

Pseudomonas spp. ve Stenotrophomonas spp.



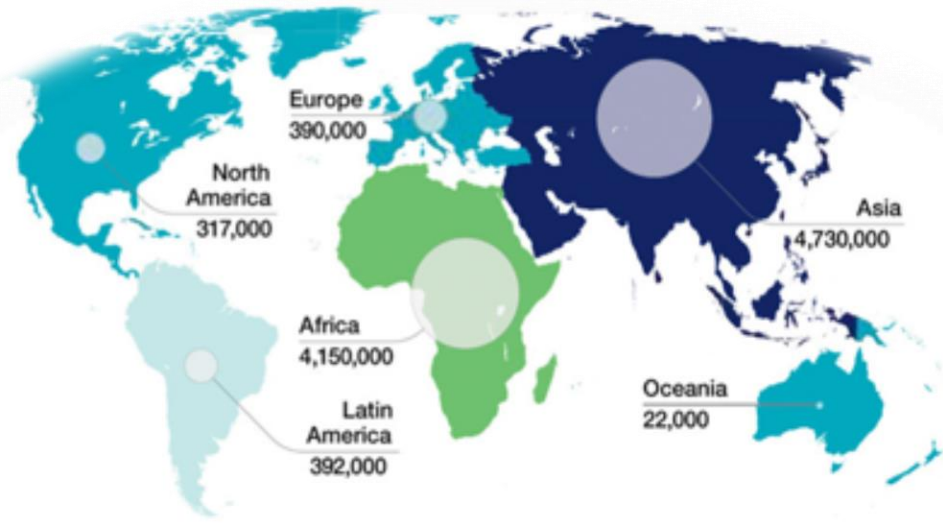
Dr. Hüseyin Aytaç Erdem
Ege Üniversitesi Enfeksiyon Hastalıkları ve
Klinik Mikrobiyoloji Anabilim Dalı

CLASSICS IN INFECTIOUS DISEASES

On the Blue and Green Coloration that Appears on Bandages

Carle Gessard
(1850-1925)





Mortality per 10,000 population



Number of deaths

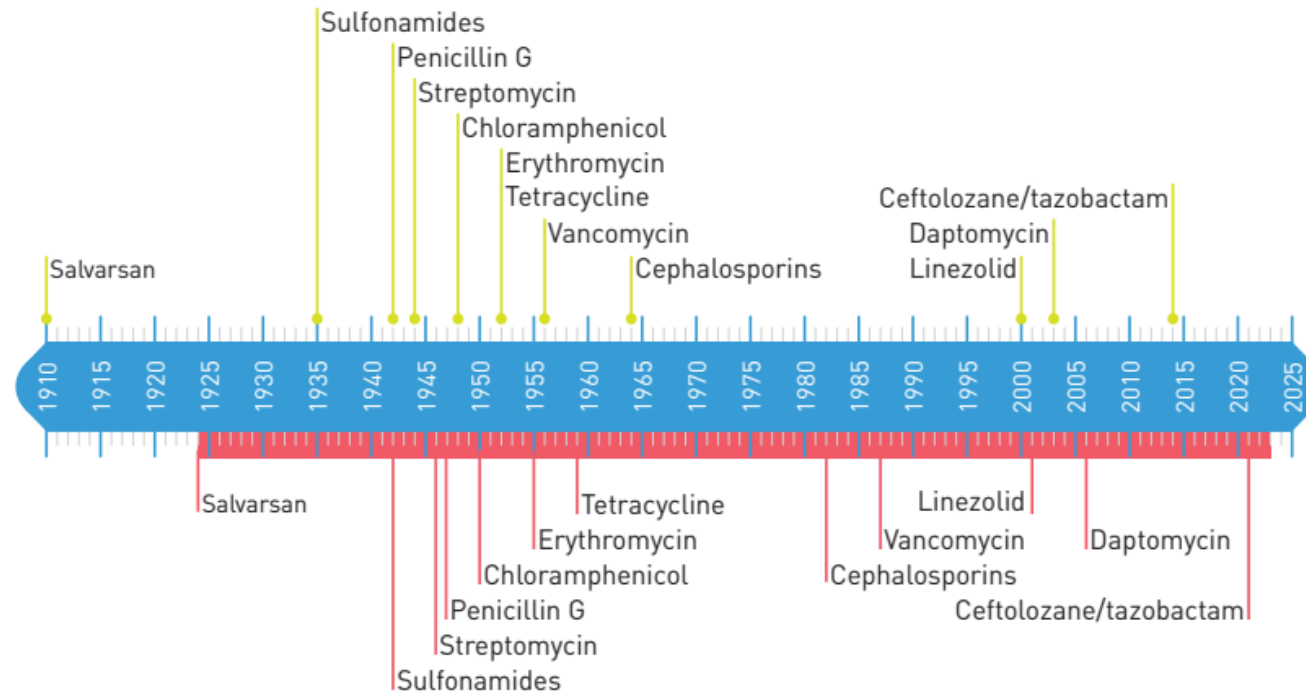


Fig. 6 *Pseudomonas aeruginosa*. Percentage of invasive isolates with resistance to carbapenems (imipenem/meropenem), by country, WHO European Region, 2021

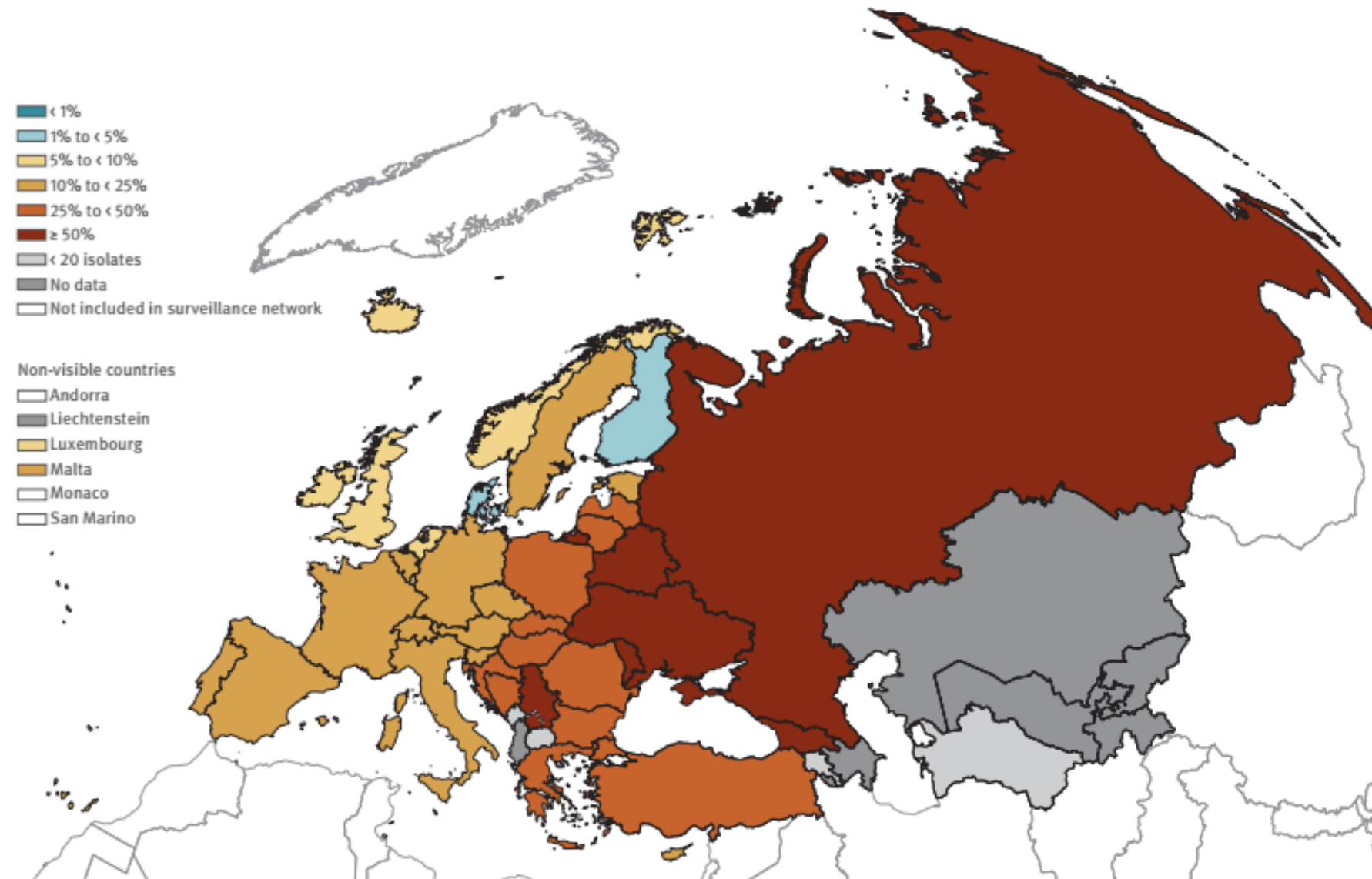


Table 7a Total number of invasive isolates tested (n) and percentage of isolates with AMR phenotype (%) in EU/EEA^a, by bacterial species and antimicrobial group/agent, population-weighted EU/EEA^a mean, 2017–2021

Bacterial species	Antimicrobial group/agent	2017		2018		2019		2020		2021		2021 EU/EEA country range ^b	
		n	%	n	%	n	%	n	%	n	%		
<i>P. aeruginosa</i>	Piperacillin-tazobactam resistance	13717	18.3	16018	18.5	16894	18.6	19799	18.8	21419	18.7	0.0–47.2	-
	Ceftazidime resistance	13801	16.0	16327	15.5	17328	15.7	20122	15.5	21750	15.8	2.3–46.0	-
	Carbapenem (imipenem/meropenem) resistance	14274	18.9	16473	18.8	17496	18.1	20517	17.9	22267	18.1	3.5–45.9	↓
	Fluoroquinolone (ciprofloxacin/levofloxacin) resistance	14118	21.8	16460	21.2	17635	20.5	20425	19.6	22129	18.7	3.3–48.0	↓*
	Aminoglycoside (gentamicin/netilmicin/tobramycin) resistance ^d	14117	14.4	16393	12.9	17552	12.6	12880	9.4	14537	8.9	0.0–41.7	↓*
	Combined resistance to ≥ 3 antimicrobial groups (among piperacillin-tazobactam, ceftazidime, carbapenems, fluoroquinolones and aminoglycosides) ^d	13022	14.1	15514	14.1	16289	13.5	12041	13.6	13684	12.6	0.0–42.1	↓

Total number of invasive isolates tested (n) and percentage of isolates with resistance phenotype (%)^a, by bacterial species and antimicrobial group/agent, Türkiye, 2017–2021

Bacterial species	Antimicrobial group/agent	2017		2018		2019		2020		2021		Trend 2017–2021 ^b
		n	%	n	%	n	%	n	%	n	%	
<i>P. aeruginosa</i>	Piperacillin-tazobactam resistance	1491	37.2	1646	34.0	1533	34.1	1365	32.1	1764	32.5	↓
	Ceftazidime resistance	1481	30.0	1700	26.8	1645	28.0	1468	27.2	1723	28.1	-
	Carbapenem (imipenem/meropenem) resistance	1552	37.4	1682	37.5	1712	38.4	1547	36.2	1718	39.0	-
	Fluoroquinolone (ciprofloxacin/levofloxacin) resistance	1525	35.6	1674	32.7	1637	35.2	1503	31.0	1735	33.1	-
	Aminoglycoside (gentamicin/tobramycin) resistance ^c	1519	26.7	1730	19.0	1681	20.8	769	15.7	1069	17.8	↓*
	Combined resistance to ≥ 3 antimicrobial groups (among piperacillin-tazobactam, ceftazidime, carbapenems, fluoroquinolones and aminoglycosides) ^c	1279	31.7	1451	27.8	1424	30.1	672	27.5	955	28.1	-

Annual number of reporting laboratories,^a number of reported isolates and percentage^b of isolates reported from patients in ICUs, Türkiye, 2017–2021

