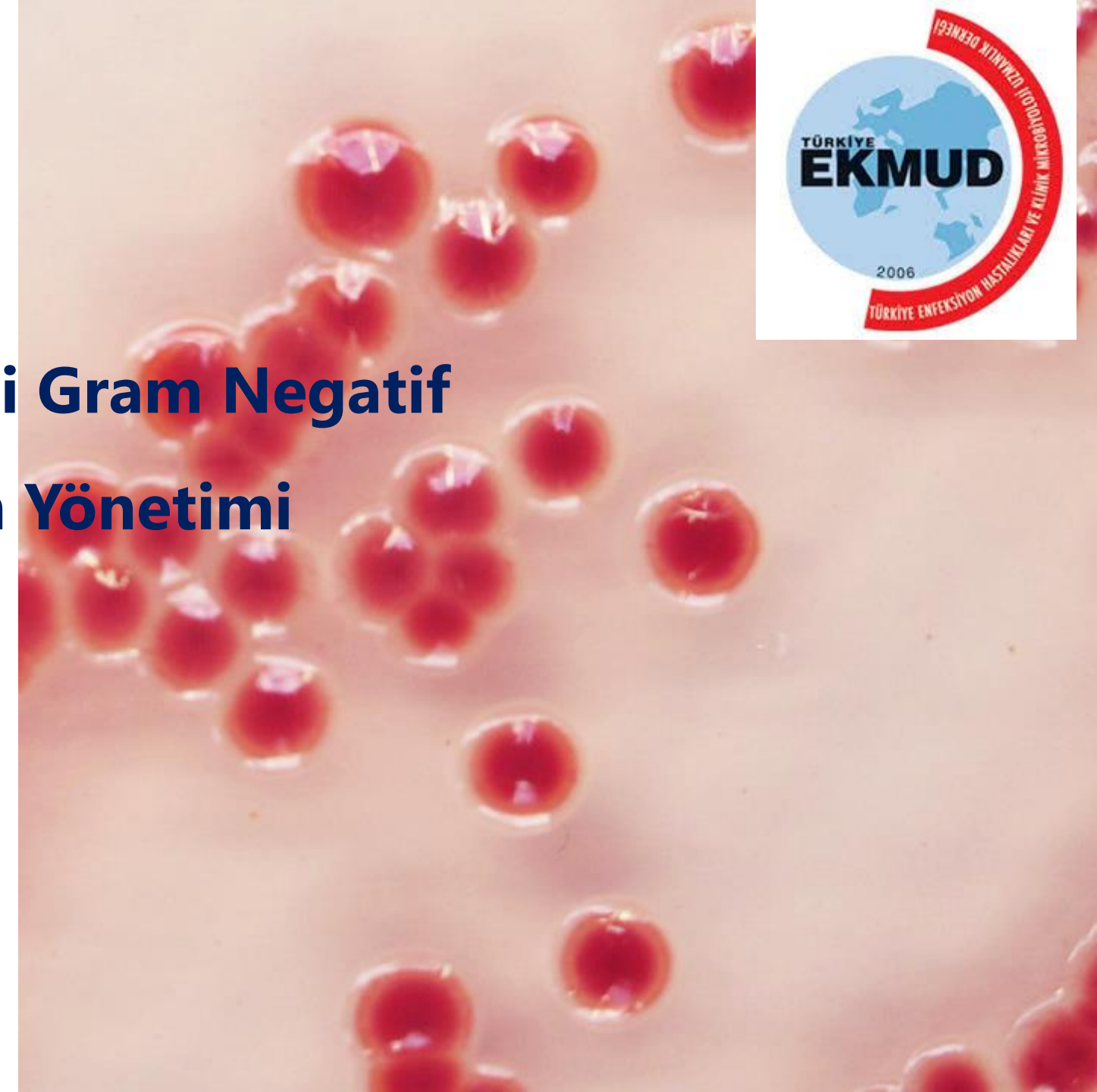
SAĞLIK BİLİMLERİ ÜNİVERSİTESİ

TÜRKİYE EKMUD 2006



Sık Rastladığımız Dirençli Gram Negatif Bakteri Enfeksiyonlarının Yönetimi

Acinetobacter spp.

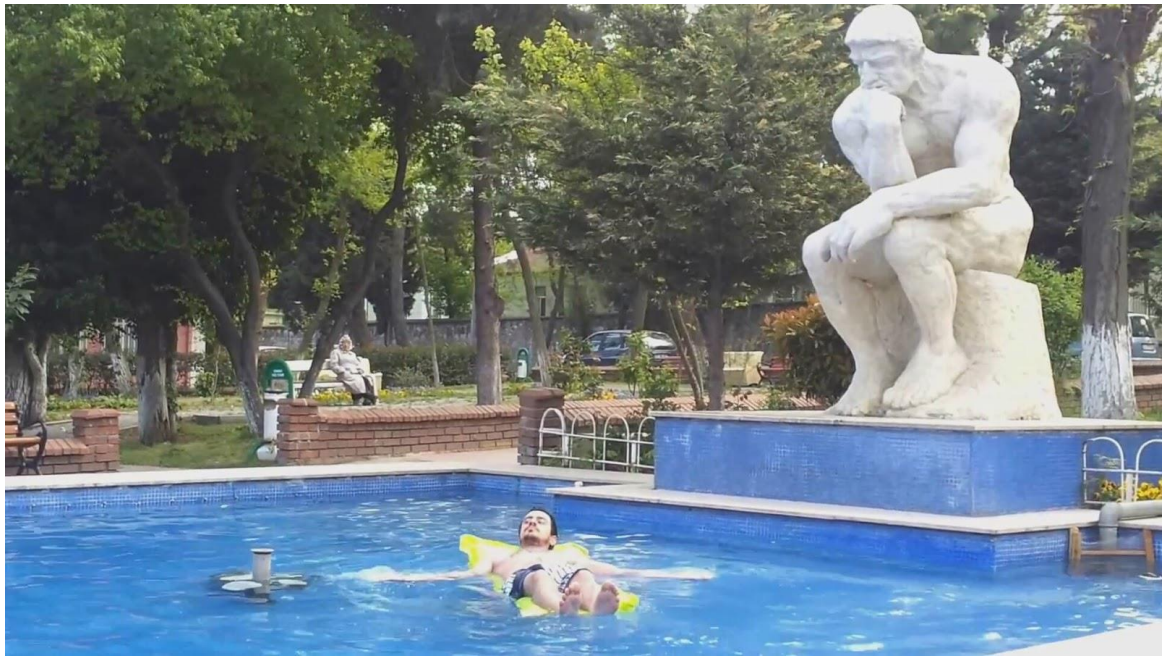
Dr. Kadriye KART YAŞAR

SBÜ Bakırköy Dr. Sadi Konuk EAH

12. EKMUD Bilimsel Kongresi

Devam eden sorunlar…

- **Çoklu ilaç direnci giderek artıyor! MDR-XDR-PDR-DTR…**
- **Direnç mekanizmaları ve lokal direnç verileri**
- **Klinik Mikrobiyoloji Laboratuvarlarının rolü**
- **Mevcut ilaçların PK/PD özellikleri ve etkinlikleri**
  - **Kolistin, polimiksin B**
  - **Tigesiklin**
  - **Sulbaktam**
  - **Minosiklin? Rifampisin? TMP-SXT?**
- **Yeni uygulama yolları**
- **Uzamış yüksek doz karbapenem infüzyonu?**
- **Son dekatta kullanıma giren ajanlarla ilgili belirsizlikler**



Multidrug-resistant, extensively drug-resistant and pandrug-resistant bacteria: an international expert proposal for interim standard definitions for acquired resistance

A.-P. Magiorakos[1], A. Srinivasan[2], R. B. Carey[2], Y. Carmeli[3], M. E. Falagas[4,5], C. G. Giske[6], S. Harbarth[7], J. F. Hindler[8], G. Kahlmeter[9], B. Olsson-Liljequist[10], D. L. Paterson[11], L. B. Rice[12], J. Stelling[13], M. J. Struelens[1], A. Vatopoulos[14], J. T. Weber[2] and D. L. Monnet[1]

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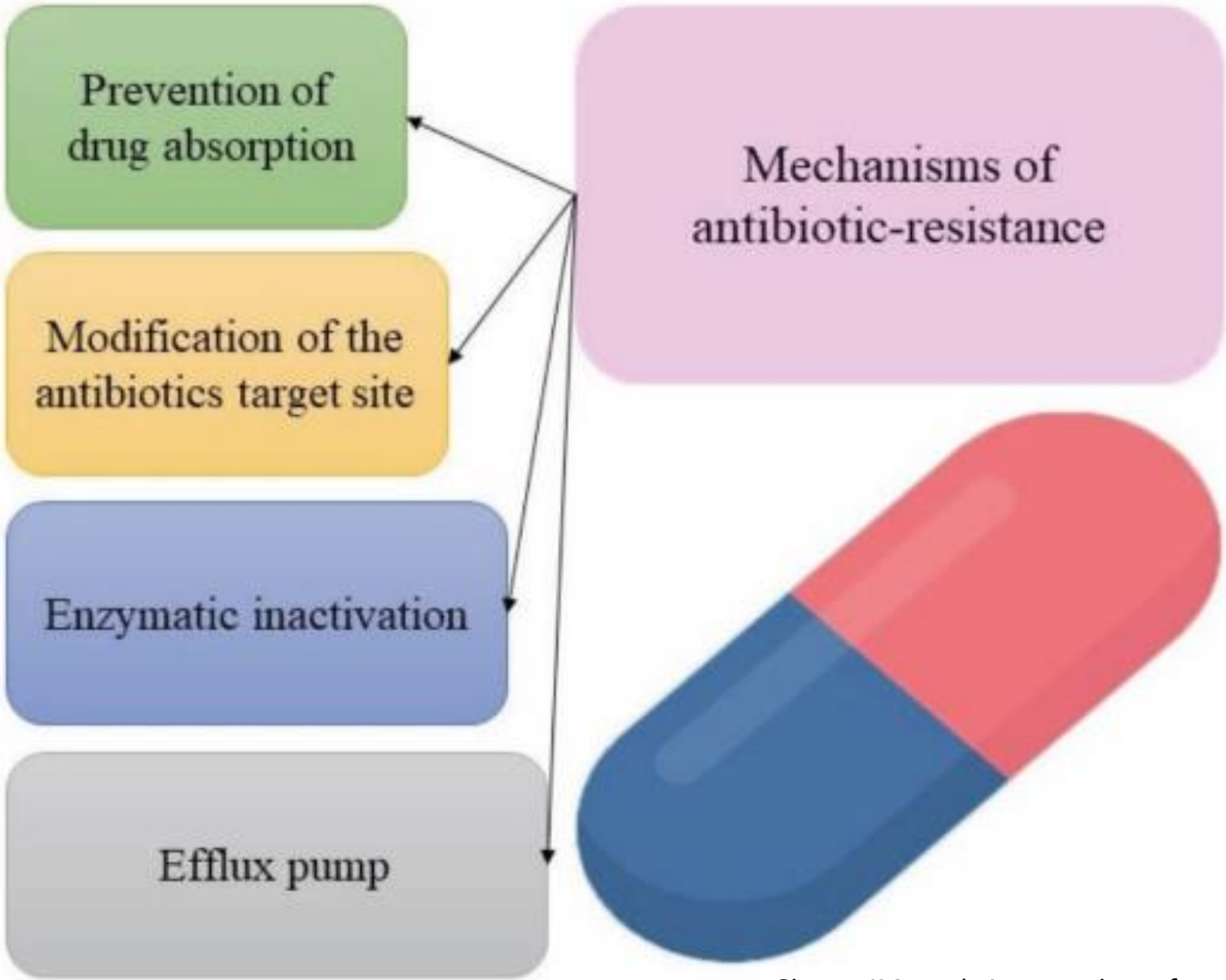
10.1111/j.1469-0691.2011.03570.x

