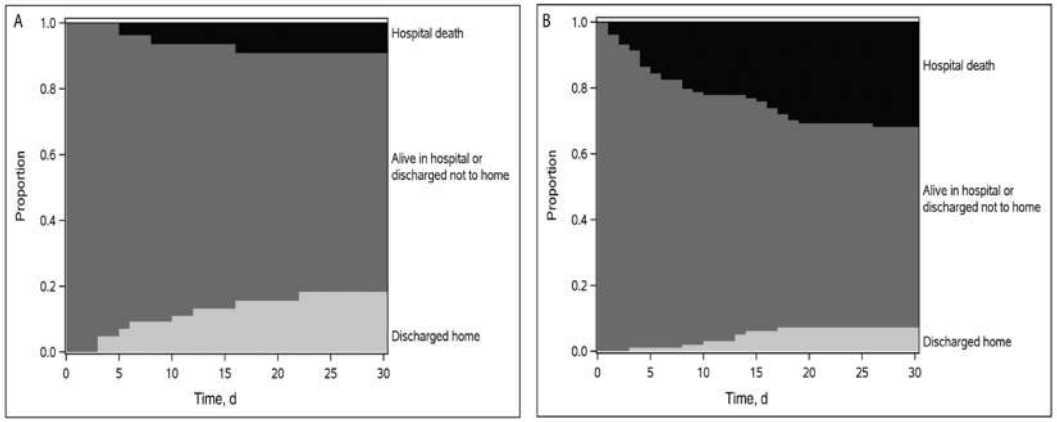
- CRE enfeksiyon tipleri: **Kan akımı enfeksiyonu (BSI) (n=63)**, solunum yolu enfeksiyonu (n=30) ve UTI (n=19)

- Patojenler: ***K. pneumoniae* (n=133)**, *Enterobacter* spp. (n=4)

van Duin D, et al. Colistin Versus Ceftazidime-Avibactam in the Treatment of Infections Due to Carbapenem-Resistant Enterobacteriaceae *Clin Infect Dis* 2018;66(2):163–71.

Ceftazidime–avibactam kolistin karşılaştırması

Karbapeneme dirençli Enterobactericeae (CRE) enfeksiyonunun tedavisinde seftazidime-avibaktam vs kolistin



Patients treated with ceftazidime-avibactam vs colistin, IPTW-adjusted all-cause hospital mortality at 30-days after starting treatment was 9% vs. 32%, respectively (Difference 23% [95% bootstrap CI: 9-35%], p=0.0012).

Patients treated with ceftazidime-avibactam had an IPTW-adjusted 64% (95% CI 57%-71%) probability of a better outcome as compared to patients treated with colistin.

van Duin D, et al. Colistin Versus Ceftazidime-Avibactam in the Treatment of Infections Due to Carbapenem-Resistant Enterobacteriaceae *Clin Infect Dis* 2018;66(2):163–71.

Seftolozan-Tazobaktam

- Zerbaxa
- FDA Aralık 2014
- Komplike iYE
- Komplike İAİ (Metronidazol ile kombine)
- Pnömoni için analiz aşamasında
- 3x1.5 gram (1 gr seftolozan, 0.5 gr tazobaktam)

Seftolozan-Tazobaktam

- İnvitro aktivite var
  - *Pseudomonas* spp.
  - Haemophilus
  - Moroxella

- Non-fermenter aktivite
  - *Acinetobacter* spp.→yok
  - *Stenetrophomonas* spp.→ yok
  - *Burcholderia pseudomallei*→ var
- Enterobacteriacea
  - CRE etkili değil
  - AmpC etkisi zayıf

Seftolozan/Tazobaktam

Çalışma	Karşılaştırma	Etkinlik	Güvenlik
ASPECT-cUTI[1] ▪cUTI ve ya AP ▪RCT; N = 1083	Levofloxacin	▪ **Noninferior**	▪ Benzer güvenlik profili
ASPECT-cIAI[2] ▪Artı metronidazole ▪cIAI ▪RCT; N = 541	Meropenem	▪ **Noninferior**	▪ Benzer güvenlik profili