Bacterial species	2017			2018			2019			2020			2021		
	Labs (n)	Isolates (n)	Isolates from ICU (%)	Labs (n)	Isolates (n)	Isolates from ICU (%)	Labs (n)	Isolates (n)	Isolates from ICU (%)	Labs (n)	Isolates (n)	Isolates from ICU (%)	Labs (n)	Isolates (n)	Isolates from ICU (%)
<i>E. coli</i>	69	4 459	16	67	5 056	13	70	4 999	12	70	4 363	14	66	4 977	26
<i>K. pneumoniae</i>	68	3 232	36	67	3 833	34	69	4 167	28	70	4 534	32	66	4 851	58
<i>P. aeruginosa</i>	66	1 605	33	65	1 771	31	64	1 727	29	66	1 556	26	65	1 868	50
<i>Acinetobacter</i> spp.	67	2 620	45	66	2 754	44	68	2 477	42	69	3 170	45	64	3 516	83
<i>S. aureus</i>	68	3 230	23	66	3 354	21	69	3 475	14	70	3 614	20	66	3 881	35
<i>S. pneumoniae</i>	45	235	24	43	253	12	40	227	16	39	132	17	35	158	29
<i>E. faecalis</i>	65	1 735	37	67	1 944	35	66	1 976	32	69	2 135	34	63	2 166	56
<i>E. faecium</i>	65	1 585	34	65	1 669	32	66	1 829	27	68	2 204	31	65	2 567	63

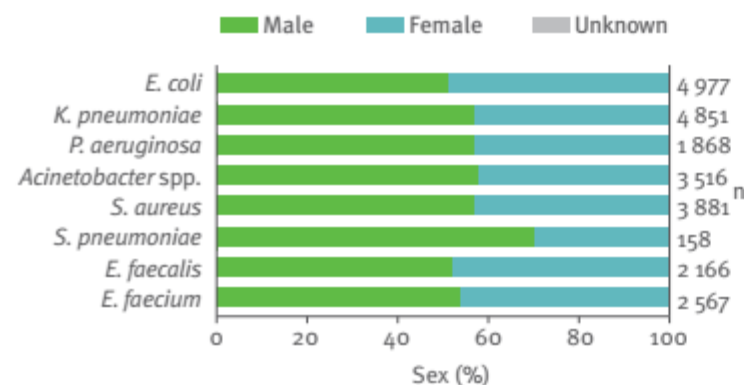
Labs: laboratories.

^a Number of laboratories reporting at least one isolate during the specific year. The total number of participating laboratories might be higher.

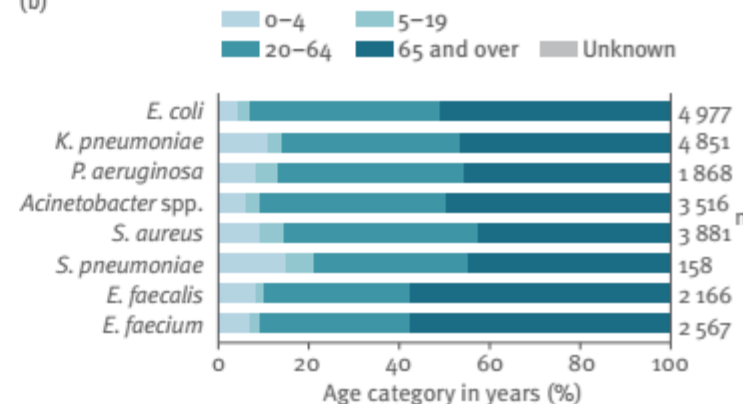
^b Isolates with missing information on hospital department are excluded from the calculation, and the percentage of isolates from ICU is presented only if there are ≥ 20 isolates of which $\geq 70\%$ have data on hospital department. If not, the percentage is presented as not applicable (NA).

Percentage of isolates by patient sex (a) and age group (b), by bacterial species, Türkiye, 2021

(a)



(b)

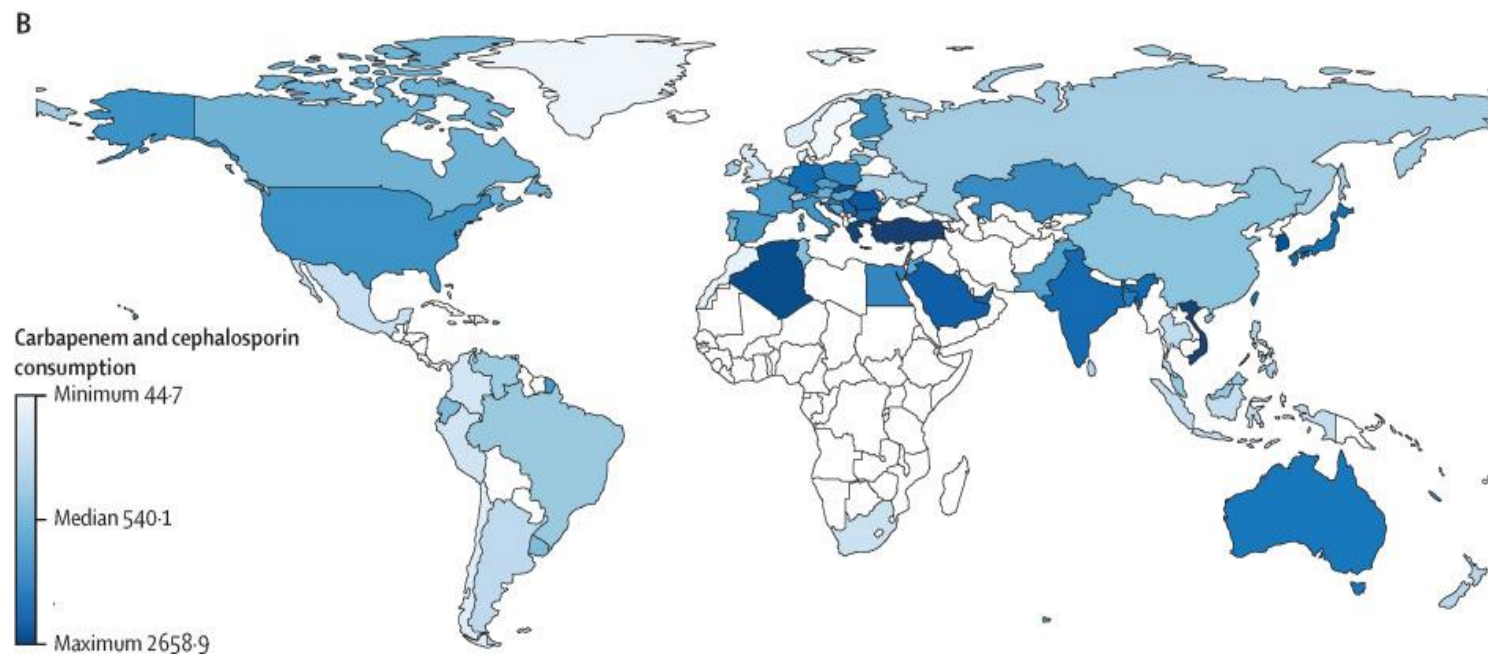
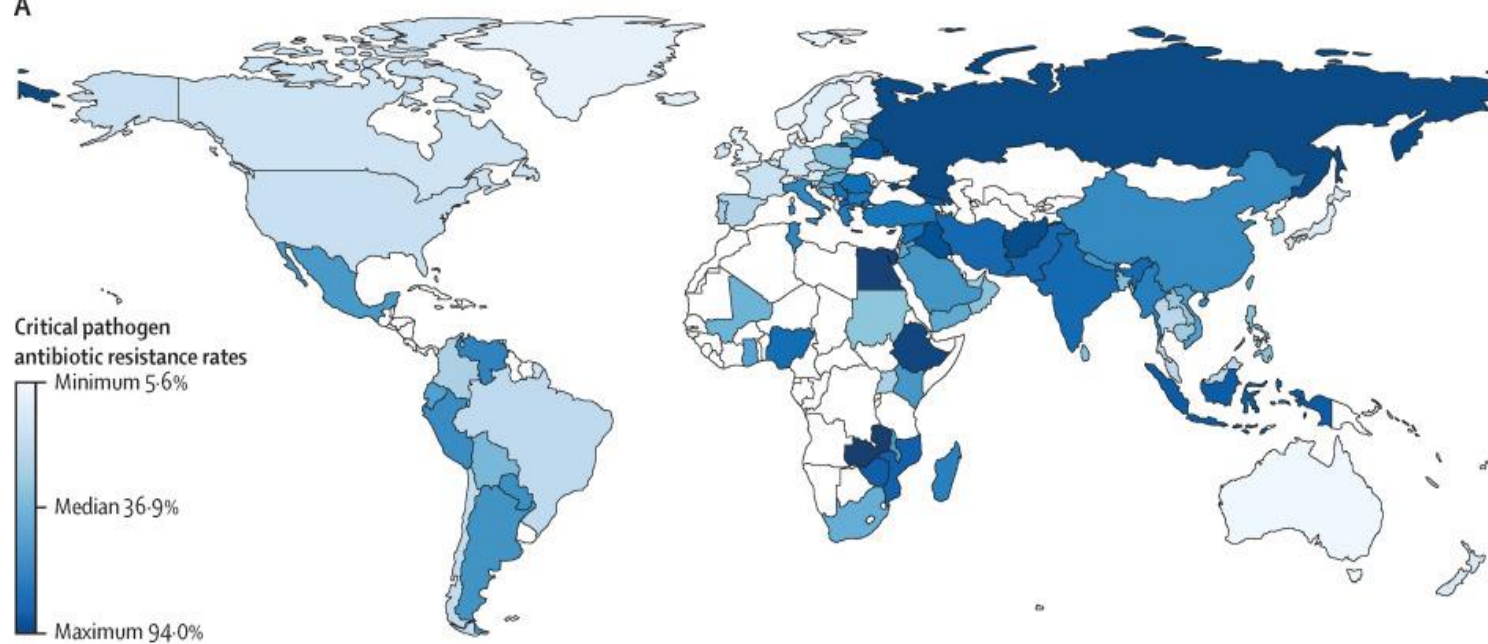


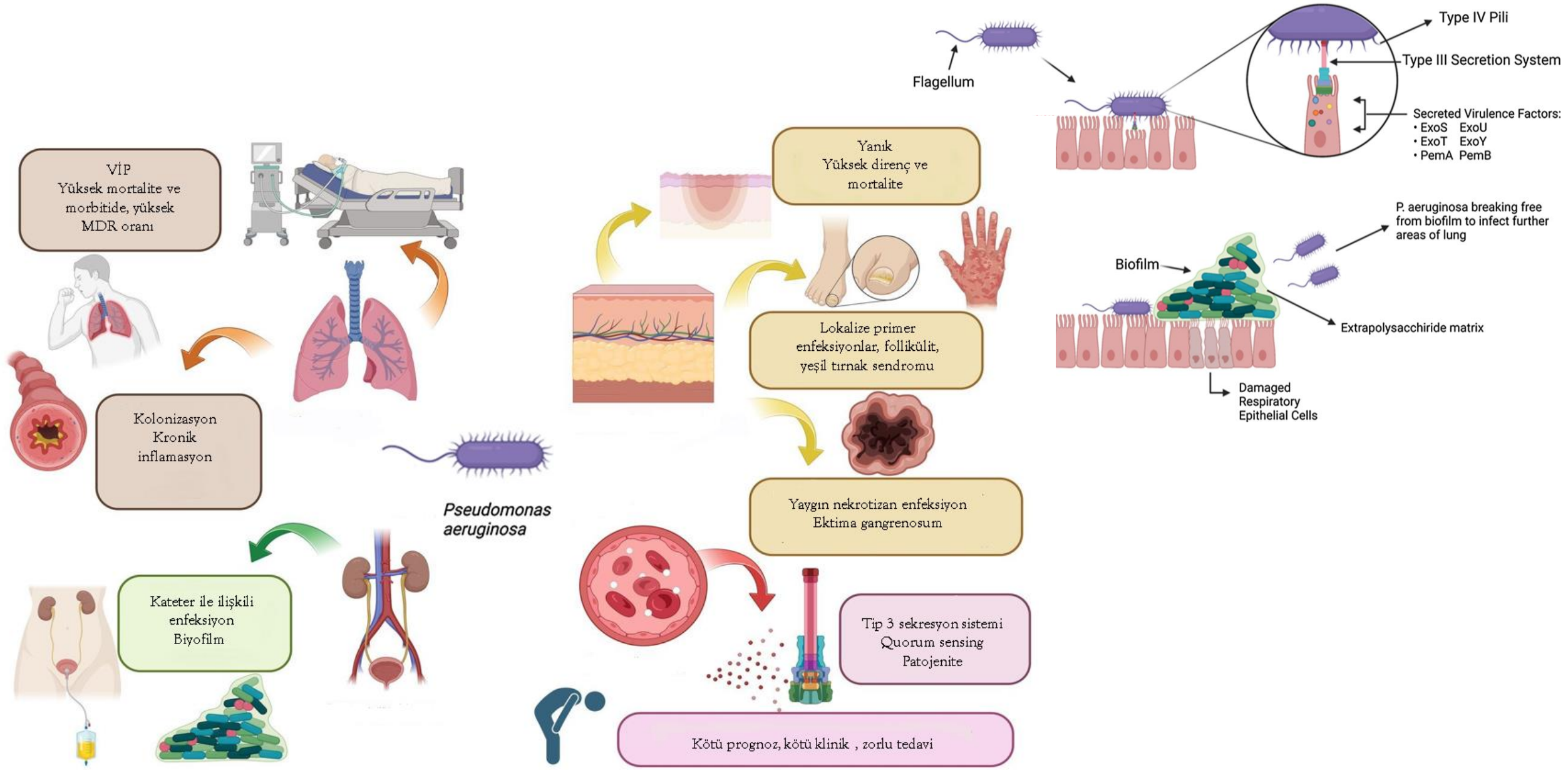
Tablo 24. Türkiye’de Sağlık Hizmeti İlişkili Enfeksiyonlarda Antimikrobiyal Direnç Oranları, 2022.