Abstract

Many different definitions for multidrug-resistant (MDR), extensively drug-resistant (XDR) and pandrug-resistant (PDR) bacteria are being used in the medical literature to characterize the different patterns of resistance found in healthcare-associated, antimicrobial-resistant bacteria. A group of international experts came together through a joint initiative by the European Centre for Disease Prevention and Control (ECDC) and the Centers for Disease Control and Prevention (CDC), to create a standardized international terminology with which to describe acquired resistance profiles in *Staphylococcus aureus*, *Enterococcus* spp., *Enterobacteriaceae* (other than *Salmonella* and *Shigella*), *Pseudomonas aeruginosa* and *Acinetobacter* spp., all bacteria often responsible for healthcare-associated infections and prone to multidrug resistance. Epidemiologically significant antimicrobial categories were constructed for each bacterium. Lists of antimicrobial categories proposed for antimicrobial susceptibility testing were created using documents and breakpoints from the Clinical Laboratory Standards Institute (CLSI), the European Committee on Antimicrobial Susceptibility Testing (EUCAST) and the United States Food and Drug Administration (FDA). MDR was defined as acquired non-susceptibility to at least one agent in three or more antimicrobial categories, XDR was defined as non-susceptibility to at least one agent in all but two or fewer antimicrobial categories (i.e. bacterial isolates remain susceptible to only one or two categories) and PDR was defined as non-susceptibility to all agents in all antimicrobial categories. To ensure correct application of these definitions, bacterial isolates should be tested against all or nearly all of the antimicrobial agents within the antimicrobial categories and selective reporting and suppression of results should be avoided.



Sierra, JM et al. An overview of antimicrobial peptides and the latest advances in their development. Expert Opinion on Biological Therapy 2017; 17(6), 663–676.

Table 2: Definitions for the determination of Multi-Drug-, Extensively Drug-, Pan-Drug Resistant Organisms in select organisms

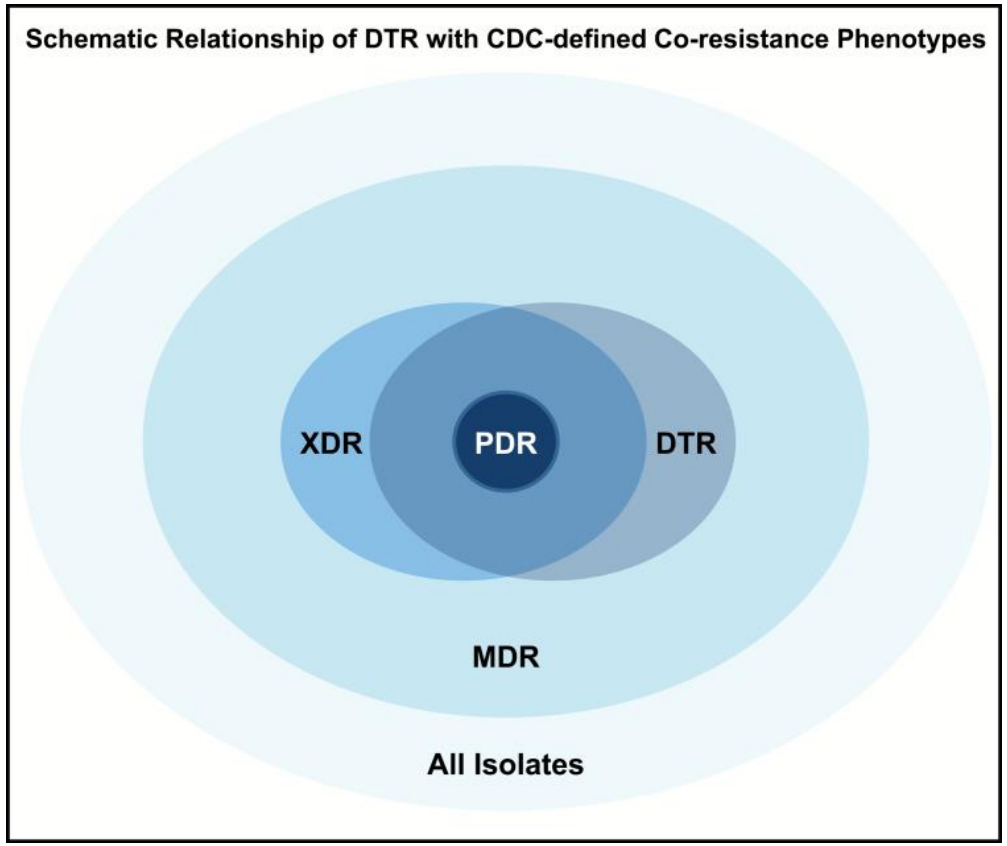
MDRO		XDRO / PDRO	
Definition	Antimicrobial Groups	Definitions	Antimicrobial Groups
Organism: *Pseudomonas aeruginosa*			
Resistance to **THREE** of the **FIVE** antimicrobial groups	Ciprofloxacin	Resistance to **FOUR** of the **SIX** antimicrobial groups = XDRO Resistance to **SIX** of the **SIX** antimicrobial groups = PDRO	Tobramycin
	Piperacillin-tazobactam **OR** piperacillin		Piperacillin-tazobactam **OR** piperacillin
	Ceftazidime **OR** cefepime		Imipenem **OR** meropenem **OR** doripenem
	Imipenem **OR** meropenem		Cefepime **OR** ceftazidime
	Tobramycin		Ciprofloxacin
			Colistin
Organism: *Acinetobacter* spp.			
Resistance to **THREE** of the **FIVE** antimicrobial groups	Ciprofloxacin	Resistance to **SIX** of the **EIGHT** antimicrobial groups = XDRO Resistance to all groups = PDRO	Gentamicin **OR** tobramycin
	Piperacillin-tazobactam		Piperacillin-tazobactam
	Ceftazidime **OR** cefepime		Imipenem **OR** meropenem **OR** doripenem
	Imipenem **OR** meropenem		Cefepime **OR** ceftazidime
	Tobramycin		Ciprofloxacin
			Colistin
			Doxycycline **OR** minocycline
			Trimethoprim-sulfamethoxazole
Organism: *Stenotrophomonas maltophilia*			
Resistance to **BOTH** antimicrobial groups	Trimethoprim-sulfamethoxazole	Resistance to the **FIRST THREE antimicrobial groups = XDRO** **Resistance to all** antimicrobial groups = PDRO	Trimethoprim-sulfamethoxazole
	Minocycline **OR** levofloxacin		Minocycline
			Levofloxacin
			Ceftazidime
			Chloramphenicol

Abbreviations: MRDO, multi-drug resistant organsims; XDRO, extensively drug resistant organisms; PDRO, pan-drug resistant organisms

Clinical Infectious Diseases
MAJOR ARTICLE

Difficult-to-Treat Resistance in Gram-negative Bacte
at 173 US Hospitals: Retrospective Cohort Analysis
Prevalence, Predictors, and Outcome of Resistanc
First-line Agents

Sameer S. Kadri,[1,2,a], Jennifer Adjemian,[3,4,a] Yi Ling Lai,[3] Alicen B. Spaulding,[3] Emily Ricotta,[3] D. Rebecca Prevots,[3] Tara N. Palmo
Michael Klompas,[6,7] John P. Dekker,[8] John H. Powers III,[9] Anthony F. Suffredini,[1] David C. Hooper,[2] Scott Fridkin,[10] and Robert L. I
Institutes of Health Antimicrobial Resistance Outcomes Research Initiative (NIH–ARORI)



DTR-AB: Tedavisi zor AB

- Birinci seçenek ilaçlara I/R
- CRAB suşlarının %18,4'ü DTR
- Duyarlı ajanların PK/PD problemleri kaynaklı etkisizlik
- Duyarlı ama enfeksiyon alanına ulaşamayan ajanlar
- Duyarlı, enfeksiyon alanında etkin ama toksisitesi yüksek ajanlar

CDC's Antibiotic Resistance Threats Report, 2019

Michael Craig
Senior Advisor for Antibiotic Resistance
Centers for Disease Control and Prevention

Current Antibiotic Resistance Threats in the U.S.

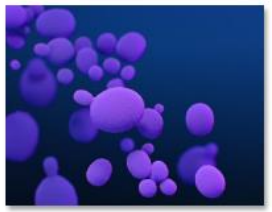
Urgent Threats

- Carbapenem-resistant *Acinetobacter*
- *Candida auris*
- *C. difficile*
- Carbapenem-resistant *Enterobacteriaceae*
- Drug-resistant *Neisseria gonorrhoeae (N. gonorrhoeae)*

Serious Threats

Concerning Threats

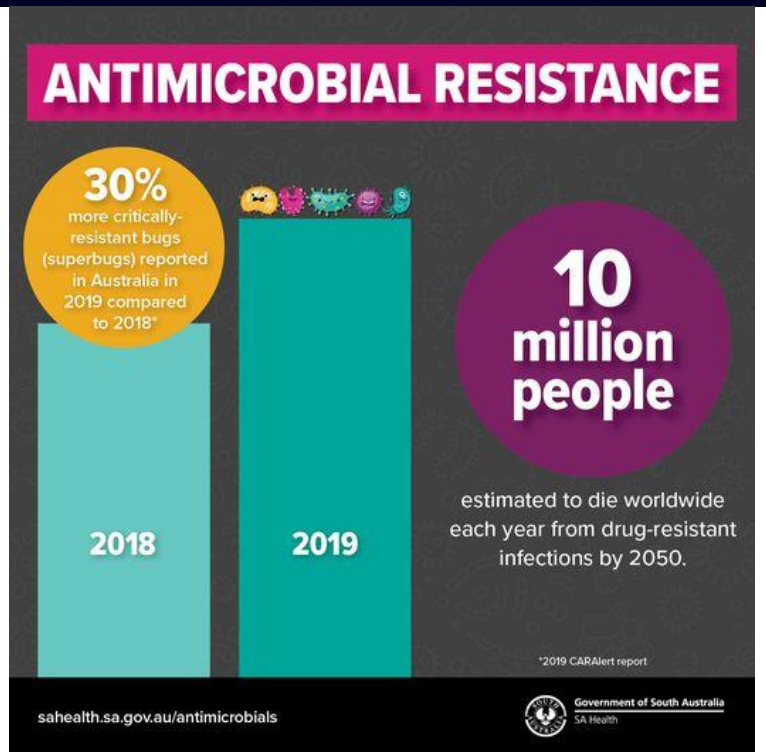
Since 2013, Ranking of Three Germs Shifted



- *C. auris*
  - Not listed in 2013. Listed as Urgent in 2019.
- Carbapenem-resistant *Acinetobacter*
  - Listed as Serious (as Multidrug-resistant *Acinetobacter*) in 2013. Listed as Urgent in 2019.
- Vancomycin-resistant *Staphylococcus aureus* (VRSA)
  - Listed as Concerning in 2013. Removed as a threat in 2019.

www.cdc.gov/DrugResistance

Source: *Lancet*, Antimicrobial Resistance Collaborators



Acinetobacter spp.