1. Wagenlehner FM, et al. Lancet. 2015;385:1949-1956. 2. Solomkin J, et al. Clin Infect Dis. 2015;60:1462-1471.

Meropenem/Vaborbaktam: Etkinlik Çalışmaları

Çalışma	Karşılaştırma	Etkinlik	Güvenlik
TANGO I[1] ▪cUTI veya AP ▪RCT; N = 545	Piperacillin/ tazobactam	▪ **Noninferior**	▪ Benzer güvenlik
TANGO II[2] ▪CRE ▪OL RCT; N = 43	BAT	▪ **HiP/VİP ve bakteriyemi : 28 gün all** cause mortalite düşük ▪ **cUTI/AP**: overall başarı oranı yüksek (7-14 gün) ▪ **cIAI**: Klinik başarı	▪ Azalmış renal yetmezlik ve buna bağlı mortalite

*Clinical cure plus microbial eradication at end of IV treatment in microbiologic mITT.

1. Kaye KS, et al. JAMA. 2018;319:788-799. 2. Kaye KS, et al. IDWeek 2017. Abstract 1862.

Meropenem-Vaborbaktam

The Gram-negative challenge

Myriad resistance mechanisms

Beta lactamases (Ambler classification)

Serine

C	A	D
AmpC CMY	ESBLs KPC-2, 3	OXA-48 like OXA-23,58

Metallo

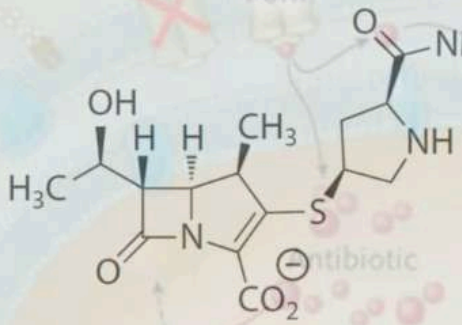
B
IMP, VIM, NDM

Multidrug resistant Gram-negative organisms

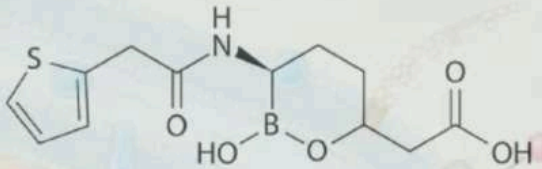
Carbapenem resistant *Enterobacteriaceae* CRE

Non-lactose fermenters

Carbapenem resistant *Acinetobacter baumannii* CRAB	Carbapenem resistant *Pseudomonas aeruginosa* CRPA
Burkholderia	*S. maltophilia*