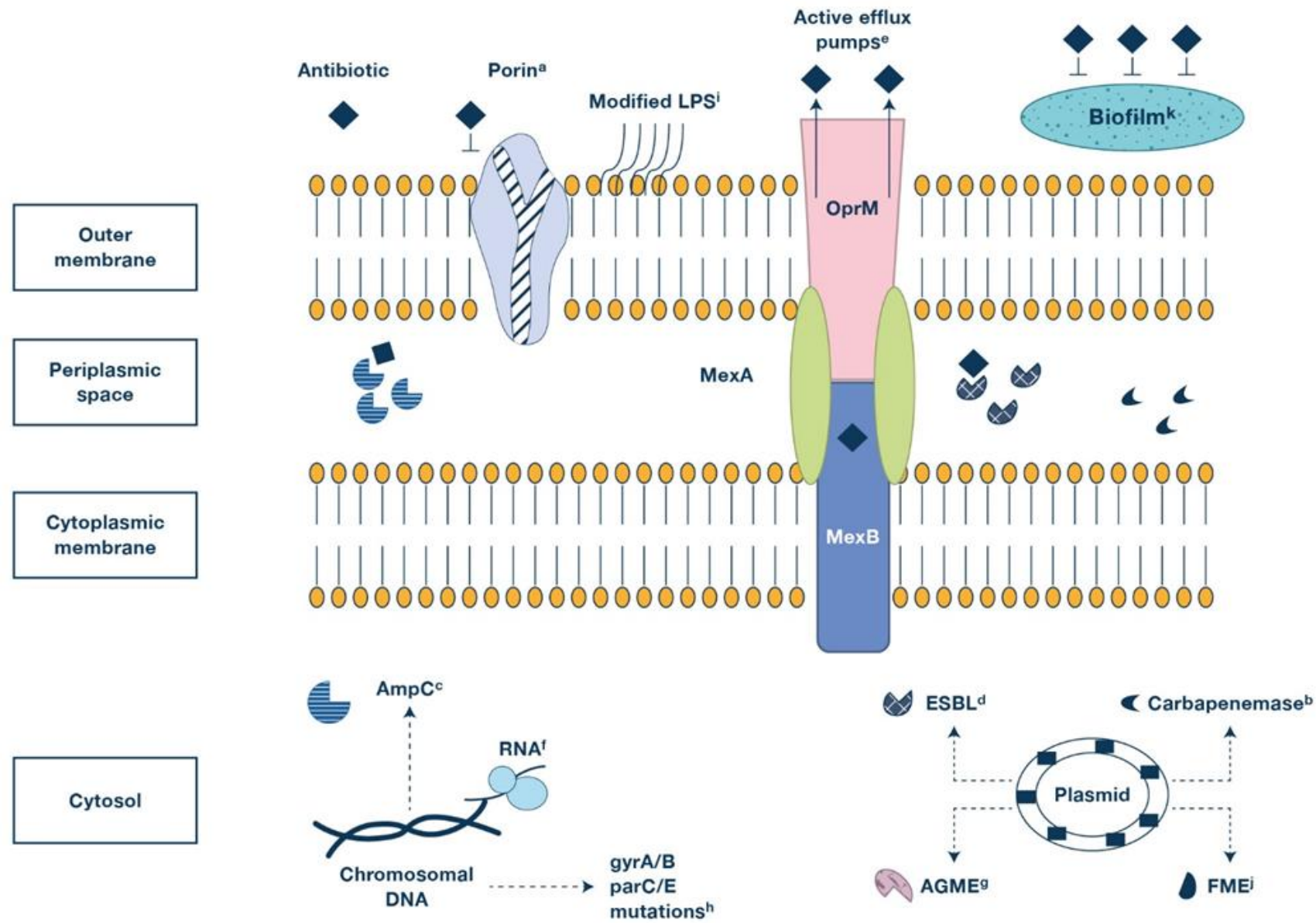
ANTİMİKROBİYAL DİRENÇLİ PATOJEN	Antimikrobiyal Direnç Oranları				PERSENTİL				
	Hastane Sayısı†	Toplam Etken Sayısı	Dirençli Etken Sayısı	Ağırlıklı Genel Ortalama	% 10	% 25	% 50 (Ortanca)	% 75	% 90
TÜRKİYE GENELİ									
Vankomisin dirençli <i>E.faecium</i>	228(57)	2340	542	23.16	0.00	8.20	20.00	29.79	52.21
Vankomisin dirençli <i>E faecalis</i>	235(46)	1799	79	4.39	0.00	0.00	0.00	5.73	9.09
MRSA	325(75)	2576	1286	49.92	25.00	32.80	42.86	63.61	81.41
MRKNS	308(41)	2569	2201	85.68	75.00	85.71	90.91	95.45	96.97
<i>E.coli</i> Suşlarında ESBL	410(118)	2583	4360	59.24	26.37	50.00	64.17	77.78	90.91
<i>Klebsiella pneumoniae</i> Suşlarında ESBL	404(197)	6179	8844	69.87	15.45	52.17	80.00	92.00	100.00
Karbapenem dirençli <i>Acinetobacter baumannii</i>	368(167)	8161	7523	92.18	81.59	90.69	95.87	100.00	100.00
Karbapenem dirençli <i>E.coli</i>	408(108)	4376	750	17.14	0.00	5.88	10.88	25.00	41.50
Karbapenem dirençli <i>Klebsiella pneumoniae</i>	411(190)	10042	6684	66.56	39.85	54.55	70.60	81.99	92.31
Karbapenem dirençli <u><i>Pseudomonas aeruginosa</i></u>	375(122)	4562	3084	<u>67.60</u>	37.95	55.97	72.47	84.90	95.26
Kolistin dirençli <i>Acinetobacter baumannii</i>	352(137)	6357	796	12.52	0.00	2.04	5.56	16.52	34.74
Kolistin dirençli <i>Klebsiella pneumoniae</i>	390(146)	6066	1893	31.21	3.70	13.83	27.27	47.47	67.71

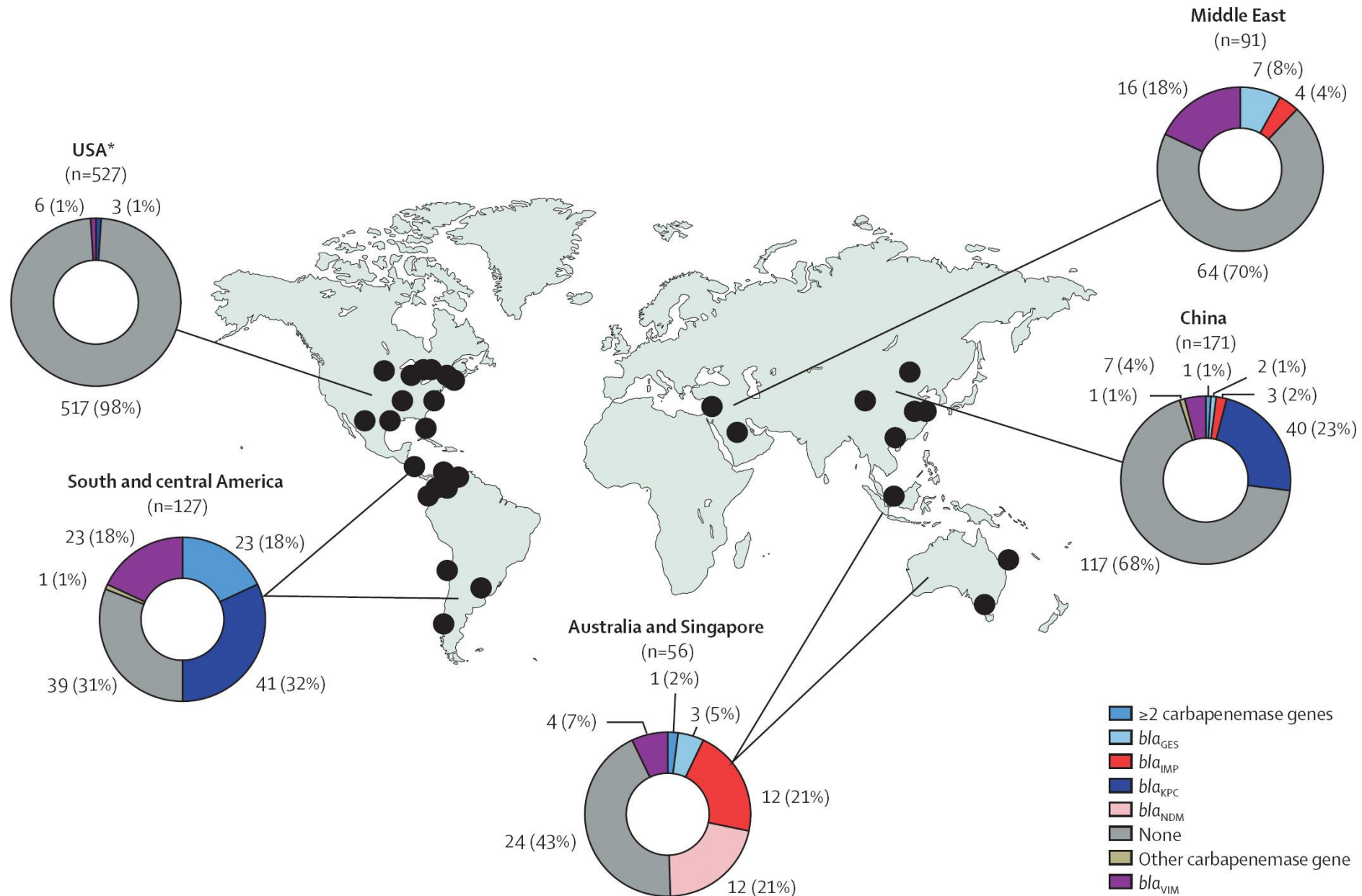
Tablo 3. Türkiye’de sađlık hizmeti iliřkili enfeksiyonların enfeksiyon türüne göre etken dađılımı, 2022.