- ***Acinetos:*** Hareketsiz, **bactrum:** Bakteri
- Gram negatif non-fermentatif, **zorunlu aerop**, kokobasil
- Katalaz pozitif, **oksidaz negatif**, **hareketsiz**, penisiline dirençli bakteriler
- Doğada yaygın olarak **toprak, su, kanalizasyon ve besinlerde** bulunur
- İnsanların cilt, mukozası veya sekresyonlarından, hastane ortamı ve gereçlerinden izole edilmiş
- Günümüze dek 50'den fazla tür tanımlanmış olsa da klinik örneklerden en sık ***A.baumannii, A.calcoaceticus, A.lwoffii, A.haemolyticus, A.junii, A.johnsonii*** izole edilir
- ***A. calcoaceticus-baumannii kompleksi (ACB),*** bazen *Acinetobacter* türlerini fenotipik özelliklere dayanarak ayırt etmenin zor olması nedeniyle kullanılır
- Sıklıkla kommensal bir cins ancak, özellikle **YBÜ'de nozokomiyal enfeksiyonlara** yol açar

- En virülan ve en sık izole edilen tür ***A.baumannii***
- *Acinetobacter spp.* özellikle YBÜ'deki hastalar arasında, **sağlık bakımıyla ilişkili enfeksiyonlarla** ilişkisi nedeniyle en çok bilinen bakteridir.
- Bununla birlikte, Asya ve Avustralya'da toplumdan edinilen enfeksiyonların yanı sıra **savaşlar ve doğal afetlerle ilgili enfeksiyonlarla** da ilişkilendirilmiştir.
  - Ventilatörle ilişkili pnömoni izolatları (% 12,8)
  - Merkezi hatla ilişkili kan dolaşımı enfeksiyonu izolatları (% 8,8)
  - Kateterle ilişkili idrar yolu enfeksiyonu izolatları (% 1,3)
  - Cerrahi alan enfeksiyonu izolatları (% 1,3)

ELSEVIER

Journal of Hospital Infection

Volume 51, Issue 1, May 2002, Pages 47-51

Regular Article

Hospital-acquired infections following the 1999 Marmara earthquake

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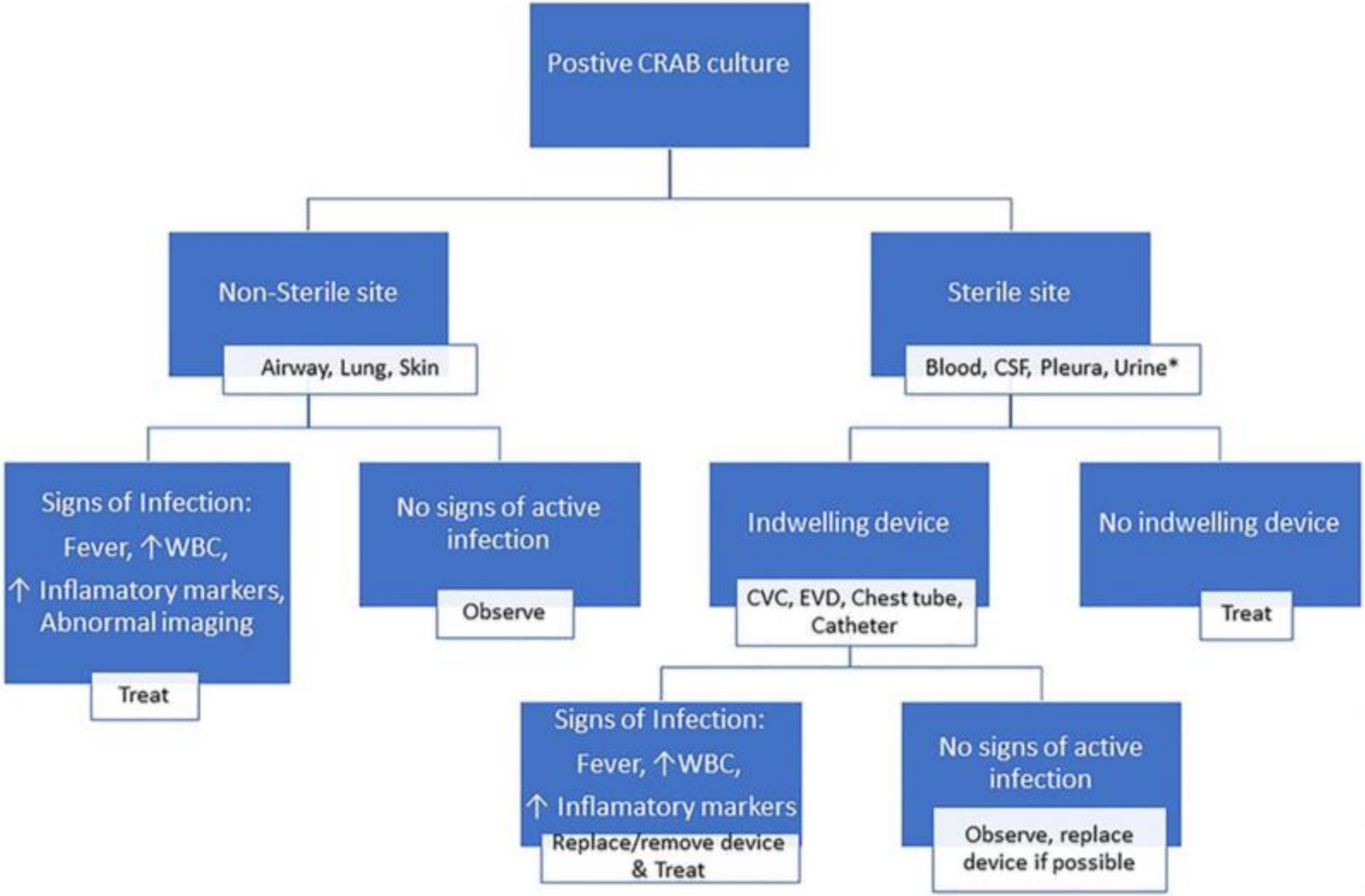
Show more

https://doi.org/10.1053/jhin.2002.1205

Abstract

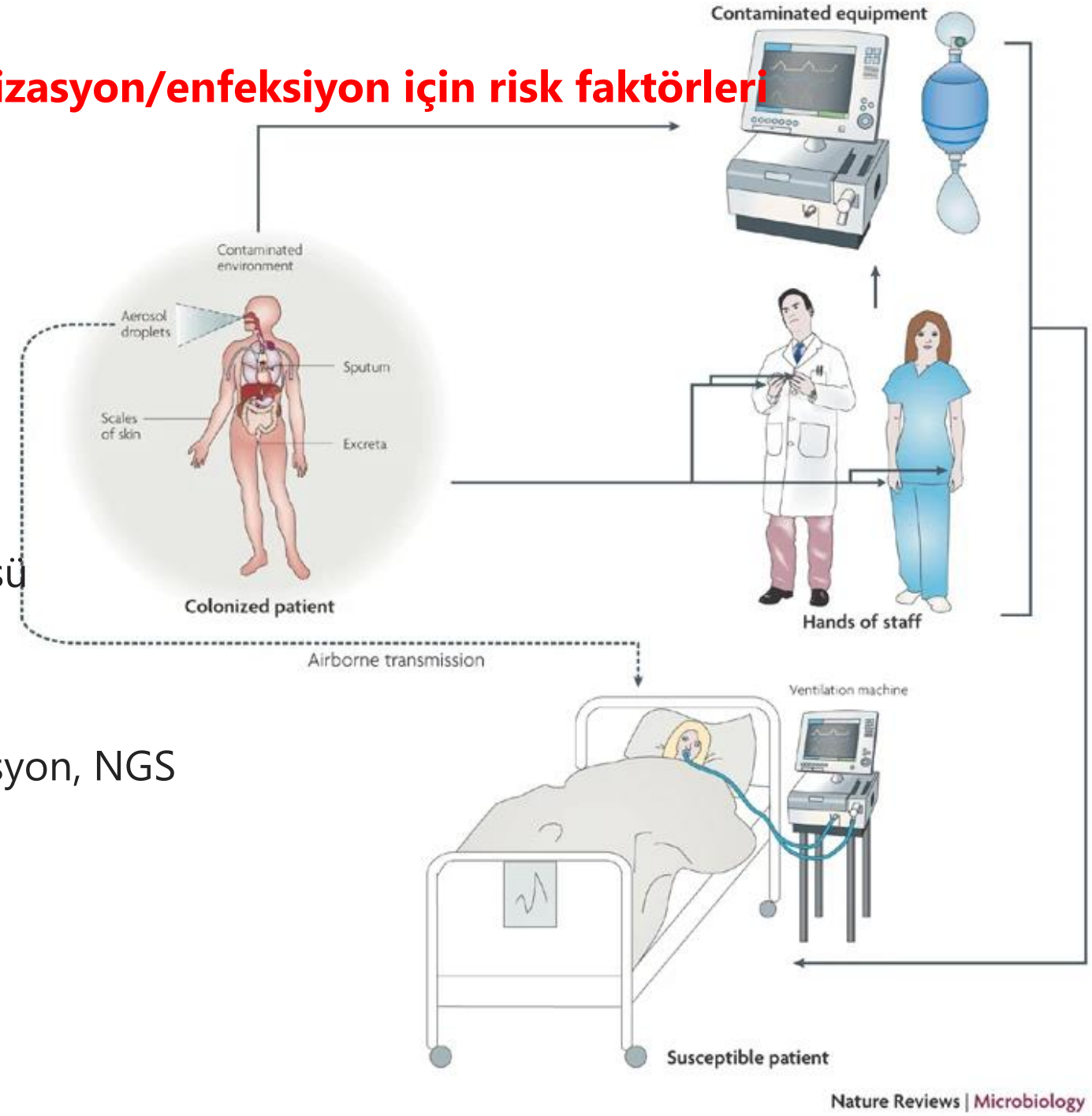
In this study, medical records of all casualties admitted to our hospital following the Marmara earthquake, which struck northwest Turkey and resulted in the destruction of several towns in the Marmara region, were evaluated retrospectively. The time buried under the rubble, demographic data, type of medical and surgical therapies performed, type of injury and data on infection were analysed. Between 17 August and 25 September 1999, 630 trauma victims were received at our hospital and 532 (84%) of them were hospitalized. The mean age of hospitalized patients (312 males, 220 females) was 32 years (2–90 years). Two hundred and twenty patients were hospitalized for more than 48 h. Forty-one of them (18.6%) had 43 hospital-acquired infection (HAI) episodes, which were mostly wound infections (46.5%). A total of 143 culture specimens was collected and 48 yielded the following potential pathogens: 15 *Acinetobacter baumanii* (31.2%), nine *Staphylococcus aureus* (18.7%), seven *Pseudomonas aeruginosa* (14.6%), six *Escherichia coli* (12.5%), six *Klebsiella pneumoniae* (12.5%), two *Stenotrophomonas maltophilia* (4.2%) and three various *Pseudomonas* spp. (6.3%). All *S. aureus* strains were found to be resistant to

- Hasta
ilişkili
- Ürine
enfek
- İnsan
kanal
enfel



MDR *Acinetobacter spp.* ile kolonizasyon/enfeksiyon için risk faktörleri

- Önceki *A.baumannii* kolonizasyonu
- Başvuruda solunum yetmezliği
- MRSA kolonizasyonu
- Önceki AB kullanımı (MEM, SS, FQ)
- Yatalak olma, operasyon, hemodiyaliz öyküsü
- Uzamış veya önceki YBÜ yatışı
- SVK, mekanik ventilasyon, üriner kateterizasyon, NGS
- Geniş yüzeyli yanık veya immunosupresyon
- Ko-morbidite varlığı
- İleri yaş