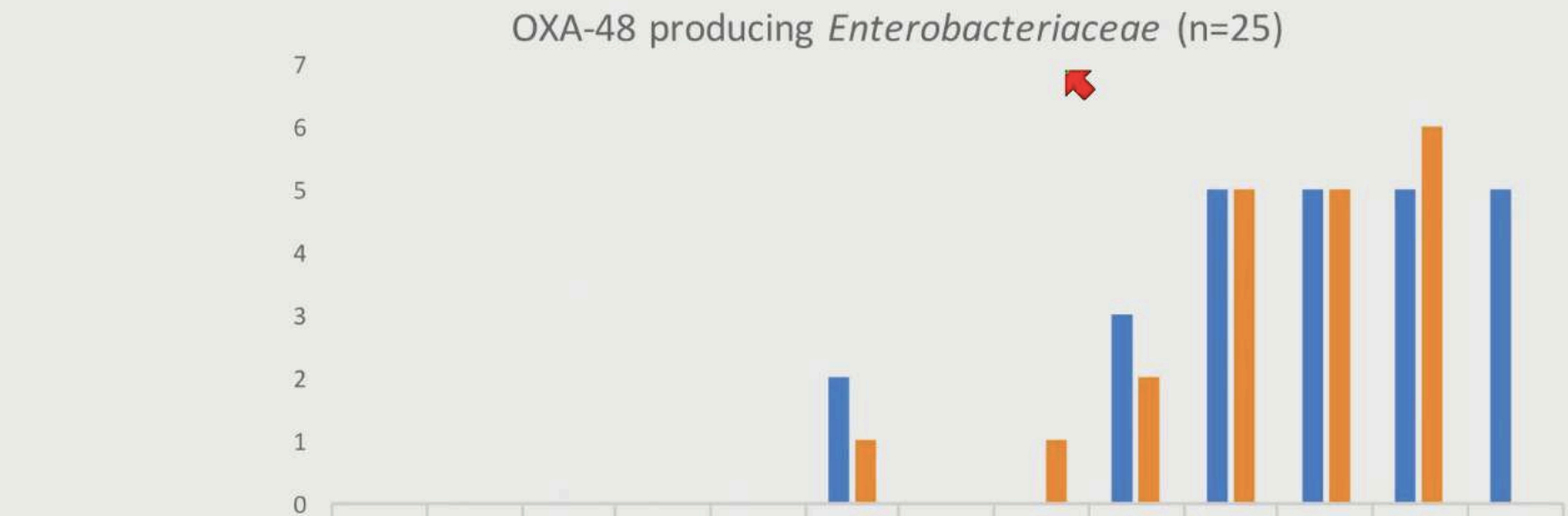


Meropenem-vaborbactam



Beta lactamases (Ambler classification)				Multidrug resistant Gram-negative pathogens			
Serine			Metallo	CR-*Enterobacteriaceae* -- mediated by KPC or non-carbapenemases (porins +/- efflux)	Non-lactose fermenters		
C	*A*	D	B		CRAB	CRPA-vaborbactam does not add to activity of meropenem	
AmpC CMY	CTX-M, SHV-12	OXA-48 like	IMP, VIM, NDM		S. maltophilia		
	KPC-2, 3	OXA-23,58			*Bcc*		

Activity of meropenem-vaborbactam according to mechanism of carbapenem resistance in *Enterobacteriaceae*



	≤0.015	0.03	0.06	0.12	0.25	0.5	1	2	4	8	16	32	>32
Meropenem-vaborbactam	0	0	0	0	0	2	0	0	3	5	5	5	5
Meropenem	0	0	0	0	0	1	0	1	2	5	5	6	0

Castanheira M et al. Antimicrob Agents Chemother. 2017 Aug 24;61(9)

Antibiyotik		CRE'ye karşı invitro aktivite
Aztreonam/avibactam	Monobactam/β-lactamase inhibitor	Evet
Imipenem/cilastatin/ relebactam	Relebaktam-Yeni Beta laktamaz inhibitörü	Evet

•1. Sader HS, et al. Antimicrob Agents Chemother. 2018;62:e01856-17.

•2. Kohira N, et al. Antimicrob Agents Chemother. 2015;60:729-734.

•3. Jacobs M, et al. ECCMID 2018. Abstract P0187.

•4. Karlowsky JA et al. Antimicrob Agents Chemother. 2018;62:pii: e00169-18.

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EPIDEMIOLOGY AND SURVEILLANCE

Antimicrobial Activit... Comparator Agent... *Enterobacteriaceae*

Helio S. Sader,[a] Rodrigo E. Mendes,[a]

- Toplam 10,451 Enterobacteriaceae suşu (2016) →
  - 116 metallo-betalaktamaz ve /veya OXA-48
- Tüm izolatlar için aztreonam-avibactam MIK→ ≤ 8 μg/ml
- En yüksek aztreonam-avibactam MIK değeri→ 4μg/ml.