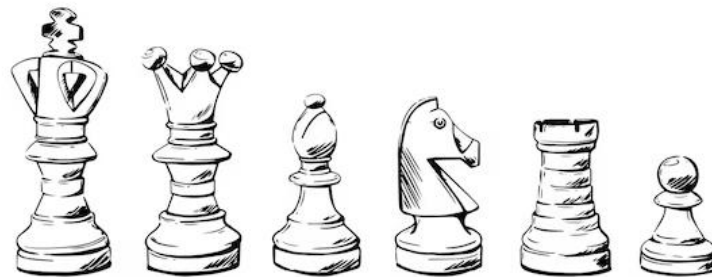
Mikroorganizmalar	Tüm Enfeksiyonlar		Pnömoni		VİP		VİO		ÜSE		Kİ-İYE		KDE		SKİ-KDE		CAE	
	Sayı	%	Sayı	%	Sayı	%	Sayı	%	Sayı	%	Sayı	%	Sayı	%	Sayı	%	Sayı	%
Non-fermantatif gram (-) bakteriler	27521	50.9	1699	61.0	5894	68.9	1218	69.8	626	38.9	3061	42.6	3524	45.0	7642	45.4	1346	40.3
<i>Acinetobacter spp</i>	12793	23.7	809	29.0	2968	34.7	694	39.7	263	16.4	1086	15.1	1705	21.8	3623	21.5	535	16.0
<i>Pseudomonas spp</i>	13785	25.5	809	29.0	2656	31.0	494	28.3	358	22.3	1954	27.2	1692	21.6	3696	22.0	791	23.7
<i>Stenotrophomonas spp</i>	683	1.3	58	2.1	193	2.3	24	1.4	4	0.2	12	0.2	82	1.0	251	1.5	13	0.4
<i>Burkholderia spp</i>	93	0.2	1	0.0	15	0.2	4	0.2	1	0.1	3	0.0	16	0.2	41	0.2	3	0.1
<i>Haemophilus spp</i>	20	0.0	11	0.4	5	0.1	0	0.0	0	0.0	0	0.0	1	0.0	1	0.0	0	0.0
Diđer non-fermantatif gram negatif basiller	147	0.3	11	0.4	57	0.7	2	0.1	0	0.0	6	0.1	28	0.4	30	0.2	4	0.1











Yeni antibiyotikler

<u>Seftolozane-tazobactam</u>	✗	✓	✓	✗	✗	✗	✗	EMA/FDA 👍 Komplike ÜSE, İAE, VİP, HGP
<u>Seftazidim-avibaktam</u>	✗	✓	✓	✚	✓	✓	✗	EMA/FDA 👍 Komplike ÜSE, İAE, VİP, HGP / EMA 👍 Gram (-) ↩↪
<u>Meropenem-vaborbaktam</u>	✗	✓	✗	✚	✓	✗	✗	FDA 👍 Komplike ÜSE EMA 👍 Komplike ÜSE, VİP, HGP, Gram (-) ↩↪
<u>İmipenem-cilastatin/relebactam</u>	✗	✓	✓	✚	✓	✗	✗	FDA 👍 Komplike ÜSE, İAE EMA 👍 VİP, HGP, Kan Dolaşımı Enfeksiyonları, Gram (-) ↩↪
<u>Plazomicin</u>	✗	✓	✚	✓	✓	✓	✚	FDA 👍 Komplike ÜSE, EMA ☹
<u>Eravacycline</u>	✓	✓	✗	✓	✓	✓	✓	EMA/FDA 👍 Komplike İAE
<u>Sefiderokol</u>	✓	✓	✓	✓	✓	✓	✓	FDA 👍 Komplike ÜSE, HGP, VİP, EMA 👍 Gram (-) ↩↪

Eski antibiyotikler

<u>Polimiksinler</u>	✓	✓	✓	✓	✓	✓	✓	
<u>Aminoglikozitler</u>	✚	✚	✚	✚	✚	✚	✚	
<u>Fosfomisin iv</u>	✗	✓	✚	✚	✚	✚	✚	
<u>Aztreonam</u>	✗	✗	✚	✗	✗	✗	✚	
<u>Tigesiklin</u>	✓	✓	✗	✓	✓	✓	✓	
<u>Temosilin</u>	✗	✓	✗	✗	✚	✗	✗	



Pseudomonas Aeruginosa

Clinical Infectious Diseases

IDSA GUIDELINES



OXFORD

Infectious Diseases Society of America 2023 Guidance on the Treatment of Antimicrobial Resistant Gram-Negative Infections

Clinical Microbiology and Infection 28 (2022) 521–547



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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)

- Çok ilaca dirençli (MDR) PSA
 - *Pseudomonas aeruginosa* genel olarak duyarlı olması beklenen 5 ilaç sınıfından (penisilin, sefalosporin, florokinolon, aminoglikozid, karbapenem) 3'ündeki en az 1 ajana direnç olması
- 2018 'den itibaren Multidrug-resistant *P. aeruginosa* MDR yerine
 - DTR* “difficult-to-treat”**
 - Piperasilin-tazobaktam, seftazidim, sefepim, aztreonam, meropenem, imipenem-silastatin, siprofloksasin, ve levofloksasin dirençli

- **Karbapenem dışı β -laktam ajanlar**

- **Eğer duyarlı ise**

Piperasilin-tazobaktam, Seftazidim, Sefepim, aztreonam tercih edilmeli
(karbapenemlerden önce)

- **Karbapenem dirençli fakat diğer β -laktam ajanlara duyarlı ise**

Yüksek doz ve uzun infüzyon , kültür duyarlılık test tekrarı

Kaynak kontrolü olmayan kritik hastalarda ise ; Seftolozane-tazobaktam, Seftazidim-avibaktam, imipenem-silastatin-relebaktam gibi yeni ajanların kullanılması uygun

- **Sistit (Komplike olmayan)**

- Seftolozane-tazobaktam,
- Seftazidime-avibaktam,
- İmipenem- cilastatin-relebaktam,
- Sefiderokol

Alternatif

Amikasin (tek doz)

Tobramisin (tek doz)

Kolistin ?

- **Piyelonefrit ve Komplike Üriner Sistem**

- Seftolozane-tazobaktam,
- Seftazidime-avibaktam,
- İmipenem- Silastatin-relebaktam,
- Sefiderokol

- **Üriner Sistem Dışı Enfeksiyonlar**
 - Seftolozane-tazobaktam,
 - Seftazidime-avibaktam,
 - İmipenem-silastatin-relebactam
 - Sefiderokol (Alternatif)
- **MLB +**
 - Sefiderokol
- **Kombinasyon tedavisi ?**
 - Yeni β -laktam duyarlı ise kombinasyon önerilmemekte*
 - Direnç mevcut ise tobramisin ile kombinasyon (MIC değerine göre tercih)
 - Tobramisin dirençli ise polimiksin B önerilmekte (Üriner sistem dışı)

Öneri	Kanıt Düzeyi
<i>Karbapenem-dirençli Pseudomonas aeruginosa (KDPA)</i> <i>Tedavi seçiminde öneriler</i>	
Ağır hastalarda DTR PA eğer duyarlı ise, Seftolozane-tazobaktam İmipenem relebaktam/ Sefiderokol/ Seftazidim-Avibaktam için kanıt yetersiz	Düşük
Ağır olmayan ve düşük riskli hastalar için enfeksiyon kaynağı ve klinik özellikler değerlendirilerek eski antibiyotikler kullanılabilir	Uzman görüşü
<i>Karbapenem-dirençli Pseudomonas aeruginosa (KDPA)</i> <i>Kombinasyon tedavisi için öneriler</i>	
Seftazidime-avibaktam and Seftolozane-tazobaktam) veya Sefiderokol için yetersiz kanıt	Öneri yok
Ağır ve yüksek riskli hastalarda in vitro iki aktif ajanla kombinasyon (polimiksin, aminoglikozit, fosfomisin)	Çok düşük
Ağır olmayan ve düşük riskli hastalar için enfeksiyon kaynağı ve klinik özellikler değerlendirilerek monoterapi önerisi	Uzman görüşü

KDAB

GSBL

**KDPA
non-MBL**

KDE
non-CP

KDE-
KPC

KDE-
OXA-48

KDE-
MBL

Yeni antibiyotikler

<u>Seftolazar</u> X <u>taizobactam</u>	✗	✓	✓	✗	✗	✗	✗	EMA/FDA 👍 Komplike ÜSE, İAE, VİP, HGP
<u>Seftazidim</u> - <u>avibaktam</u>	✗	✓	✓	+ -	✓	✓	✗	EMA/FDA 👍 Komplike ÜSE, İAE, VİP, HGP / EMA 👍 Gram (-) ↗
<u>Meropenem</u> - <u>vaborbaktam</u>	✗	✓	✗	+ -	✓	✗	✗	FDA 👍 Komplike ÜSE EMA 👍 Komplike ÜSE, VİP, HGP, Gram (-) ↗
<u>Imipenem</u> - <u>cilastatin</u> / <u>relebactam</u>	✗	✓	✓	+ -	✓	✗	✗	FDA 👍 Komplike ÜSE, İAE EMA 👍 VİP, HGP, Kan Dolaşımı Enfeksiyonları, Gram (-) ↗
<u>Plazomicin</u>	✗	✓	+ -	✓	✓	✓	+ -	FDA 👍 Komplike ÜSE, EMA ☹
<u>Eravacycline</u>	✓	✓	✗	✓	✓	✓	✓	EMA/FDA 👍 Komplike İAE
<u>Sefiderokol</u>	✓	✓	✓	✓	✓	✓	✓	FDA 👍 Komplike ÜSE, HGP, VİP, EMA 👍 Gram (-) ↗

Eski antibiyotikler

<u>Polimiksinler</u>	✓	✓	✓	✓	✓	✓	✓	
<u>Aminoglikozitler</u>	+ -	+ -	+ -	+ -	+ -	+ -	+ -	
<u>Fosfomisin iv</u>	✗	✓	+ -	+ -	+ -	+ -	+ -	
<u>Astreonom</u>	✗	✗	+ -	✗	✗	✗	+ -	
<u>Tigesiklin</u>	✓	✓	✗	✓	✓	✓	✓	
<u>Temosilin</u>	✗	✓	✗	✗	+ -	✗	✗	

Colistin alone versus colistin plus meropenem for treatment of severe infections caused by carbapenem-resistant Gram-negative bacteria: an open-label, randomised controlled trial



Mical Paul, George L Daikos, Emanuele Durante-Mangoni, Dafna Yahav, Yehuda Carmeli, Yael Dishon Benattar, Anna Skiada, Roberto Andini, Noa Eliakim-Raz, Amir Nutman, Oren Zusman, Anastasia Antoniadou, Pia Clara Pafundi, Amos Adler, Yaakov Dickstein, Ioannis Pavleas, Rosa Zampino, Vered Daitch, Roni Bitterman, Hiba Zayyad, Fidi Koppel, Inbar Levi, Tanya Babich, Lena E Friberg, Johan W Mouton, Ursula Theuretzbacher, Leonard Leibovici

Randomize kontrollü çalışma
(2013-2016)

Çok merkezli
(İsrail-Yunanistan-İtalya, altı hastane)
Pseudomonas spp. 21 hasta !

Kolistin vs kolistin+meropenem (3x2 gr, 3 saat inf.)

14 ve 28 günlük mortalite
Klinik başarısızlık ?

Infection characteristics and treatment		
Acquisition of infection in the intensive care unit	77 (39%)	71 (34%)
Pathogen		
<i>Acinetobacter baumannii</i>	151 (76%)	161 (77%)
Enterobacteriaceae	34 (17%)	39 (19%)
<i>Pseudomonas</i> /other	13 (7%)	8 (4%)
Meropenem MIC distribution	n=142	n=148
>8 mg/L	137 (97%)	144 (97%)
8 mg/L	1 (2%)	2 (1%)
>2 to <8 mg/L	4 (3%)	2 (1%)
Type of infection		
Bacteraemia	76 (38%)	97 (47%)
Ventilator-associated or hospital-acquired pneumonia	97 (49%)	85 (41%)
Probable ventilator-associated pneumonia	11 (6%)	14 (7%)
Urinary tract infection	14 (7%)	12 (6%)

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	Colistin	Colistin and meropenem	Risk ratio (95% CI) for outcome with combination	p value
Main pathogen				
n	198	208
Clinical failure				
<i>Acinetobacter baumannii</i>	125 (83%), n=151	130 (81%), n=161	0.97 (0.87–1.09)	0.643
Enterobacteriaceae‡	23 (68%), n=34	18 (46%), n=39	0.78 (0.54–1.13)	0.185
<i>Pseudomonas</i> or others§	8 (62%), n=13	4 (50%), n=8	0.81 (0.36–1.84)	0.673
28-day mortality				
<i>A baumannii</i>	70 (46%), n=151	84 (52%), n=161	1.11 (0.87–1.41)	0.404
Enterobacteriaceae	12 (35%), n=34	8 (21%), n=39	0.62 (0.29–1.36)	0.235
<i>Pseudomonas</i> or others	4 (31), n=13	2 (25%), n=8	0.81 (0.19–3.47)	1.0
14-day mortality				
<i>A baumannii</i>	54 (36%), n=151	62 (39%), n=161	1.11 (0.82–1.52)	0.495
Enterobacteriaceae	6 (18%), n=34	6 (15%), n=39	0.90 (0.32–2.51)	0.838
<i>Pseudomonas</i> or others	4 (31%), n=13	2 (25%), n=8	0.81 (0.19–3.47)	1.0

Infection characteristics and treatment		
Acquisition of infection in the intensive care unit	77 (39%)	71 (34%)
Pathogen		
<i>Acinetobacter baumannii</i>	151 (76%)	161 (77%)
Enterobacteriaceae	34 (17%)	39 (19%)
<i>Pseudomonas</i> /other	13 (7%)	8 (4%)
Meropenem MIC distribution	n=142	n=148
>8 mg/L	137 (97%)	144 (97%)
8 mg/L	1 (2%)	2 (1%)
>2 to <8 mg/L	4 (3%)	2 (1%)
Type of infection		
Bacteraemia	76 (38%)	97 (47%)
Ventilator-associated or hospital-acquired pneumonia	97 (49%)	85 (41%)
Probable ventilator-associated pneumonia	11 (6%)	14 (7%)
Urinary tract infection	14 (7%)	12 (6%)

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Colistin Monotherapy versus Combination Therapy for Carbapenem-Resistant Organisms

Keith S. Kaye, M.D., M.P.H.¹, Dror Marchaim, M.D.², Visanu Thamlikitkul, M.D.³, Yehuda Carmeli, M.D.⁴, Chena-Hsun Chiu, M.D., Ph.D.⁵, George Daikos, M.D.⁶, Sorabh Dhar, M.D.⁷.