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	%	
E. coli	Aminopenicillin (amoxicillin/ampicillin) resistance	3652	77.7	4154	76.7	4290	78.8	3562	76.1	4365	74.8	↓*
	Third-generation cephalosporin (cefotaxime/ceftriaxone/ceftazidime) resistance	4337	52.7	4923	53.2	4847	54.7	4342	53.4	4852	50.2	↓*
	Carbapenem (imipenem/meropenem) resistance	4321	2.7	4759	2.6	4966	3.0	4347	3.7	4551	4.7	↑*
	Fluoroquinolone (ciprofloxacin/levofloxacin/ofloxacin) resistance	4022	52.3	4606	52.2	4853	51.7	4193	50.1	4707	50.9	↓
	Aminoglycoside (gentamicin/tobramycin) resistance	4083	26.6	4785	24.4	4617	25.8	4211	23.7	4569	24.6	↓
	Combined resistance to third-generation cephalosporins, fluoroquinolones and aminoglycosides	3755	18.8	4477	17.7	4496	18.3	4078	16.5	4395	15.9	↓*
K. pneumoniae	Third-generation cephalosporin (cefotaxime/ceftriaxone/ceftazidime) resistance	3157	72.0	3766	72.0	3977	74.0	4501	76.9	4738	75.4	↑*
	Carbapenem (imipenem/meropenem) resistance	3165	32.5	3641	34.4	4028	39.4	4517	48.2	4421	49.1	↑*
	Fluoroquinolone (ciprofloxacin/levofloxacin/ofloxacin) resistance	3009	61.1	3557	62.6	3933	64.8	4276	69.0	4483	68.6	↑*
	Aminoglycoside (gentamicin/tobramycin) resistance	2991	44.6	3632	45.9	3925	44.8	4405	46.6	4482	43.2	-
	Combined resistance to third-generation cephalosporins, fluoroquinolones and aminoglycosides	2821	38.9	3442	39.9	3689	40.5	4156	43.3	4203	38.7	-
P. aeruginosa	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	-
Acinetobacter spp.	Carbapenem (imipenem/meropenem) resistance	2540	91.5	2643	92.2	2390	90.4	3165	93.1	3279	93.3	↑
	Fluoroquinolone (ciprofloxacin/levofloxacin) resistance	2505	92.6	2575	94.4	2391	90.7	3064	93.6	3233	94.6	↑
	Aminoglycoside (gentamicin/tobramycin) resistance	2558	78.3	2704	79.1	2404	80.3	3117	86.1	3405	85.3	↑*
	Combined resistance to carbapenems, fluoroquinolones and aminoglycosides	2421	77.8	2526	79.3	2362	79.6	3039	84.7	3089	84.8	↑*
S. aureus	MRSA[d]	3142	25.8	3316	29.6	3407	31.3	3591	33.4	3562	30.7	↓*
S. pneumoniae	Penicillin non-wild-type[e]	213	46.0	243	43.6	212	50.9	128	53.9	147	53.7	↑
	Macrolide (azithromycin/clarithromycin/erythromycin) resistance	205	39.5	217	37.3	211	37.0	119	34.5	126	34.1	-
	Combined penicillin non-wild-type and resistance to macrolides[e]	186	29.0	211	28.0	200	32.5	117	27.4	123	26.0	-
E. faecalis	High-level gentamicin resistance	1125	38.0	1337	36.9	1914	33.5	2040	29.6	1899	24.7	↓*
E. faecium	Vancomycin resistance	1551	13.2	1570	13.6	1797	13.3	2201	15.4	2242	15.8	↑

[a] Percentages of isolates with resistance phenotype are presented only if data are available for ≥20 isolates. If not, the percentage is presented as not applicable (NA).
[b] ↑ and ↓ indicate statistically significant increasing and decreasing trends, respectively, in the overall data; * indicates confirmation in the form of a significant trend in the data that only included laboratories reporting continuously for all five years; - indicates no statistically significant trend. NA: not applicable indicates that the data were not reported for all years, a significant change in data source occurred during the period, or the number of isolates was < 20 in any year during the period.
[c] The aminoglycoside group includes only tobramycin from 2020 onwards.
[d] MRSA is based on cefoxitin, or, if unavailable, oxacillin. If neither were available, data from molecular confirmation tests (detection of *mecA* gene by PCR or a positive PBP2A-agglutination test) are accepted as a marker for MRSA.
[e] Penicillin results are based on penicillin or, if unavailable, oxacillin. For *S. pneumoniae*, the term penicillin non-wild-type is used in this report, referring to *S. pneumoniae* isolates reported by the local laboratories as susceptible increased exposure (I) or resistant (R) to penicillin, assuming MIC to benzylpenicillin above those of wild-type isolates (> 0.06 mg/L). The qualitative susceptibility categories (S/I/R) as reported by the laboratory are used, since quantitative susceptibility information is missing for a large part of the data. Laboratories not using EUCAST clinical breakpoints may have used different interpretive criteria for susceptibility categories.

Tablo 3. Türkiye'de sağlık hizmeti ilişkili enfeksiyonların enfeksiyon türüne göre etken dağılımı, 2022.

Mikroorganizmalar	Tüm Enfeksiyonlar		Pnömoni		VİP		VİO		ÜSE		Kİ-İYE		KDE		SKİ-KDE		CAE	
	Sayı	%	Sayı	%	Sayı	%	Sayı	%	Sayı	%	Sayı	%	Sayı	%	Sayı	%	Sayı	%
Tüm mikroorganizmalar	**54030**	**100.0**	**2786**	**100.0**	**8558**	**100.0**	**1746**	**100.0**	**1608**	**100.0**	**7191**	**100.0**	**7825**	**100.0**	**16824**	**100.0**	**3338**	**100.0**
Gram pozitif koklar	**6678**	**12.4**	**117**	**4.2**	**222**	**2.6**	**53**	**3.0**	**133**	**8.3**	**564**	**7.8**	**1563**	**20.0**	**2753**	**16.4**	**706**	**21.2**
S. aureus	1658	**3.1**	91	3.3	164	1.9	40	2.3	9	0.6	35	0.5	440	5.6	449	2.7	266	8.0
Koagülaz negatif stafilokoklar	1678	**3.1**	8	0.3	14	0.2	4	0.2	2	0.1	9	0.1	339	4.3	920	5.5	209	6.3
***Enterococcus* spp**	3167	**5.9**	8	0.3	20	0.2	4	0.2	121	7.5	512	7.1	739	9.4	1345	8.0	215	6.4
***Streptococcus* spp**	131	**0.2**	10	0.4	19	0.2	4	0.2	1	0.1	5	0.1	30	0.4	25	0.1	14	0.4
Diğer gram (+) koklar	44	**0.1**	0	0.0	5	0.1	1	0.1	0	0.0	3	0.0	15	0.2	14	0.1	2	0.1
Gram (-) koklar	**2**	**0.0**	**0**	**0.0**	**0**	**0.0**	**0**	**0.0**	**0**	**0.0**	**0**	**0.0**	**1**	**0.0**	**1**	**0.0**	**0**	**0.0**
Gram (+) basiller	**148**	**0.3**	**23**	**0.8**	**40**	**0.5**	**4**	**0.2**	**0**	**0.0**	**1**	**0.0**	**11**	**0.1**	**30**	**0.2**	**20**	**0.6**
Enterobacterales	**16951**	**31.4**	**895**	**32.1**	**2319**	**27.1**	**461**	**26.4**	**845**	**52.5**	**3472**	**48.3**	**2058**	**26.3**	**4340**	**25.8**	**1225**	**36.7**
***Citrobacter* spp**	86	**0.2**	7	0.3	7	0.1	2	0.1	5	0.3	11	0.2	14	0.2	17	0.1	15	0.4
***Enterobacter* spp**	1025	**1.9**	63	2.3	130	1.5	15	0.9	38	2.4	186	2.6	123	1.6	254	1.5	120	3.6
Escherichia coli	3197	**5.9**	103	3.7	186	2.2	33	1.9	313	19.5	1004	14.0	404	5.2	457	2.7	445	13.3
***Klebsiella* spp**	11259	**20.8**	668	24.0	1820	21.3	378	21.6	445	27.7	2013	28.0	1341	17.1	3195	19.0	536	16.1
***Proteus* spp**	596	**1.1**	24	0.9	85	1.0	18	1.0	29	1.8	167	2.3	40	0.5	129	0.8	46	1.4
***Serratia* spp**	548	**1.0**	28	1.0	68	0.8	11	0.6	10	0.6	26	0.4	112	1.4	226	1.3	30	0.9
Diğer Enterobacterales'ler	240	**0.4**	2	0.1	23	0.3	4	0.2	5	0.3	65	0.9	24	0.3	62	0.4	33	1.0
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**
***Acinetobacter* spp**	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
***Pseudomonas* spp**	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
***Stenotrophomonas* spp**	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
***Burkholderia* spp**	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
***Haemophilus* spp**	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
Diğer 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

Tablo 4. *Acinetobacter baumannii*'nin etken olduğu sağlık hizmeti ilişkili pnömoni tanıları için antibiyogram sonuç dağılımı, 2022.

Antibiyotik	Bağışıklık sistemi baskılanmış hastada pnömoni			Spesifik laboratuvar bulguları olan pnömoni			Ventilatör ilişkili pnömoni			Ventilatör İlişkili Olay			Toplam		
	Dirençli	Toplam	Dirençli %	Dirençli	Toplam	Dirençli %	Dirençli	Toplam	Dirençli %	Dirençli	Toplam	Dirençli %	Dirençli	Toplam	Dirençli %
Amikasin	19	21	**90.5**	634	745	**85.1**	2196	2547	**86.2**	581	705	**82.4**	3430	4018	**85.4**
Gentamisin	15	18	**83.3**	581	664	**87.5**	1996	2257	**88.4**	578	648	**89.2**	3170	3587	**88.4**
İmipenem	18	18	**100.0**	662	678	**97.6**	2231	2303	**96.9**	648	658	**98.5**	3559	3657	**97.3**
Kolistin	2	18	**11.1**	38	520	**7.3**	127	1747	**7.3**	38	457	**8.3**	205	2742	**7.5**
Levofloksasin	14	15	**93.3**	518	530	**97.7**	1746	1784	**97.9**	519	525	**98.9**	2797	2854	**98.0**
Meropenem	21	22	**95.5**	715	737	**97.0**	2373	2433	**97.5**	669	682	**98.1**	3778	3874	**97.5**
Netilmisin	1	1	**100.0**	26	29	**89.7**	112	128	**87.5**	33	39	**84.6**	172	197	**87.3**
Siprofloksasin	22	22	**100.0**	666	673	**99.0**	2274	2308	**98.5**	676	681	**99.3**	3638	3684	**98.8**
Tigesiklin	6	11	**54.5**	172	355	**48.5**	534	1289	**41.4**	194	407	**47.7**	906	2062	**43.9**

Tablo 6. *Acinetobacter baumannii*'nin etken olduğu sağlık hizmeti ilişkili kan dolaşımı enfeksiyonu tanıları için antibiyogram sonuç dağılımı, 2022.