Aztreonam/Avibaktam

ClinicalTrials.gov

Find Studies ▾ About Studies ▾ Submit Studies ▾ Resources ▾ About Site ▾

Home > Search Results > Study Record Detail

Save this study

A Study to Determine the Efficacy, Safety and Tolerability of Aztreonam-Avibactam (ATM-AVI) ± Metronidazole (MTZ) Versus Meropenem (MER) ± Colistin (COL) for the Treatment of Serious Infections Due to Gram Negative Bacteria. (REVISIT)

Aztreonam/ avibactam	REVISIT ▪ ± MTZ ▪ N = 300	Meropenem ± colistin	▪ HİP/VİP veya cIAI ▪ gr(-)'lere bağlı

Actual Study Start Date : **April 5, 2018**

Estimated Primary Completion Date : **February 7, 2022**

Estimated Study Completion Date : **February 23, 2022**

Antimicrobial Agents

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Susceptibility

In Vitro A

Negative

of the SM

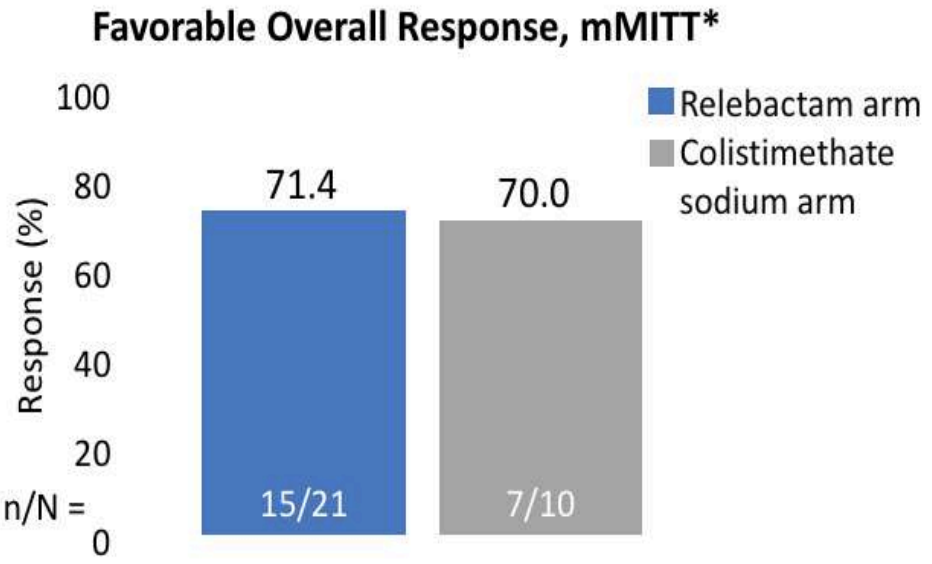
James A. Karlowsky, S

DOI: 10.1128/AAC.001

- Relebactam non-β-laktam β-laktamaz inhibitörü
- Class A and class C β-laktamaz (*Klebsiella pneumoniae* carbapenemases (KPCs) dahil inhibe eder.)
- Bu faz III çalışma
- İmipenem-relebactamın invitro aktivitesini değerlendirir
- 2016 yılında 3419 *Enterobacteriaceae* ve 896 *Pseudomonas aeruginosa* suşu toplandı.
- SMART (Study for Monitoring Antimicrobial Resistance Trends) global surveillance program. Kapsamında Relebactam 4 µg/ml düzeyinde test edildi
- imipenem-relebactam ve imipenem duyarlılıkları *Enterobacteriaceae* (*n* = 3,143) ve *P. aeruginosa* için→ 99.1% ve 74.7%
- Relebaktam imipenemin duyarlılığını artırmakta

İmipenem/Cilastatin-Relebaktam ve Colistimethate/İmipenem/Cilastatin→RESTORE-IMI 1

- Randomize, çift kör faz III çalışma
- HAP, VAP, kIAI, kIYE
- İmipenem dirençli 47 vaka
- kIAI ce kIYE için 5-21 gün
- HİP, VİP için 7-21 gün