Randomize kontrollü

2012-2020 yılları arasında

ABD, Taiwan, Tayland, İsrail, Yunanistan, İtalya, Bulgaristan

Kolistin vs Kolistin + Meropenem

28 gün mortalite

Klinik yanıtız

Mikrobiyolojik başarı ?

Table 4. Secondary Outcomes.*

Outcome	Colistin plus Placebo	Colistin plus Meropenem	Difference (95% CI)† or P Value
Clinical failure‡			
Overall	119/184 (65)	110/190 (58)	6.8 (-3.1 to 16.6)
Death by 7 days' posttreatment	52/184 (28)	39/190 (21)	7.7 (-0.9 to 16.4)
Need for rescue therapy	44/184 (24)	42/190 (22)	1.8 (-6.7 to 10.3)
Discontinue due to adverse event	12/184 (7)	21/190 (11)	-4.5 (-10.2 to 1.2)
BSI >5 days§	4/59 (7)	2/67 (3)	3.8 (-3.8 to 11.4)
Oxygenation failure¶	72/123 (59)	53/117 (46)	12.9 (0.3-25.4)
Pneumonia	96/132 (73)	87/134 (65)	7.8 (-3.3 to 18.9)
Bloodstream infection	23/52 (44)	23/56 (41)	3.2 (-15.5 to 21.8)
<i>Acinetobacter baumannii</i>	95/140 (68)	88/146 (60)	7.6 (-3.5 to 18.7)
CRE	18/32 (56)	16/33 (48)	7.8 (-16.4 to 32.0)
<i>Pseudomonas aeruginosa</i>	12/20 (60)	11/19 (58)	2.1 (-28.8 to 33.0)
Microbiologic cure			
Overall	106/163 (65)	103/171 (60)	4.8 (-5.6 to 15.2)
Pneumonia	59/114 (52)	48/115 (42)	10.0 (-2.8 to 22.9)
BSI	47/49 (96)	55/56 (98)	-2.3 (-8.8 to 4.2)
<i>A. baumannii</i>	76/121 (63)	74/130 (57)	4.9 (-7.2 to 17.0)
CRE	23/29 (79)	24/32 (75)	4.3 (-16.7 to 25.3)
<i>P. aeruginosa</i>	9/19 (47)	6/17 (35)	12.1 (-19.9 to 44.0)
Adverse events of interest			
Acute kidney injury**	88/170 (52)	85/174 (49)	0.55
Risk	36/169 (21)	30/174 (17)	
Injury	31/169 (18)	29/174 (17)	
Failure	21/169 (12)	26/174 (15)	
Hypersensitivity reaction††	3/229 (1)	7/227 (3)	0.22
Neurotoxicity††	11/229 (5)	5/227 (2)	0.29
Seizures††	3/229 (1)	3/227 (1)	1.00

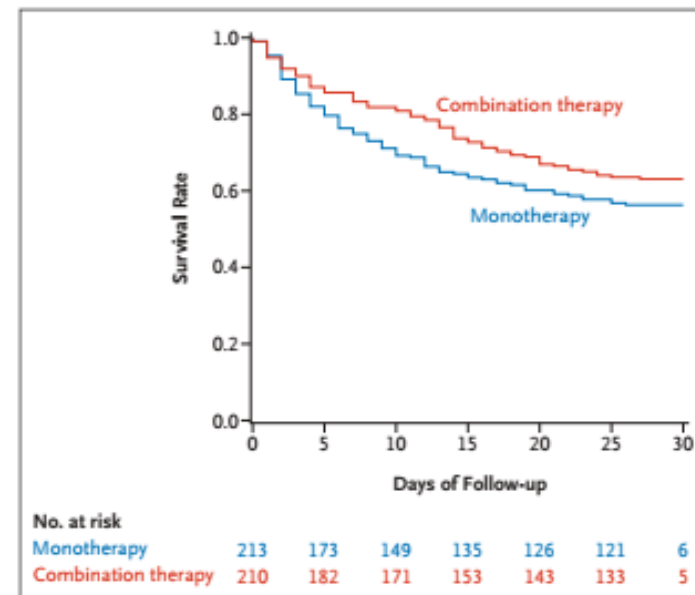


Table 3. Twenty-Eight-Day Mortality.*

Cause of Mortality	Colistin plus Placebo	Colistin plus Meropenem	Difference (95% CI)†	P Value
Overall	92/213 (43)	77/210 (37)	6.5 (-2.8 to 15.8)	0.17
Pneumonia	69/152 (45)	59/146 (40)	5.0 (-6.2 to 16.2)	
BSI	23/61 (38)	18/64 (28)	9.6 (-6.8 to 26.0)	
<i>Acinetobacter baumannii</i>	76/165 (46)	69/164 (42)	4.0 (-6.7 to 14.7)	
CRE	11/34 (32)	6/35 (17)	15.2 (-4.9 to 35.3)	
<i>Pseudomonas aeruginosa</i>	10/23 (43)	5/20 (25)	18.5 (-9.3 to 46.2)	

Active monotherapy and combination therapy for extensively drug-resistant *Pseudomonas aeruginosa* pneumonia

Thana Khawcharoenporn^{a,*}, Alan Chuncharunee^b, Chailat Maluangnon^b,
Thitiporn Taweesakulvashra^b, Pimsiri Tiamsak^b

^aDivision of Infectious Diseases, Faculty of Medicine, Thammasat University, Pathumthani, Thailand

^bThammasat University Hospital, Pathumthani, Thailand

Retrospektif, 2011-2016 yılları arasında

136 hasta

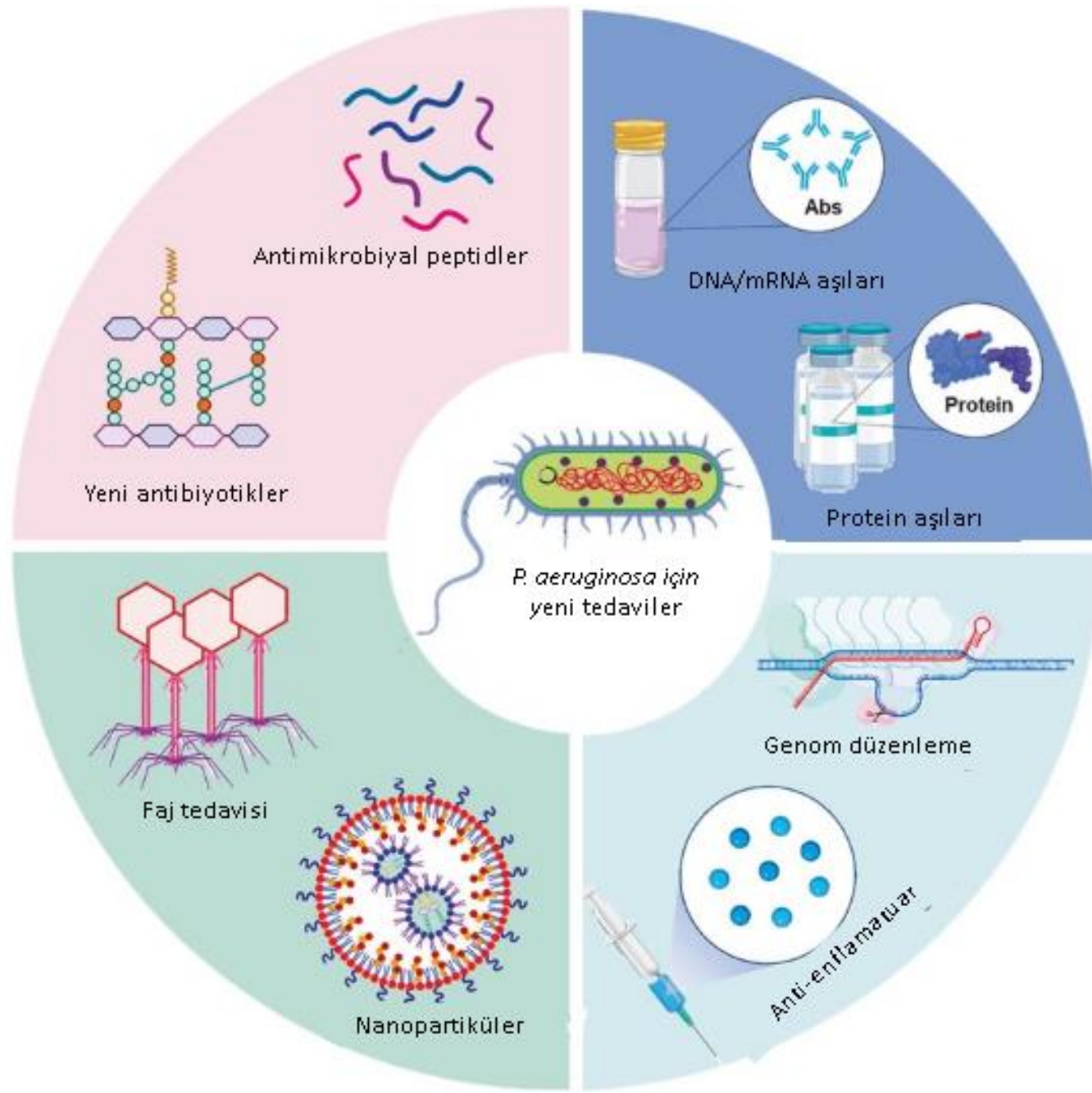
inaktif tedavi, aktif monoterapi ve aktif iki ilaçlı kombinasyon tedavisi karşılaştırma

Sağ kalım 14 ve 28 günler

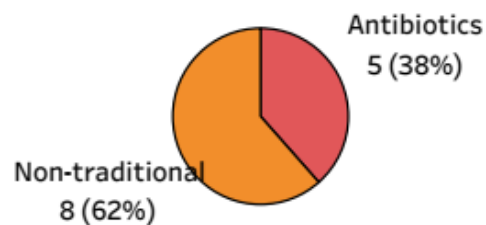
Mikrobiyolojik başarı ?