Antibiyotik	Laboratuvar tarafından doğrulanmış kan dolaşımı enfeksiyonu			Santral kateter ilişkili kan dolaşımı enfeksiyonu			Toplam		
	Dirençli	Toplam	Dirençli %	Dirençli	Toplam	Dirençli %	Dirençli	Toplam	Dirençli %
Amikasin	501	664	**75.5**	1603	1937	**82.8**	2104	2601	**80.9**
Gentamisin	480	605	**79.3**	1490	1735	**85.9**	1970	2340	**84.2**
İmipenem	505	561	**90.0**	1584	1669	**94.9**	2089	2230	**93.7**
Kolistin	23	420	**5.5**	93	1272	**7.3**	116	1692	**6.9**
Levofloksasin	378	409	**92.4**	1123	1176	**95.5**	1501	1585	**94.7**
Meropenem	571	645	**88.5**	1797	1899	**94.6**	2368	2544	**93.1**
Netilmisin	26	33	**78.8**	77	85	**90.6**	103	118	**87.3**
Siprofloksasin	613	633	**96.8**	1778	1817	**97.9**	2391	2450	**97.6**
Tigesiklin	140	321	**43.6**	480	1022	**47.0**	620	1343	**46.2**

Scand J Infect Dis. 2010 Oct;42(10):741-6. doi: 10.3109/00365548.2010.489568.

Nosocomial imipenem-resistant Acinetobacter baumannii infections: epidemiology and risk factors

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Affiliations + expand

PMID: 20500117 DOI: 10.3109/00365548.2010.489568

Eur J Intern Med. 2009 Sep;20(5):540-4. doi: 10.1016/j.ejim.2009.05.005. Epub 2009 May 29.

Factors influencing survival in patients with multi-drug-resistant Acinetobacter bacteraemia

Gokhan Metan [1], Fatma Sariguzel, Bulent Sumerkan

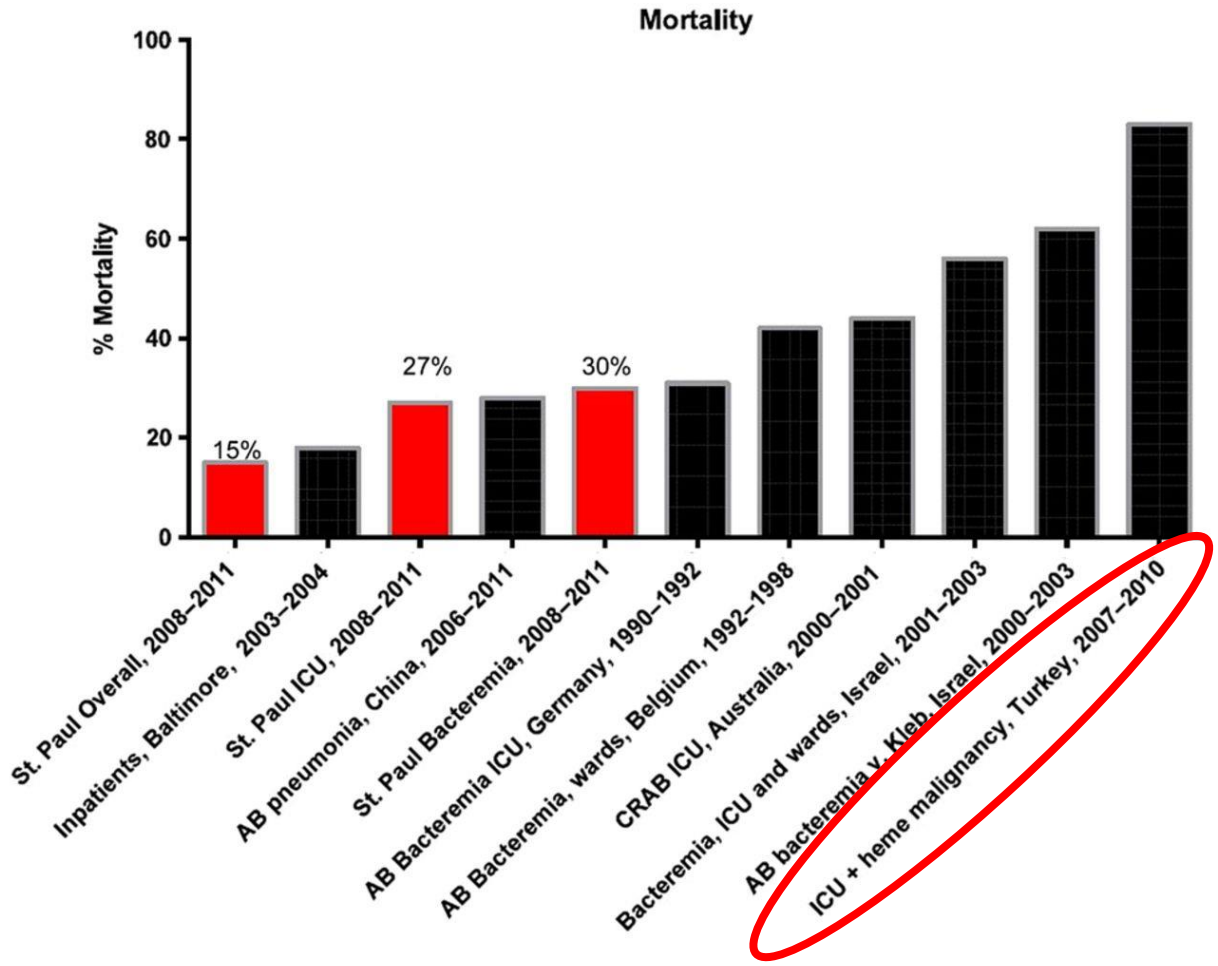
Affiliations + expand

PMID: 19712862 DOI: 10.1016/j.ejim.2009.05.005

***Acinetobacter* enfeksiyonlu hastalarda mortalite için risk faktörleri:**

İmipenem direnci, YBÜ'de kalış süresi, *Acinetobacter* kolonizasyonu, kadın cinsiyet, yaşlılık, pnömoni, diyabet ve septik şok

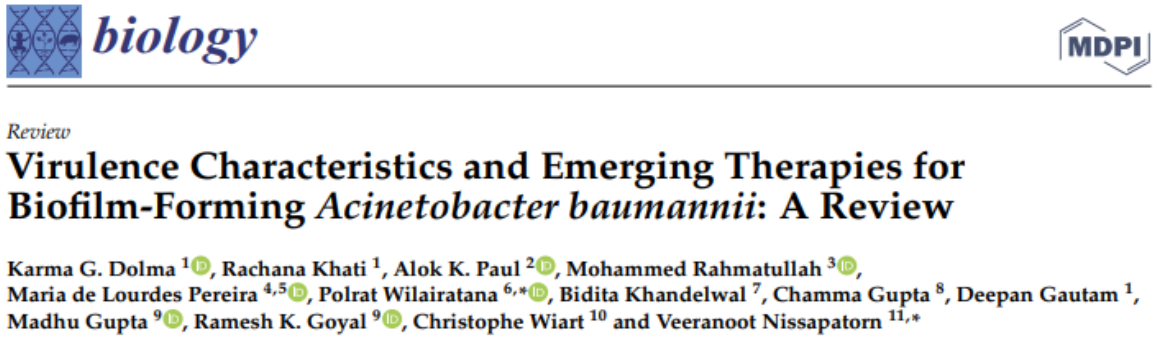
Figure 2. Comparative mortality of Acinetobacter infections in various settings worldwide.



Open Forum Infect Dis, Volume 2, Issue 1, Winter 2015, ofv023, https://doi.org/10.1093/ofid/ofv023

Virülans Faktörleri

- **Biyofilm oluşumu**
- **Dış membran proteini A (OmpA):** OmpA, sağlam bir biyofilm oluşturmak ve epitel hücrelerine tutunma için gerekli, hücre apoptozunu indükler, ayrıca alternatif kompleman yolunun bir inhibitörü olan Faktör H'nin bağlanmasına yardımcı
- **K1 kapsülü:** Suşların yaklaşık **üçte biri,** kompleman aktivasyonunu önlemek için hücre duvarı liposakkaritiyle birlikte çalışan bir polisakkarit kapsülü üretir. Kapsül fagositozu da geciktirir
- **Siderofor aracılı demir toplama sistemi:** *Acinetobacter'in* demir eksikliği koşullarında uzun süre hayatta kalabilmesi, demiri konakçıdan ayırabilen bir **katekol sideroforu olan asinetobaktin** ile sağlanır
- **Fimbrialar:** Etkenin çevresel yüzeylere bağlanmasına yardımcı, bronşiyal epitel hücrelerde kolonizasyona yardımcı
- **Lipid A ve LPS yapı**
- **Quorum sensing**
- **AB direnç genleri**



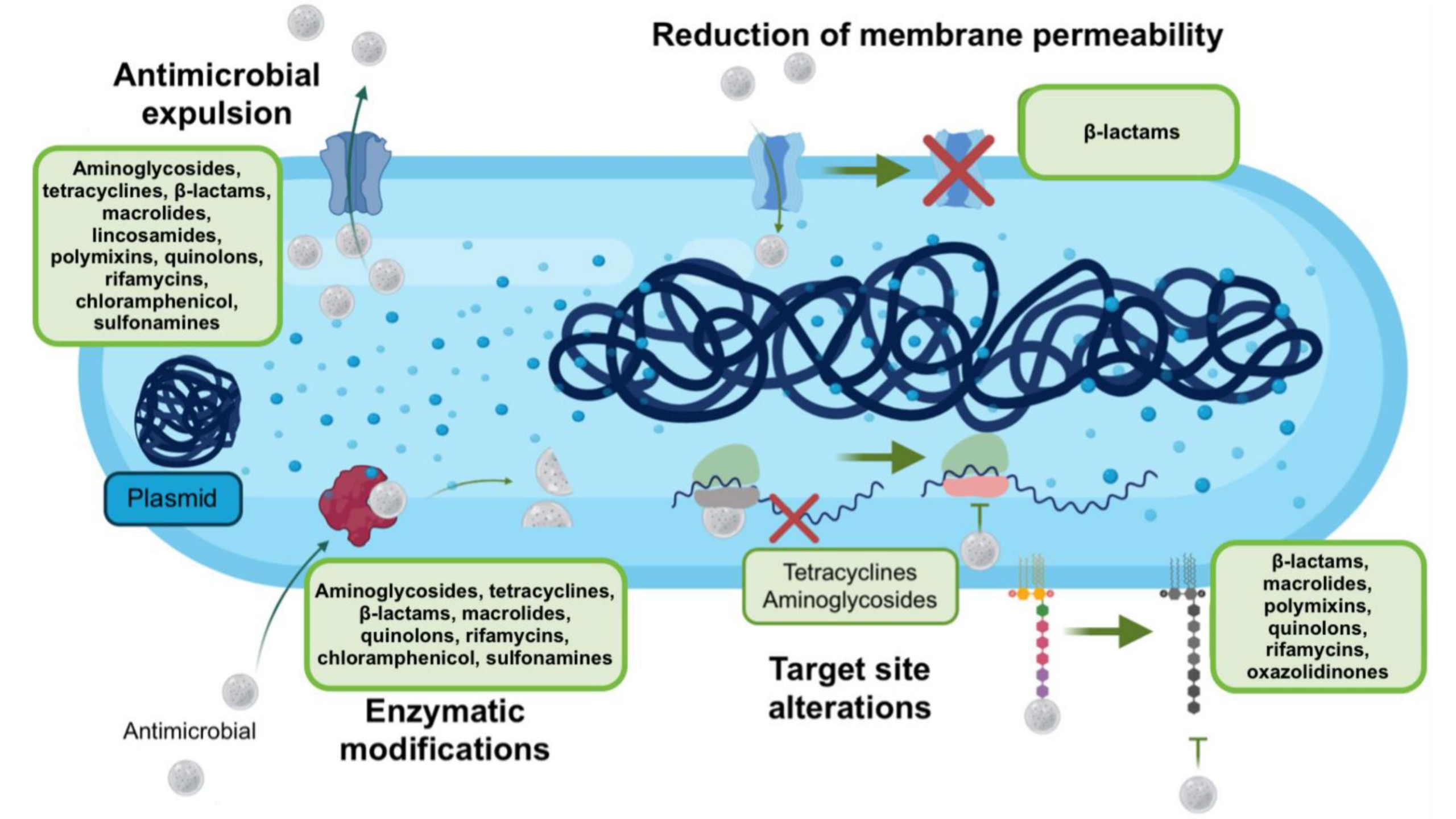

Antimicrobial expulsion
Aminoglycosides, tetracyclines, β-lactams, macrolides, lincosamides, polymixins, quinolons, rifamycins, chloramphenicol, sulfonamines
Plasmid
Antimicrobial
Aminoglycosides, tetracyclines, β-lactams, macrolides, quinolons, rifamycins, chloramphenicol, sulfonamines
Enzymatic modifications
Reduction of membrane permeability
β-lactams
Tetracyclines
Aminoglycosides
Target site alterations
β-lactams, macrolides, polymixins, quinolons, rifamycins, oxazolidinones

Table I. Mechanisms of resistance employed by *Acinetobacter baumannii*.