1. Motsch J, et al. ECCMID 2018. Abstract 00427. Abstract data only. 2. ClinicalTrials.gov. NCT02493764.

Cefepim-Zidebactam

- Zidebaktam Beta laktam güçlendiricisi
- Cefepim düzeyini artırmaya gerek kalmadan etkiyi artırır (PBP-1,2,3'e bağlanarak etki eder)

- PBP 2'ye güçlü bağlanma ile hücre membranı sferoplast hale getirir
- Dış membranda bozulma dış membran üzerinden oluşan direnç mekanizmalarında değişikliğe neden olur (eflüks pompası, beta laktamaz üretimi)
- Cefepim hücre duvarına bu şeklide bağlanarak bakteri lizisine neden olur

Sefepime/zidebactam
Enterobacteriaceae spp., *P. aeruginosa* b-lactamases üreten (ESBLs, KPCs, AmpC and MBLs) etkili

Beta-Laktamaz ür
yöntemi ile cefe
duyarlılıkla
Cefepime/zi
KPC ve meta
Cefepime/zidebactam
(AmpC +), ve MBLs (VIM ve IMP) için etkili bulundu.
Zidebactam tek başına bazı *Enterobacteriaceae* spp. ve *P. aeruginosa*, için etkili bulundu.
Cefepime/zidebactam MIK değerleri diğer ajanlardan daha düşük bulundu.
Cefepime/zidebactam OXA-23/24/58-üreten *Acinetobacter baumannii* için etkili bulundu.

Activity of Ceftaroline-Avibactam Tested against Gram-Negative Organism Populations, including Strains Expressing One or More β-Lact… Var…

Maria…

JMI Lab…

Seftarolin avibaktam → Enterobacteriaceae suşları clas A, B, C, D enzimleri üretenlere karşı etkili

Pseudomonas aeruginosa, Acinetobacter spp., methicillin-duyarlı ve methicillin-dirençli Staphylococcus aureus (MRSA)

KPC üreten suşlara karşı meropeneme göre çok daha etkili (MIK > 8 **µ**g/dL 0.5-1 **µ**g/dL)

Acinetobacter spp. ve P. aeruginosa (MIC50s, 32 ve 16 **µ**g/ml) sınırlı etki gösterir.

→KPC ve ESBL (CTX-M) üreten Enterobacteriaceaetürlerine karşı etkili olduğu gösterilmiş.

Polimiksin B

- Colistin ile benzer etki spektrumu ve toksik potansiyeli var
- İdrar ile atılmaz
- ÜSE de işe yaramaz
- Mümkünse polimiksin B iv tercih edilecek
  - Colistin gibi ön ilaç olmadığı için doz hesabı kolay
  - Böbrek yetmezliğinde doz ayarlaması yok

Fosfomisin

- Geniş spektrumlu hücre duvar sentezi inhibitörü (MurA)
- KPC- *K. pneumoniae*,tedavisinde başarılı ancak kullanıldıkça direnç gelişiyor
- Çin'de duyarlılık oranları %30-40
- Kombinasyonun parçası olarak kullanılıyor

- Ceftazidime-avibactam
  - KPC ve OXA (çoğu)
- Meropenem-vaborbactam
  - KPC
- Ceftolozane-tazobactam
  - CRPA
- Plazomicin (daha iyi farmakokinetik, daha az toksik AG)
  - MDR Gram negatif

- Eravacycline
  - CRAB (tigesiklinden daha iyi farmakokinetik, geniş spektrumlu)
- Fosfomisin iv
  - CRE, Pseudomonas da kombinasyonda

News antibiotics for CP-CRE

	KPC	OXA-48	VIM/IMP/NDM
Ceftazidime Avibactam			
Meropenem Vaborbactam			
Imipenem Relebactam			
Aztreonam Avibactam			
Cefiderocol			
Plazomicina			
Eravacycline			

- Active
- Activity depending on MICs and/or target concentrations
- Not active