Active monotherapy (n=74)	Active combined two-drug therapy (n=40)	Inactive therapy (n=22)
Colistin and non-active carbapenem (n=40; 54%)	Colistin and fosfomycin (n=22; 55%)	Piperacillin-tazobactam (n=10; 46%)
Colistin alone (n=22; 30%)	Doripenem ^a and fosfomycin (n=12; 30%)	Non-active carbapenems (n=10; 46%)
Colistin and non-active fosfomycin (n=6; 8%)	Colistin and doripenem ^a (n=6; 15%)	Non-active fosfomycin and non-active carbapenems (n=2; 9%)
Fosfomycin and non-active carbapenem (n=4; 5%)		
Doripenem ^a and non-active fosfomycin (n=2; 3%)		

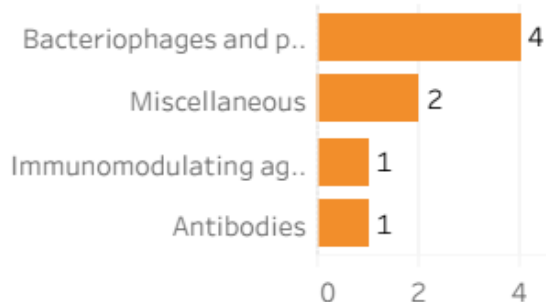
Variables	All (n=136)	Active monotherapy(n=74)	Active combined two-drug therapy(n=40)	Inactive therapy(n=22)	P-value ^a
Treatment characteristics					
Time to receipt of the active therapy ^b (h, median, IQR)	72 (48–96)	72 (48–96)	60 (48–120)	–	0.30
Infectious diseases consultation	98 (72)	58 (78)	40 (100)	0 (0)	<0.001
Colistin use	92 (68)	66 (89)	26 (65)	0 (0)	<0.001
Intravenous colistin	54/92 (59)	38/66 (58)	16/26 (61)	–	0.73 ^c
Nebulized colistin	38/92 (41)	28/66 (42)	10/26 (39)	–	<0.001
Outcomes					
<u>Survival at 28 days</u>					
All pneumonia	74 (54)	<u>38 (51)</u>	<u>36 (90)</u>	0 (0)	<0.001
HAP	42/86 (49)	18/42 (43)	24/26 (92)	0/18 (0)	0.007
VAP	32/50 (64)	20/32 (63)	12/14 (86)	0/4 (0)	<0.001
<u>Survival at 14 days</u>					
Mean survival time by log rank test (days)	86 (68)	<u>48 (65)</u>	<u>36 (90)</u>	2 (9)	<0.001
All pneumonia	20	20	26	8	<0.001
HAP	19	19	27	8	0.001
VAP	21	22	25	8	<0.001
<u>Microbiological cure at the end of therapy</u>					
All pneumonia	76 (56)	<u>40 (54)</u>	<u>36 (90)</u>	0 (0)	0.11
Adverse reaction					
Nephrotoxicity	16 (12)	12 (16)	4 (10)	0 (0)	0.09
Diarrhoea	2 (2)	0 (0)	2 (5)	0 (0)	<0.001



A.1. Products by type



A.2. No. of non traditional products by category



A.3. Products by pathogen category and phase

Pathogen category	Phase I	Phase II	Phase III	Total
Priority pathogens	5	6	2	13
Total	5	6	2	13

Pathogen c..	Product type	Product name	Antibacterial class	Phase
Priority pathogens	Antibiotics	MRX-8	Polymyxin	Phase I
		QPX7728 + QPX2014	Boronate-BLI + undisclosed	Phase I
		SPR-206	Polymyxin	Phase I
		Taniborbactam + cefepime	Boronate BLI + β -lactam (cephalosporin)	Phase III
		Zidebactam + cefepime	DBO-BLI/ PBP2 binder + cephalosporin	Phase I
Non-traditional		"Bacteriophage"	Bacteriophage	Phase III
		AP-PA02	Bacteriophage	Phase II
		BX004-A	Bacteriophage	Phase II
		Ftortiazinon + cefepime	Type III secretion system inhibition + cefepime	Phase II
		OligoG	Alginate oligosaccharide (G-block) fragment	Phase II
		Rhu-pGSM	Recombinant human plasma gelsolin protein	Phase II
		TRL1068	Antibody	Phase I
		YPT-01	Bacteriophage	Phase II

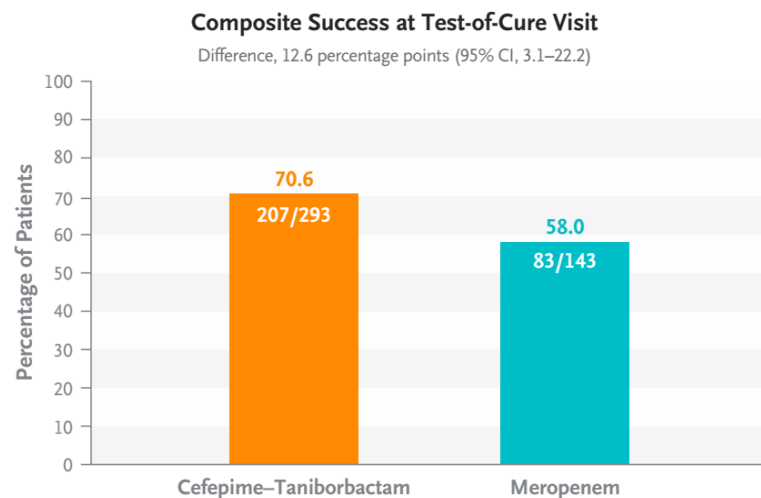
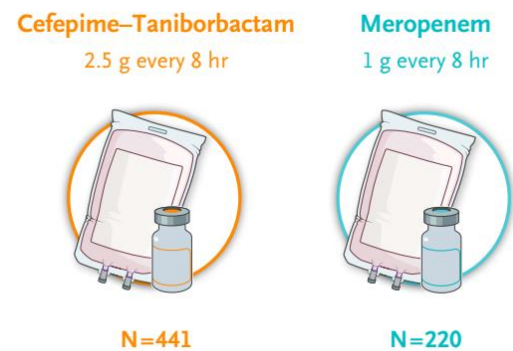
ORIGINAL ARTICLE

Cefepime–Taniborbactam in Complicated Urinary Tract Infection

Florian M. Wagenlehner, M.D., Leanne B. Gasink, M.D., Paul C. McGovern, M.D., Greg Moeck, Ph.D., Patrick McLeroth, M.D., MaryBeth Dorr, Ph.D., Aaron Dane, M.Sc., and Tim Henkel, M.D., Ph.D., for the CERTAIN-1 Study Team*

Table 3. Composite, Microbiologic, and Clinical Success at Test of Cure, According to Pathogen (Microbiologic Intention-to-Treat Population).*

Baseline Pathogen and Outcome	Cefepime–Taniborbactam	Meropenem
	no./total no. of patients (%)	
Microbiologic success		
Enterobacterales species or category	224/281 (80)	91/137 (66)
<i>E. cloacae</i> complex	11/14 (79)	1/3 (33)
<i>E. coli</i>	163/202 (81)	67/99 (68)
<i>K. pneumoniae</i>	27/40 (68)	14/20 (70)
<i>P. mirabilis</i>	9/10 (90)	4/10 (40)
Cefepime-resistant	50/66 (76)	18/30 (60)
ESBL-producing	57/76 (75)	25/40 (62)
Multidrug-resistant	71/100 (71)	38/55 (69)
<i>P. aeruginosa</i>	5/12 (42)†	4/6 (67)
Clinical success		
Enterobacterales species or category	241/281 (86)	111/137 (81)
<i>E. cloacae</i> complex	14/14 (100)	3/3 (100)
<i>E. coli</i>	177/202 (88)	80/99 (81)
<i>K. pneumoniae</i>	29/40 (72)	14/20 (70)
<i>P. mirabilis</i>	9/10 (90)	9/10 (90)
Cefepime-resistant	54/66 (82)	25/30 (83)
ESBL-producing	64/76 (84)	32/40 (80)
Multidrug-resistant	87/100 (87)	46/55 (84)
<i>P. aeruginosa</i>	10/12 (83)	5/6 (83)



Effect of Cefepime/Enmetazobactam vs Piperacillin/Tazobactam on Clinical Cure and Microbiological Eradication in Patients With Complicated Urinary Tract Infection or Acute Pyelonephritis: A Randomized Clinical Trial

Keith S Kaye¹, Adam Belley², Philip Barth², Omar Lahlou², Philipp Knechtle³, Paola Motta⁴, Patrick Velicitat²

POPULATION

573 Women
468 Men



Adults >18 years with a clinical diagnosis of complicated UTI or acute pyelonephritis caused by gram-negative urinary pathogens

Mean age: 54.7 years

LOCATIONS

90 Sites worldwide



INTERVENTION



1041 Patients randomized
1034 Patients analyzed

520

Cefepime/enmetazobactam

Cefepime, 2 g/enmetazobactam, 0.5 g, given by 2-hour infusion every 8 hours for 7 days



521

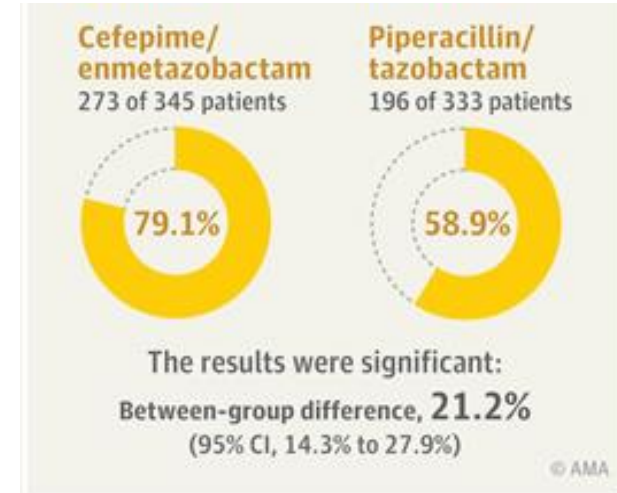
Piperacillin/tazobactam

Piperacillin, 4 g/tazobactam, 0.5 g, given by 2-hour infusion every 8 hours for 7 days

PRIMARY OUTCOMES

Proportion of patients in the primary analysis set who achieved overall treatment success, defined as clinical cure combined with microbiological eradication (10^3 CFU/mL in urine) of infection

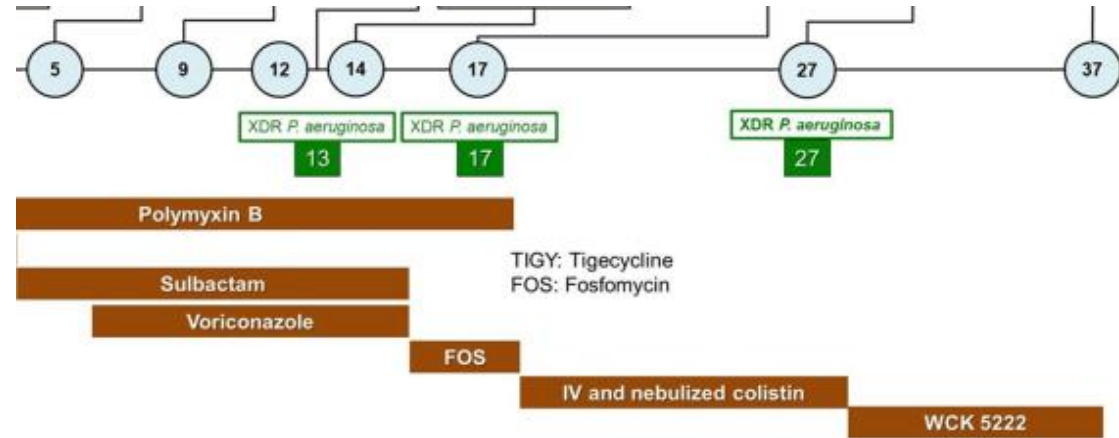
	No. (%)		Treatment difference, % (95% CI) ^a
	Cefepime/enmetazobactam (n = 345)	Piperacillin/tazobactam (n = 333)	
Response at visit			
Day 14^b			
Overall success ^c	273 (79.1)	196 (58.9)	21.2 (14.3 to 27.9)
Clinical cure	319 (92.5)	296 (88.9)	3.5 (-1.0 to 8.0)
Microbiological eradication	286 (82.9)	216 (64.9)	19.0 (12.3 to 25.4)
Day 3 of treatment			
Overall success	318 (92.2)	293 (88.0)	4.1 (-0.6 to 8.9)
Clinical cure	18 (5.2)	16 (4.8)	0.5 (-3.1 to 4.0)
Improvement ^d	317 (91.9)	302 (90.7)	Not determined
Microbiological eradication	323 (93.6)	299 (89.8)	3.8 (-0.6 to 8.3)
End of treatment			
Overall success	318 (92.2)	311 (93.4)	-1.3 (-5.3 to 2.9)
Clinical cure	323 (93.6)	315 (94.6)	-1.1 (-4.8 to 2.7)
Microbiological eradication	332 (96.2)	322 (96.7)	-0.7 (-3.7 to 2.5)
Day 21^e			
Overall success	236 (68.4)	196 (58.9)	10.7 (3.4 to 17.8)
Clinical cure	299 (86.7)	279 (83.8)	2.8 (-2.7 to 8.3)
Microbiological eradication	258 (74.8)	221 (66.4)	9.5 (2.6 to 16.3)