Antibiotic	Resistance mechanism	Enzyme or target	Key point
β-lactams	β-lactamases	Ambler class A	TEM, SHV, CTX-M, KPC
		Ambler class B	NDM, VIM, SIM, IMP
		Ambler class C	AmpC, ADC
		Ambler class D	OXA
	Permeability lesions	Outer membrane porin	CarO
			OmpA
	Efflux pump overactivity	RND pump	AdeABC
Tetracyclines	Efflux pump overactivity	RND pump	AdeABC, AdeIJK
		Tet pump	TetA, TetG
Quinolones	Target mutation	DNA gyrase	GyrA
		DNA topoisomerase IV	ParC
	Efflux pump overactivity	RND pump	AdeABC
Aminoglycosides	Drug inactivating enzymes	Aminoglycoside modifying enzymes	aadB, apa6, aadA, aacc1
	Target mutation	16s RNA methylase genes	armA
	Efflux pump overactivity	RND pumps	AdeABC
Polymyxins	Target mutation	Abnormalities of lipid A and LPS	PmrC, PmrB, lpx gene

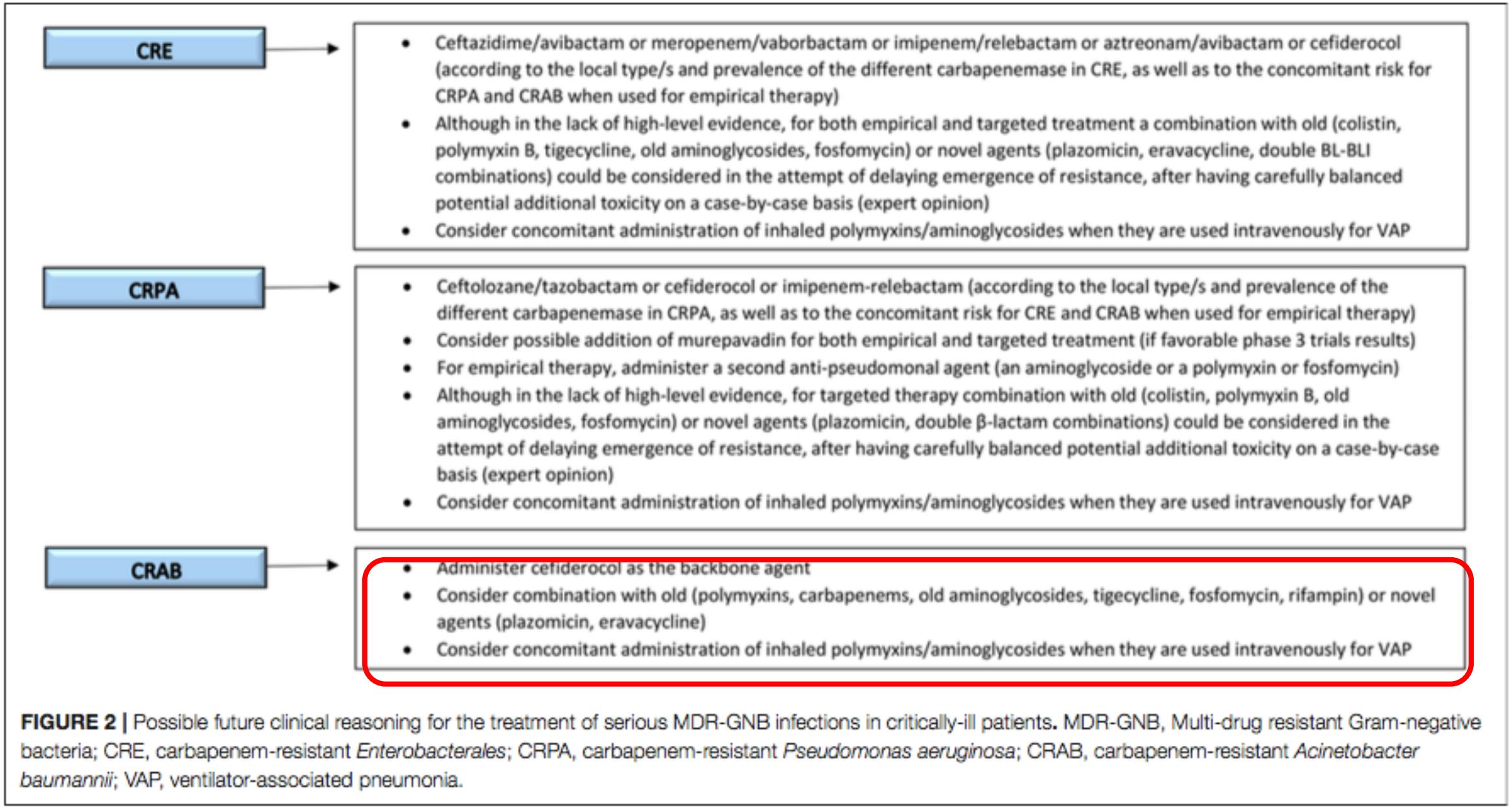


FIGURE 2 | Possible future clinical reasoning for the treatment of serious MDR-GNB infections in critically-ill patients**.** MDR-GNB, Multi-drug resistant Gram-negative bacteria; CRE, carbapenem-resistant *Enterobacterales*; CRPA, carbapenem-resistant *Pseudomonas aeruginosa*; CRAB, carbapenem-resistant *Acinetobacter baumannii*; VAP, ventilator-associated pneumonia.

Karbapenemler

Kolistin

Polimiksin B

Aminoglikozitler

TMP-SXT

Sefiderokol

Plazomisin

Eravasiklin

Sulbaktam-Durlobaktam

Intensive Care Med (2015) 41:2057–2075
DOI 10.1007/s00134-015-4079-4

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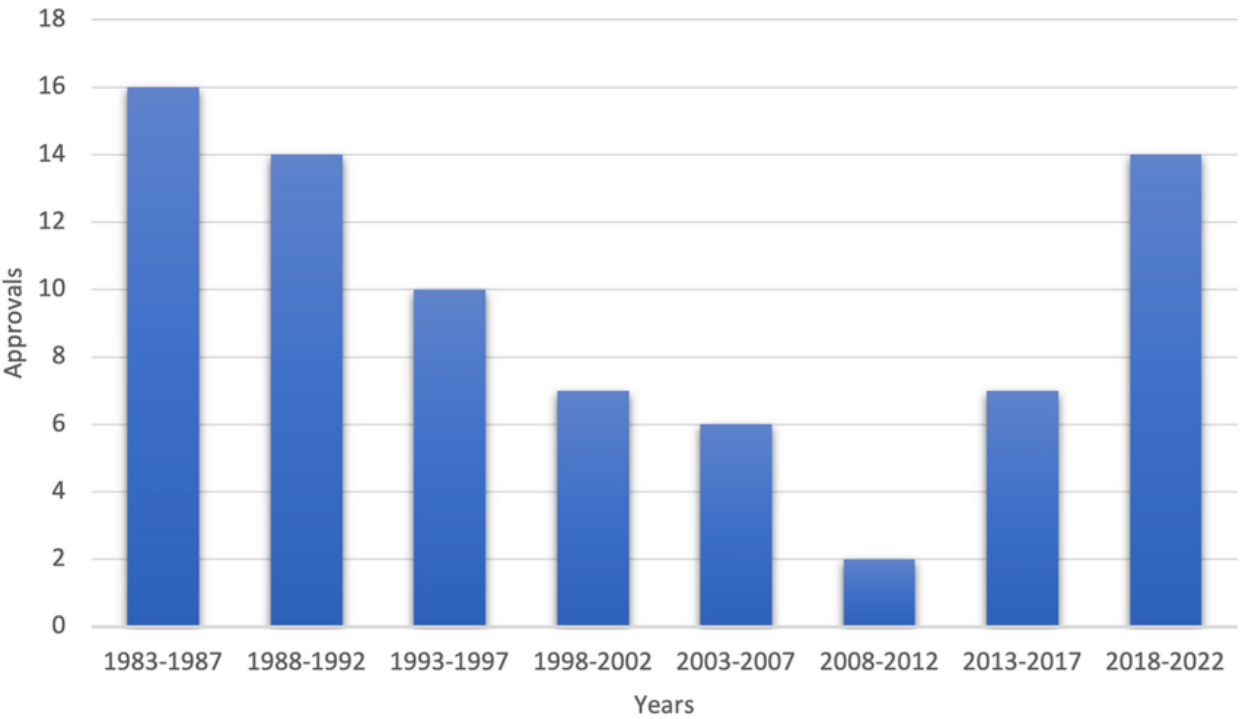
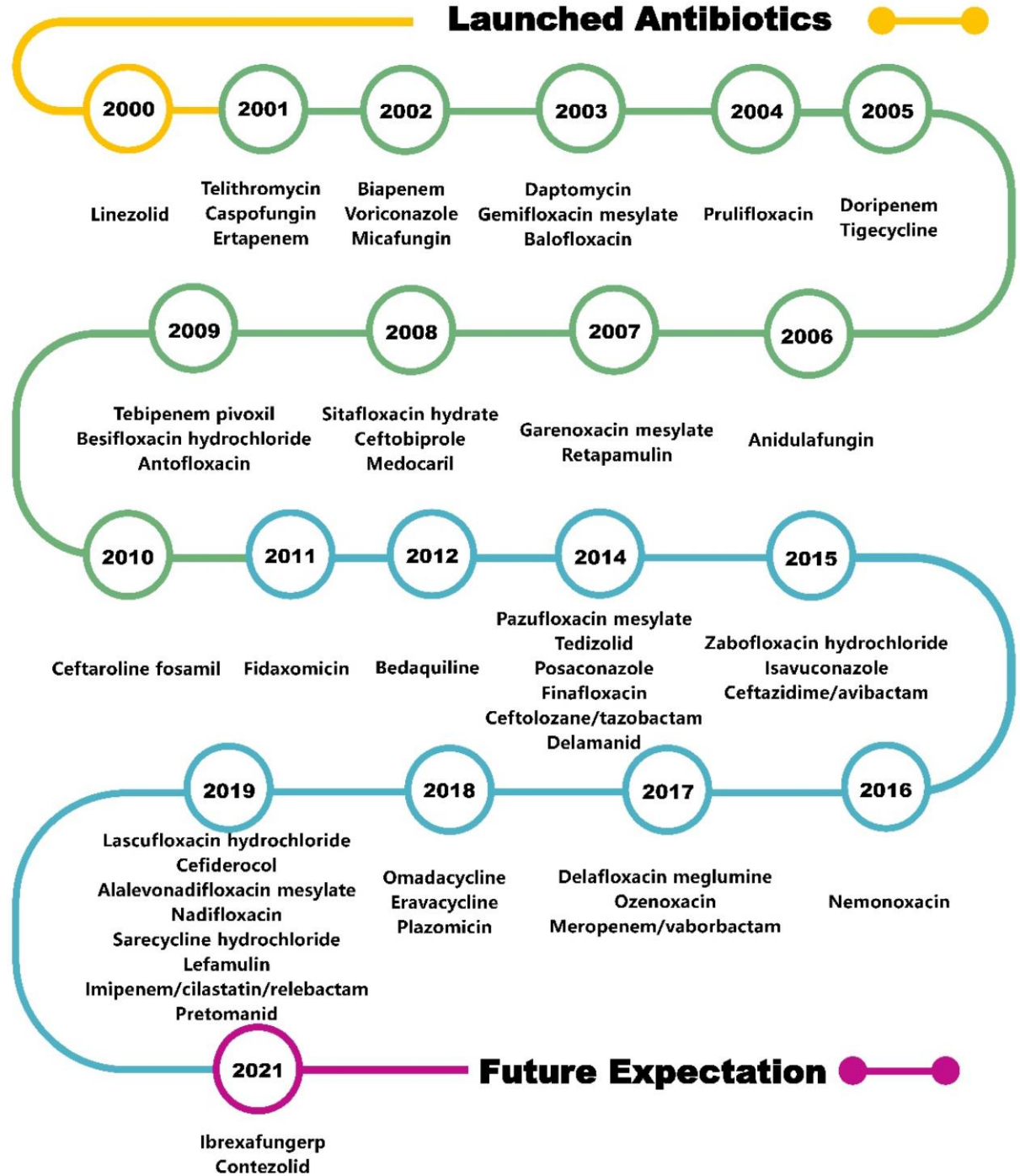
Task force on management and prevention of *Acinetobacter baumannii* infections in the ICU