BRIEF REPORT

Open Access

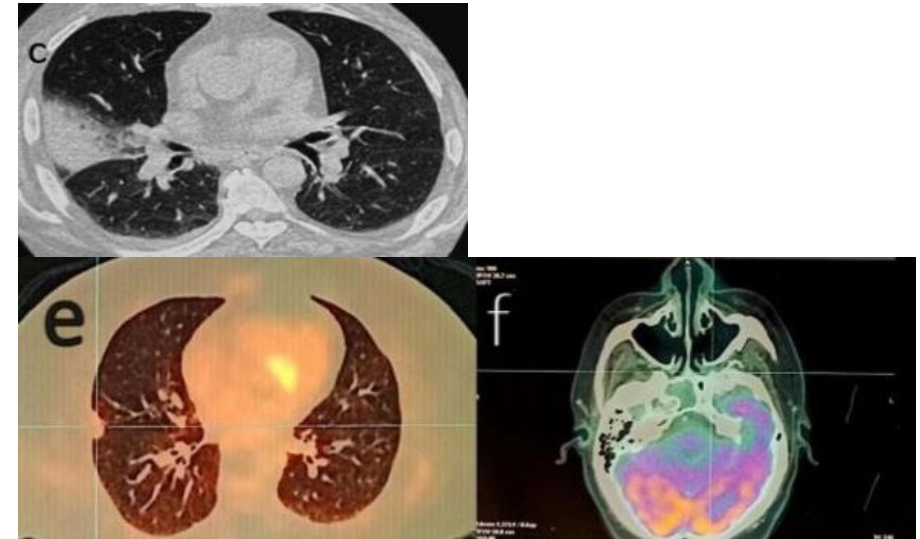
Compassionate use of a novel β -lactam enhancer-based investigational antibiotic cefepime/zidebactam (WCK 5222) for the treatment of extensively-drug-resistant NDM-expressing *Pseudomonas aeruginosa* infection in an intra-abdominal infection-induced sepsis patient: a case report



BRIEF REPORT

Successful treatment of sino-pulmonary infection & skull base osteomyelitis caused by New Delhi metallo- β -lactamase-producing *Pseudomonas aeruginosa* in a renal transplant recipient by using an investigational antibiotic cefepime/zidebactam (WCK 5222)

Rajeev Soman^{1,2} · Rasika Sirsat³ · Ayesha Sunavala⁴ · Neha Punatar³ · Jugal Mehta³ · Camilla Rodrigues⁵ · Balaji Veeraraghavan⁶



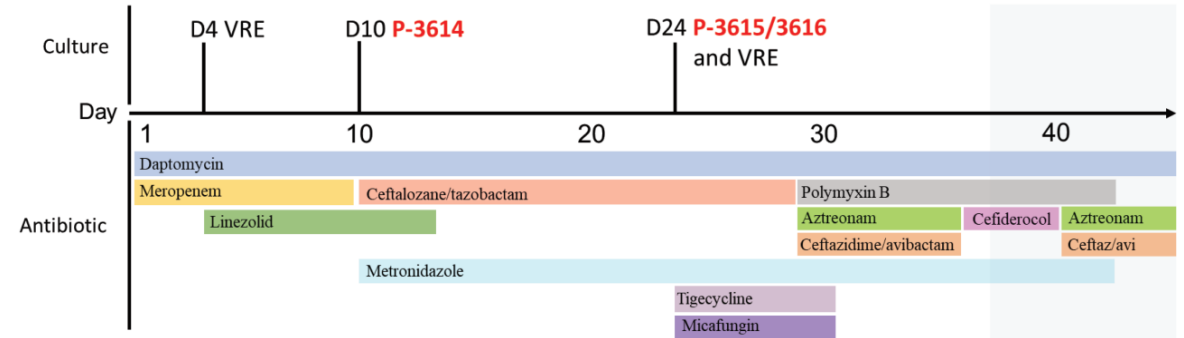
Modifiable Risk Factors for the Emergence of Ceftolozane-tazobactam Resistance

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. Simner⁸

Variable	Increase in TOL-TAZ MIC (mcg/mL) (n = 14, 50%)	No Increase in TOL-TAZ MIC (mcg/mL) (n = 14, 50%)	P-value
Demographics			
Age in years (median, IQR)	56 (40–65)	56 (48–60)	.95
Female	5 (36%)	3 (21%)	.40
Weight in kilograms (median, IQR)	62 (56–79)	63 (56–76)	.87
Renal replacement therapy	4 (29%)	1 (7%)	.14
Underlying medical condition			
Cystic fibrosis	2 (14%)	1 (7%)	.54
Chronic ventilator dependence	3 (21%)	4 (29%)	.66
Burn	1 (7%)	1 (7%)	.99
Active immunosuppressive therapy	8 (57%)	5 (36%)	.26
Complex cardiovascular disease with foreign material ^a	3 (21%)	1 (7%)	.28
Site of infection			
Pneumonia	9 (64%)	10 (71%)	.69
Bacteremia	4 (29%)	1 (7%)	.14
Intra-abdominal infection	1 (7%)	3 (21%)	.28
Treatment data			
3 grams IV every 8 hours of TOL-TAZ	12 (86%)	14 (100%)	.14
1.5 grams IV every 8 hours of TOL-TAZ	2 (14%)	0	.14
1-hour TOL-TAZ infusion	14 (100%)	10 (71%)	.04
3-hour TOL-TAZ infusion	0	4 (29%)	.04
Duration of TOL-TAZ therapy	15 (8–22)	8.5 (6–14)	.32
Combination therapy for > 48 hours	6 (43%)	4 (29%)	.43
No source control ^a	4 (29%)	0	.04

Evolution of Cefiderocol Non-Susceptibility in *Pseudomonas aeruginosa* in a Patient Without Previous Exposure to the Antibiotic

Ana Paula Streling,^{1,2,†} Mohanad M. Al Obaidi,^{3,4,†} William D. Lainhart,^{3,4,5} Tirdad Zangeneh,^{3,4} Ayesha Khan,^{1,6,7} An Q. Dinh,^{1,8,9} Blake Hanson,^{1,8,9} Cesar A. Arias,^{1,7,8,9,10} and William R. Miller^{1,8}



Antimicrobial Agents
and Chemotherapy



Antimicrobial Chemotherapy | Short Form

Emergence of cefiderocol resistance during ceftazidime/avibactam treatment caused by a large genomic deletion, including *ampD* and *piuCD* genes, in *Pseudomonas aeruginosa*

María A. Gomis-Font,¹ María A. Clari,² Carla López-Causapé,¹ David Navarro,² Antonio Oliver¹

Prevalence of *in vitro* synergistic antibiotic interaction between fosfomycin and nonsusceptible antimicrobials in carbapenem-resistant *Pseudomonas aeruginosa*

Lindsay M. Avery¹, Christina A. Sutherland¹ and David P. Nicolau^{1,2,*}

İnvitro çalışma

Karbapenem dirençli PSA izolatlarında

Fosfomisinin sinerjistik etkinliği ?

153 izolat

Sinerji en sık

Seftazidim (42/81, 51.9%) Seftolozane/tazobaktam (7/14, 50.0%)

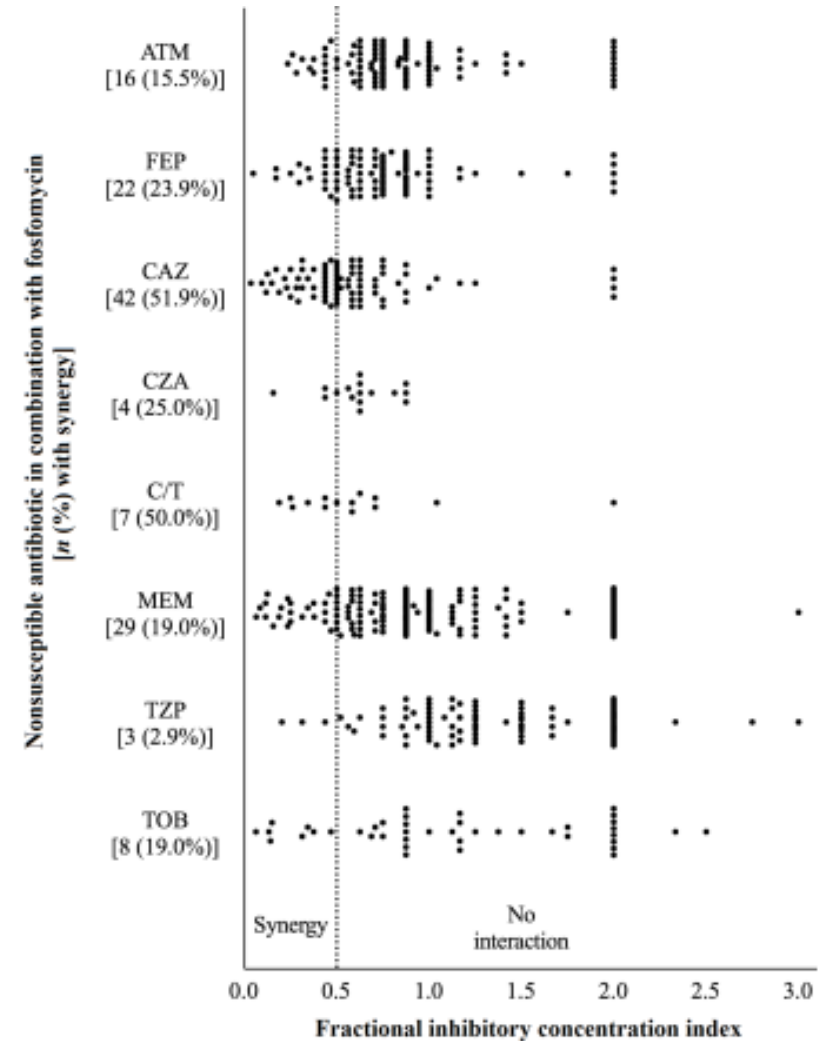
Restoration of susceptibility !

Fosfomisin ile kombinasyonu sonrası duyarlılıkta düzelme

10 (%71.4) fosfomisin–Seftolozane/tazobaktam

11 (%68.8) fosfomisin–Seftazidime/avibaktam

Meropenem 21/153 (%13.7)



Case Report

Azithromycin: An Underappreciated Quinolone-Sparing Oral Treatment for *Pseudomonas aeruginosa* Infections

Erlinda R. Ulloa ^{1,2,*} and George Sakoulas ^{3,4}

P. aeruginosa bağı otolaringolojik enfeksiyonlar

Üç olgu ; Eksternal Otit ve Kronik Sinüzit

Azitromisin 500mg /gün

3-8 hafta süre ile tedavi

Klinik başarı !

Antibiotic	Case 1		Case 2		Case 3	
	MIC (mg/L)	Interpretation	MIC (mg/L)	Interpretation	MIC (mg/L)	Interpretation
Amikacin	>32	R	-	-	-	-
Aztreonam	>16	R	≤4	S	≤4	S
Cefepime	>16	R	≤2	S	8	S
Cefidericol	8	I	-	-	-	-
Ceftazidime	>16	R	≤1	S	4	S
Ceftazidime/avibactam	>16	R	-	-	-	-
Ceftolozane/tazobactam	>8	R	-	-	-	-
Ciprofloxacin	>2	R	≤0.25	S	>2	R
Delafloxacin	>2	R	-	-	-	-
Colistin	2	I	-	-	-	-
Eravacycline	4	(ND)	-	-	-	-
Gentamicin	>8	R	≤2	S	>8	R
Imipenem	>16/4	R	-	-	>8	R
Levofloxacin	>4	R	≤0.50	S	>4	R
Meropenem	>8	R	≤1	S	2	S
Meropenem/vaborbactam	>16/8	R	-	-	-	-
Piperacillin/tazobactam	>64	R	≤8	S	≤8	S
Tobramycin	>8	R	≤2	S	≤2	S

Bacteriophage–Antibiotic Combination Therapy against *Pseudomonas aeruginosa*

Guillermo Santamaría-Corral ¹, Abrar Senhaji-Kacha ^{1,2}, Antonio Broncano-Lavado ¹, Jaime Esteban ^{1,2,*} and Meritxell García-Quintanilla ^{1,2}