Table 2 Recommended doses of antimicrobials for *A. baumannii* infections in patients with normal renal function

Antibiotic	Loading dose[a]	Daily dose	Observations
Imipenem[b]	Not required	0.5–1 g/6 h	Extended infusion is not possible due to drug instability High doses are associated with seizures
Meropenem[b]	Not required	2 g/8 h	Extended infusion (3–4 h) is recommended, In this case, first dose (2 g) should be administered in 30-min
Sulbactam[b]	Not required	9–12 g/day (in 3 or 4 doses)	4-h infusion is recommended
Polymyxin E[b] (Colistin)	6–9 million IU[c]	9 million IU/day in 2 or 3 doses	One million IU of colistin is equivalent to 80 mg of CMS. See text for doses on intermittent hemodyalisis and CRRT[d]
Polymyxin B	2–2.5 mg/kg	1.5–3 mg/kg/day in 2 doses.	Continuous infusion may be suitable. Same dose in patients on CRRT[d]
Tigecycline	100 mg	50 mg/12 h	May be adequate in secondary bacteremia for approved indications (abdominal infections and SSTI[e])
	200 mg	100 mg/12 h	For other sources including pneumonia and primary bloodstream infection (consider combination with another active antimicrobial). Without approval by regulatory agencies
Rifampicin	Not required	600 mg/day or 600 mg/12 h	Always in combination therapy
Fosfomycin[b]	Not required	12–24 g/day (in 3 or 4 doses)	Always in combination therapy

[a] The loading dose should be administered in all patients including those with renal dysfunction
[b] Dose adjustment is necessary in case of renal dysfunction
[c] *IU* International Units
[d] *CRRT* continuous renal replacement therapy
[e] *SSTI* skin and soft tissue infection





Molecules **2023**, *28*, 1762. https://doi.org/10.3390/molecules28041762

DTR/PDR *Acinetobacter spp.* ile tedavide sorunlar

- Kolonizasyon-enfeksiyon ayrımının net olarak yapılamıyor
- Klinik mikrobiyoloji laboratuvarları erken ve doğru direnç tayininde kısmen etkin (merkezi laboratuvar sorunu, alt yapı farklılıkları)
- %100 etkili bir antibiyotik yok!
- Monoterapiye karşı kombinasyonun üstünlüğü var mı?
- Yeni tedavi seçenekleri ile ilgili çalışmalar yeterli ve doyurucu veriyi henüz sunamıyor (Farklı hasta grupları ve sayıları, farklı kombinasyonlar vb)
- …

Table 1. Characteristics of novel approved anti-Gram-negative antimicrobial agents.

Drug	Drug Class	Bacterial Spectrum	Drug Stable to Beta-Lactamase Type					Approval Year/Indication in Adults		Recommendations		Route//Dosage
			KPC	MBL	AmpC	OXA	ESBL	FDA	EMA	IDSA	ESCMID	
Cefiderocol	BL	GNB; not GPB and anaerobes	yes	yes	yes	yes	yes	2019/cUTI, HAP/VAP	2020/aerobic GNB when limited treatment options	CRE: cUTI	CRE [#], CRAB, CRPA *	IV//2 g TDS (2 g QDS if augmented renal clearance)
Meropenem/ vaborbactam	CP/BLI	GNB, GPB, anaerobes; not MRSA, VRE; VARB cannot enhance activity against *A. baumannii* and *Pseudomonas aeruginosa*	yes §	no	yes	no	yes	2017/cUTI	2018/cUTI, cIAI, HAP/VAP, when limited options	CRE: cUTI, infections elsewhere	CRE	IV//4 g TDS
Imipenem/ cilastatin/ relebactam	CP/ BLI	GNB, GPB, anaerobes; not MRSA, VRE; RELE enhances activity against *P. aeruginosa*, contrary to *A. baumannii*; not *Morganellaceae*	yes	no	yes	no	yes	2019/cUTI and cIAI with limited options, HAP, VAP	2021/HAP/VAP, BSI possibly secondary to pneumonia, when limited options	CRE: cUTI, infections elsewhere CRPA: cUTI	CRPA *	IV//1.25 g QDS
Eravacycline	TC	GNB, GPB, anaerobes; MRSA, VRE active; possibly against *A. baumannii*; not *P. aeruginosa*; less active against *Morganellaceae*	-	-	-	-	-	2018/cIAI	2018/cIAI	-	CRAB: No data	IV//1 mg/kg BD
Omadacycline	TC	GNB, atypical, GPB, anaerobes; MRSA, VRE active; may display activity against *A. baumannii*; not against *P.aeruginosa* and *Morganellaceae*	-	-	-	-	-	2018/CAP, ABSSSI	-	-	CRAB: No data	IV//1st day 200 mg, later 100 mg OD; oral//450 mg for 2 days followed by 300 mg
Plazomicin	AG	Aerobic GNB, ESBL-E, CRE (including MBL); stable against some AG-resistant *Enterobacterales*	-	-	-	-	-	2018/cUTI	No	-	CRE: cUTI	IV//15 mg/Kg/day

Table 2. Characteristics of novel anti-Gram-negative antimicrobial agents in phase 3 clinical trials.

Drug	Drug Class	Bacterial Pectrum	Drug Stable to Beta-Lactamase Type					Potential Indications	Ongoing Trials (Phase 3)	Route//Dosage	Comment
			KPC	MBL	AmpC	OXA	ESBL				
Aztreonam/ avibactam	MB/BLI	GNB; less effective against MBL-producing *P. aeruginosa*	yes	yes	yes	yes	yes	cIAI, HAP, VAP, cUTI, BSI	NCT03580044	IV//500/167 mg loading dose, 1500/500 mg QDS	Combination that covers both serine and MBL carbapenemases
Cefepime/ enmetazobactam	BL/BLI	GNB, GPB; ineffective against *A. baumannii*, CRE, and MRSA	no	no	yes/no	no	yes	cUTI, HAP, VAP	NCT03687255	IV//2 g/500 mg TDS	Excellent class A, anti-ESBL activity; Potential carbapenem-sparing drug; Penetrates ELF easily
Cefepime/ zidebactam	BL/BLI	GPB (no MRSA); GNB (not *A. baumannii*)	yes	yes	yes	yes	yes	cUTI	NCT04979806	IV//2 g/1 g TDS	Phase 3 study recruiting patients
Cefepime/ taniborbactam	BL/BLI	GPB (not MRSA), GNB, (not *A. baumannii*)	yes	yes	yes	yes	yes	cUTI	NCT03840148	IV//2 g/0.5 g TDS	Preliminary results from phase 3 cUTI study: comparable efficacy to MER
Sulbactam/ durlobactam	BL/BLI	GNB, particularly *Acinetobacter* spp.; active against *Burkholderia cepacia*; not *P. aeruginosa*	yes	no	yes	yes	yes	*Acinetobacter* infections	NCT03894046	1 g/1 g QDS	Phase 3, pneumonia and BSI study. Better clinical cure and less nephrotoxicity than colistin (preliminary results)
Sulopenem	CP	GPB (not MRSA); GNB (not *P.aeruginosa, Stenotrophomonas maltophilia, B. cepacia)*	no	no	yes	no	yes	cUTI, uUTI, cIAI	NCT03357614, NCT03358576	Oral//sulopenem etzadroxil 500 mg/probenecid 500 mg BD; IV//1000 mg OD	Phase 3 trial of uncomplicated UTI, recruiting patients
Tebipenem	CP	GPB (not MRSA); GNB (not *P.aeruginosa, A. baumannii*)	no	no	yes	no	yes	cUTI	NCT03788967	Oral//600 mg TDS	Excellent anti-ESBL activity
Benapenem	CP	Like other CPs	no	no	yes	no	yes	cUTI	NCT04505683	IV//1000 mg OD	Excellent anti-ESBL activity

ESCMID 2022 Rehber Önerileri

- VAP/HAP tedavisinde SAM invitro duyarlıysa kullanılmasını, dirençliyse polimiksin veya yüksek doz TGC,
- Polimiksinin MEM veya RIF ile kombinasyonunu kesinlikle önermiyor!
- Ciddi ve yüksek riskli CRAB enfeksiyonunda polimiksin, AG, TGC veya SAM ile ikili kombinasyon
- MEM MİK değeri < 8 mg/L ise uzamış yüksek doz MEM infüzyonu
- Sefiderokol bazlı terapilerin etkinliği, CRAB tedavisinde diğer ajanlara benzer (düşük kanıt düzeyi)

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)

Mical Paul [1,2,§], Elena Carrara [3,§], Pilar Retamar [4,5], Thomas Tängdén [6], Roni Bitterman [1,2], Robert A. Bonomo [7,8,9], Jan de Waele [10], George L. Daikos [11], Murat Akova [12], Stephan Harbarth [13], Celine Pulcini [14,15], José Garnacho-Montero [16], Katja Seme [17], Mario Tumbarello [18], Paul Christoffer Lindemann [19], Sumanth Gandra [20], Yunsong Yu [21,22,23], Matteo Bassetti [24,25], Johan W. Mouton [26,†], Evelina Tacconelli [3,27,28,*,§], Jesús Rodríguez-Baño [4,5,§]