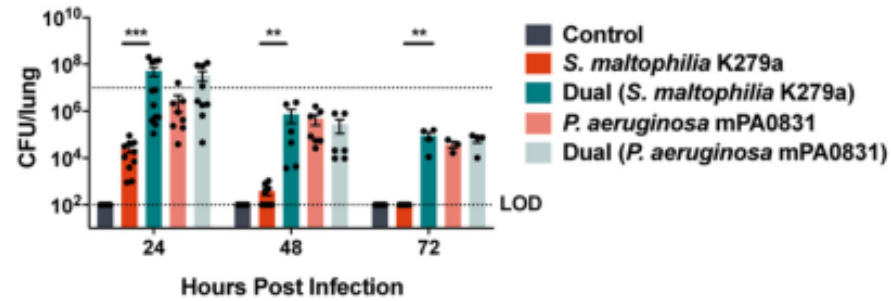
Disease	Bacteria	Phage Therapy	Antibiotic Combination	Outcome	Reference
Prosthetic joint infection (PJI)	<i>P. aeruginosa</i>	Three-phage cocktail (10 ⁹ PFU/mL)	Ciprofloxacin Ceftazidime	Rapid improvement of patient's health	Akturk, E.;
Catheter-related bacteremia	Pandrug-resistant <i>P. aeruginosa</i>	Personalized three-phage cocktail (10 ⁶ PFU/mL) IV 3 h for 21 days	IV Cefiderocol 2 weeks later IV Colistin	Favorable to patient after 21 months follow-up	Tkhilaishvili, T.
Catheter-related bacteremia	<i>P. aeruginosa</i> XDR	Phage cocktail (10 ⁸ PFU/mL) by direct contact with the infected bone for 4 h	Colistin (local) IV Ceftolozane/Tazobactam	Favorable, with no bacterial growth and rapid healing of bone	Lin, Y.;
Liver infection	<i>P. aeruginosa</i> XDR	IV BFC1 cocktail (10 ⁷ PFU/mL)	IV Gentamycin, Colistin and Aztreonam	Controlled the bloodstream infection, and retransplantation was possible after 72 days	Van Nieuwenhuysse, B.
Cystic fibrosis	<i>P. aeruginosa</i> MDR	IV AB-PA01 (10 ⁹ PFU/mL) ev for 8 weeks	Ciprofloxacin and Piperacilin-tazobactam for 3 weeks; added Doripenem	No <i>P. aeruginosa</i> recurrence or CF exacerbation	Duplessis, C
Pneumonia	<i>P. aeruginosa</i> MDR	1) Nebulized AB-PA01 (10 ⁹ PFU/mL) for 2 weeks 2) AB-PA01-m1 and Navy-1 phage cocktail (10 ⁹ PFU/mL)	Piperacilin-Tazobactam and Colistin	No active <i>P. aeruginosa</i> pneumonia after 3 months	Cafora, M.;
Recurrent infections post-transplant	<i>P. aeruginosa</i> MDR	IV AB-PA01 for 4 weeks (10 ⁶ PFU/mL)	Inhaled Colistin Piperacilin-Tazobactam from day 60 to 90	No additional <i>P. aeruginosa</i> was cultured	Cafora, M.;
Pneumonia	Carbapenem-resistant <i>P. aeruginosa</i>	Personalized two-phage cocktail preparations (10 ⁸ PFU/mL). Nebulized administration and intrapleural for 24 days	IV Amikacin, Azhitromycin, Imipenem, and Ceftazidime-Avibactam	Clearance of the pathogen and clinical improvement	Ferry, T.;
Graft infection, bacteremia	<i>P. aeruginosa</i>	OMK01 (10 ⁷ PFU/mL)	Ceftazidime	General clinical improvement	Ferry, T.;
Wound infection	<i>P. aeruginosa</i>	PA5 and PA10 (10 ¹⁰ PFU/mL)	IV Ceftazidime-Avibactam and Colistin	The wound completely healed, with no <i>P. aeruginosa</i> detection	Ferry, T.;
Relapsing bacteremia	<i>P. aeruginosa</i> MDR	Local application of BFC 1.10 (10 ⁷ PFU/mL) cocktail	IV Ceftazidime-Avibactam	Bacterial eradication	Racenis, K.
Bacteremia	<i>P. aeruginosa</i> MDR	Local application (10 ⁸ PFU/mL) during surgery every 8 h for 5 days	IV Colistin, Meropenem, and Ceftazidime	No <i>P. aeruginosa</i> detection	Law, N.;



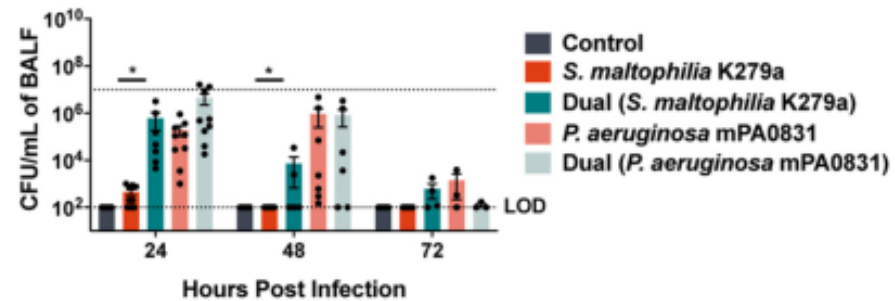
Cooperativity between *Stenotrophomonas maltophilia* and *Pseudomonas aeruginosa* during Polymicrobial Airway Infections

Melissa S. McDaniel,^{a,b} Trenton Schoeb,^c W. Edward Swords^{a,b}

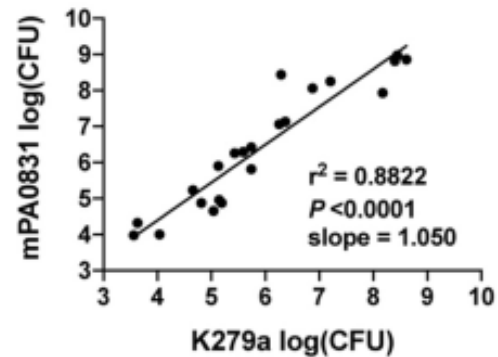
A. Bacterial Burden (Lung)



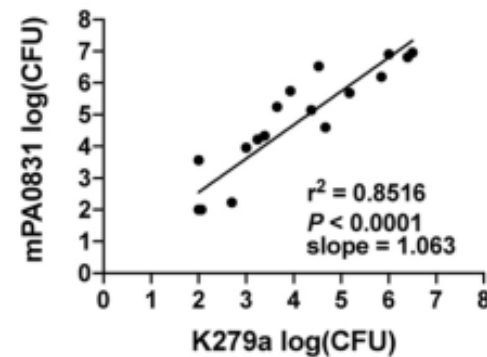
B. Bacterial Burden (BALF)



C. CFU correlation (Lung)



D. CFU correlation (BALF)





Stenotrophomonas maltophilia

- Biyofilm üretmesi ve virülans faktörleri nedeniyle altta yatan akciğer hastalığı olanlar ve hematolojik malignitesi olanlarda enfeksiyon riski !
- Kolonizasyon / hastalık ??
- Beta laktam direnci !!
- Polimiksinler için tanımlanmış CLSI duyarlılık kriteri yok , polimiksin altında tam olmayan bakteri çoğalması mevcut , heterorezistans ??
- Tedavide polimiksinler önerilmemekte

Tedavide genel yaklaşım ;

- TMP-SMX, minosiklin/tigesiklin, sefiderokol, levofloksasin ajanlarından ikisini kombine et

ya da

- Seftazidim-avibaktam +aztreonam (diğer ajanlarla yan etki var veya belirgin klinik instabilite varsa)
- Tekli tedavi ile kombinasyon tedavilerini kıyaslayan çalışma sayısı kısıtlı

TMP-SMX duyarlı ise kombinasyon tedavisinin temel taşı olmalı

- 8-12 mg/kg (TMP dozuna göre) önerilmekte
- Duyarlılık oranı yüksek ve klinik deneyim oldukça fazla

Tigesiklin tedavide TMP-SMX'e başarılı bir alternatif

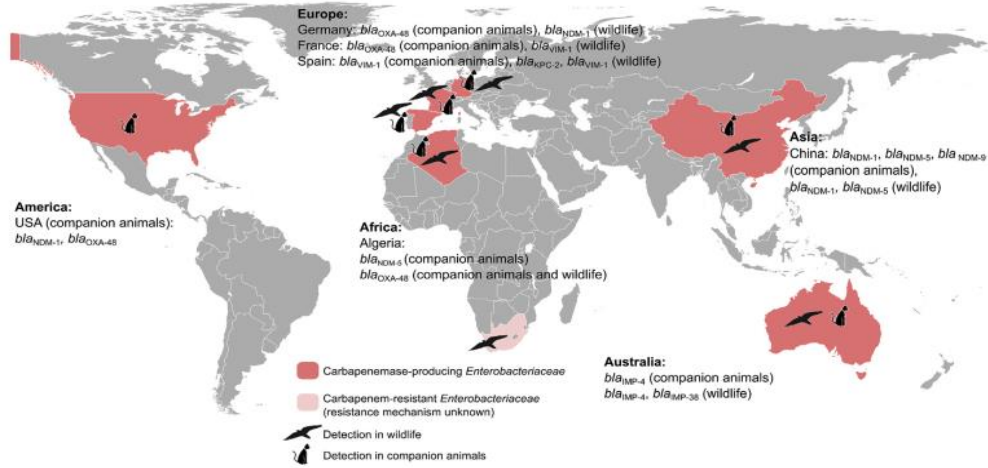
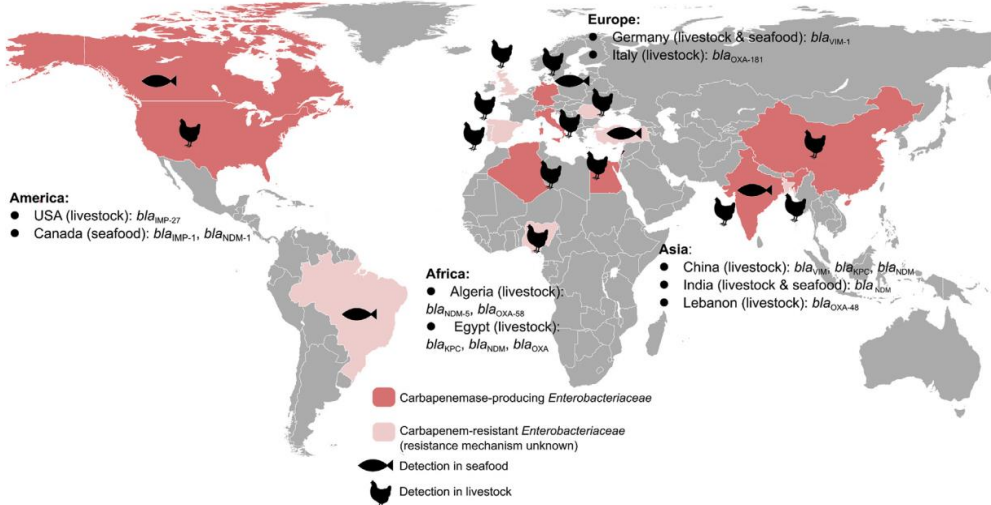
- TMP-SMX monoterapisi ile tigesiklin monoterapisini karşılaştıran çalışmalarda benzer klinik ve mikrobiyolojik başarı

Levofloksasin sadece kombinasyon tedavisi dahilinde önerilmekte , monoterapi olarak önerilmiyor

- Tedavi başında duyarlı olarak saptanmasına rağmen tedavi sırasında MİK değerlerinin yükselmesi olası

Tedavide seftazidim önerilmemekte

- İntrinsik L1 ve L2 beta laktamazların seftazidimi inaktive etmesi beklenir
- %30-40 suş duyarlı görünse de klinik başarı paralel değil



Köck, R., et al. "Carbapenem-resistant Enterobacteriaceae in wildlife, food-producing, and companion animals: a systematic review." *Clinical Microbiology and Infection* 24.12 (2018): 1241-1250.

United Nations Environment Programme (2023). Bracing for Superbugs: Strengthening environmental action in the One Health response to antimicrobial resistance. Geneva

<https://www.ama.com.au/antimicrobial-resistance>

ECDC One Health Framework

May 2024

Country	1. WHO AMR focal point appointed by the ministry of health agency	2. Multisectoral and One Health collaboration/coordination	3. AMR action plan developed	4. National surveillance system for AMR in humans	5. Submitted data to a regional network for AMR surveillance, for the year 2021	6. Participated in a regional EQA scheme, for the year 2021/2	7. Enrolled in GLASS	8. IPC in human healthcare	9. Optimising antimicrobial use in human health
Türkiye	Yes	Poor	Yes	Very good	Yes	Yes	Yes	Excellent	Fair