Table 1 (*continued*)

Recommendation	Strength of recommendation	Level of evidence
Carbapenem-resistant *Acinetobacter baumannii* (CRAB)		
Recommendations on the choice of antibiotic treatment for CRAB		
For patients with CRAB susceptible to sulbactam and HAP/VAP, we suggest ampicillin-sulbactam.	Conditional	Low
For patients with CRAB resistant to sulbactam, a polymyxin or high-dose tigecycline can be used if active *in vitro*. Lacking evidence, we cannot recommend on the preferred antibiotic.	No recommendation	
We conditionally recommend against cefiderocol for the treatment of infections caused by CRAB.	Conditional	Low
Recommendations on combination therapy for CRAB		
For all patients with CRAB infections, we do not recommend polymyxin-meropenem combination therapy or polymyxin-rifampin combination therapy.	Strong	High/moderate
For patients with severe and high-risk CRAB infections, we suggest combination therapy including two *in vitro* active antibiotics among the available antibiotics (polymyxin, aminoglycoside, tigecycline, sulbactam combinations).	Conditional	Very low
For patients with CRAB infections with a meropenem MIC ≤8 mg/L, we consider carbapenem combination therapy, using high-dose extended-infusion carbapenem dosing, as good clinical practice.	Good practice statement	Expert opinion
All carbapenem-resistant Gram-negative bacteria		
For pan-resistant CR-GNB (resistant also to polymyxins), treatment with the least resistant antibiotic/s based on MICs relative to the breakpoints is considered as good clinical practice.	Good practice statement	Expert opinion

Abbreviations: BLBLI, β-lactamase/β-lactamase inhibitors; BSI, bloodstream infections; cUTI, complicated urinary tract infections; HAP, hospital-acquired pneumonia; IV, intravenous; VAP, ventilator-associated pneumonia.

ESCMID 2022 Rehber Önerileri

Table 2
Potential *in vitro* activity of antibiotics against target carbapenem-resistant Gram-negative bacteria and approved indications

	CRAB	ESBLs	CRPA non-MBL	CRE non-CP	CRE-KPC	CRE-OXA-48	CRE-MBL	Current clinical indications/approval
New antibiotics								
Ceftolozane-tazobactam	No	Yes	Yes	No	No	No	No	FDA and EMA approved for cUTI, cIAI, HAP and VAP
Ceftazidime-avibactam	No	Yes	Yes	+/−	Yes	Yes	No	FDA and EMA approved for cIAI and cUTI, HAP and VAP, and (in EMA only) for the treatment Gram-negative infections in patients with limited treatment options
Meropenem-vaborbactam	No	Yes	No	+/−	Yes	No	No	FDA approved for cUTI, EMA approved for cUTI, HAP and VAP, and for the treatment Gram-negative infections in patients with limited treatment options
Imipenem-cilastatin/ relebactam	No	Yes	Yes	+/−	Yes	No	No	FDA approved for cUTI and cIAI; EMA approved for HAP and VAP and for BSI with a suspected respiratory source, and for the treatment Gram-negative infections in patients with limited treatment options
Plazomicin	No	Yes	+/−	Yes	Yes	Yes	+/−	FDA approval cUTI, EMA application withdrawn
Eravacycline	Yes	Yes	No	Yes	Yes	Yes	Yes	FDA and EMA approved for cIAI
Cefiderocol	Yes	Yes	Yes	Yes	Yes	Yes	Yes	FDA cUTI, HAP and VAP; EMA for the treatment of infections due to aerobic Gram-negative organisms in adults with limited treatment options
Old antibiotics								
Polymyxins	Yes	Yes	Yes	Yes	Yes	Yes	Yes	FDA: serious infections caused by susceptible strains, when less potentially toxic drugs are ineffective or contraindicated. EMA: treatment of serious infections due to aerobic Gram-negative pathogens in patients with limited treatment options
Aminoglycosides	+/−	+/−	+/−	+/−	+/−	+/−	+/−	EMA and FDA: for the treatment of a variety of bacterial infections
Fosfomycin iv	No	Yes	+/−	+/−	+/−	+/−	+/−	EMA: to treat serious infections when other antibiotic treatments are not suitable. FDA: under review
Aztreonam	No	No	+/−	No	No	No	+/−	EMA and FDA: for the treatment of infections caused by susceptible Gram-negative microorganisms
Tigecycline	Yes	Yes	No	Yes	Yes	Yes	Yes	EMA and FDA: complicated SSTI and IAI (FDA also CAP)
Temocillin	No	Yes	No	No	+/−	No	No	EMA and FDA: orphan drug status for the treatment of infections caused by *Burkholderia cepacia* in patients with cystic fibrosis

CRAB-ESCMID 2022 Rehber Önerileri-Polimiksin&SAM

- Kolistin ağırlıklı az sayıda VAP olgusu [illegible] RCT ile **mortalite/mikrobiyolojik/klinik cevap farkı yok, koli[illegible]** nen çalışma sonuçları da aynı)
- Çoğu BSI/VAP o[illegible] **talite kolistin grubunda fazla**
- 98 VAP olgulu [illegible] olistin kıyaslanmış, **kolistin kolunda** [illegible] görülürken klinik cevap farklı bulunmamış
- Küçük bir RCT ile kolistin ve uzamış infüzyonla SAM tedavisi, her iki gruba yüksek doz LEV ile kombine edildiğinde, **mortalite, klinik cevap ve nefrotoksiste açısından SAM kolu oldukça avantajlı** bulunmuş
- Çoğu çalışmada SAM MİK: < 8/4 mg/L SAM (2:1) dozu değişken: 3-16 gr/8 saatte bir İV

SAM, kolistine oranla CRAB ilişkili VAP tedavisinde avantajlı (düşük kanıt düzeyi)

antibiotics

MDPI

Systematic Review

Efficacy of Cefoperazone Sulbactam in Patients with *Acinetobacter* Infections: A Systematic Review of the Literature

Gowthami Sai Kogilathota Jagirdhar [1], Kaanthi Rama [2], Shiva Teja Reddy [2], Harsha Pattnaik [3], Rakhtan K. Qasba [4], Praveen Reddy Elmati [5], Rahul Kashyap [6], Marco Schito [7] and Nitin Gupta [8,*]

Antibiotics **2023**, *12*, 582. https://doi.org/10.3390/antibiotics12030582

- Hindistan
- Sefoperazon-sulbaktam(CS) mono&kombine tedavisine klinik ve mikrobiyolojik cevaplar ile mortalitenin irdelendiği sistematik bir derlemede;
- 11 **CS monoterapisi** ile 10 **CS kombinasyon terapisi** karşılaştırılmış ve iki grup arasında **benzer sonuçlar** bulunmuştur
- Klinik/mikrobiyolojik yanıt/mortalite oranları monoterapi kolunda 70%, 44%, and 20%, kombinasyon kolunda 72%, 43%, and 21%

Jung et al. Critical Care (2017) 21:319
DOI 10.1186/s13054-017-1916-6

Critical Care

RESEARCH Open Access

Antimicrobials for the treatment of drug-resistant *Acinetobacter baumannii* pneumonia in critically ill patients: a systemic review and Bayesian network meta-analysis

Su Young Jung[1,2], Seung Hee Lee[1], Soo Young Lee[3,4], Seungwon Yang[5], Hayeon Noh[5], Eun Kyoung Chung[3*†] and Jangik I. Lee[1,2*†]

J Antimicrob Chemother 2018; **73**: 22–32
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Journal of Antimicrobial Chemotherapy

Journal of Global Antimicrobial Resistance 24 (2021) 136–147

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Review

Comparative efficacy and safety of combination therapy with high-dose sulbactam or colistin with additional antibacterial agents for multiple drug-resistant and extensively drug-resistant Acinetobacter baumannii infections: A systematic review and network meta-analysis

Jiating Liu[a,b], Yunfeng Shu[a,b], Feilong Zhu[c], Bimin Feng[a], Zhengjie Zhang[a,b], Liang Liu[a,b], Guojun Wang[b,*]

Comparative efficacy and safety of treatment options for MDR and XDR *Acinetobacter baumannii* infections: a systematic review and network meta-analysis

Kirati Kengkla[1], Khachen Kongpakwattana[2], Surasak Saokaew[1–3,6], Anuc Nathorn Chaiyakunapruk[2,3,5,6*]

Research Article

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Meropenem/colistin versus meropenem/ampicillin–sulbactam in the treatment of carbapenem-resistant pneumonia

Hossein Khalili[1], Lida Shojaei*[,2], Mostafa Mohammadi[3], Mohammad-Taghi Beigmohammadi[3], Alireza Abdollahi[4] & Mahsa Doomanlou[5]

Journal of Comparative Effectiveness Research

Le Infezioni in Medicina, n. 1, 11-16, 2019

ORIGINAL ARTICLE

Triple combination therapy with high-dose ampicillin/sulbactam, high-dose tigecycline and colistin in the treatment of ventilator-associated pneumonia caused by pan-drug resistant *Acinetobacter baumannii*: a case series study

Stelios F. Assimakopoulos[1], Vassilis Karamouzos[2], Aikaterini Lefkaditi[2], Christina Sklavou[2], Fevronia Kolonitsiou[3], Mirto Christofidou[3], Fotini Fligou[2], Charalambos Gogos[1], Markos Marangos[1]

Table 1. Summary of comparative studies examining efficacy of sulbactam in patients with *A. baumannii* infections.

Study (Year)	No. of Evaluable	Infection	Antibacterial Regimens No. Pts				Cure and/or Improvement (%)			Bacteriological Eradication (%)		
			Comparator 1		Comparator 2		Comparator 1	Comparator 2	*p*-Value	Comparator 1	Comparator 2	*p*-Value
[21]	65	Pneumonia	A/S	22	A/S + V	43	63.6	65.1	0.906	89.5	81.3	0.69
							M:36.4	M:37.2	0.947			
[22]	98	VAP	A/S	32	COL	66	47	56	0.34	82	52	0.03
							M:9.4	M:25.8	0.07			
								aOR: 6.5 (1.34–31.34) 0.0				
[23]	84	VAP + B	A/S+I/C	56	TG+I/C	28	NR	NR		NR	NR	
							M:14.3	M:64.3	0.007	NR	NR	
[24]	106	Pneumonia	C/S	35	CARB	46	71.4	29.3	0.003	NR	NR	
					TG	25		60	0.355			
							M:5.7	M:6.5				
								M:8				
[25]	130	VAP	C/S	66	TG	42	70	62	0.402	50	33	0.21
					C/S+TG	22	M:5	45	0.208	41	33	0.54
								M:12	0.295 *			
								M:27	0.231 **			
							aOR: 0.115 (0.015–0.89)		0.038			
[28]	47	VAP	A/S+MR	23	COL+MR	24	69.6	75	0.75	91.3	87.5	0.59
							M:39.13	M:41.67	0.99			
[29]	23	VAP	A/S+L	12	COL+L	11	83	27	0.007	75	100	NR
							M:41.66	M:81.81	0.04			
[26]	42	VAP	C/S+TG	21	TG	21	85.7	47.6	0.01	NR	NR	
[30]	28	VAP	A/S+nCOL	16	COL+nCOL	12	31.2	33.3	NS	43.7	12.5	0.37
							M:16.7	M:37.5	0.22			
[27]	180	VAP/HAP	A/SorC/S+COL	90	CARB+COL	90	NR	NR	0.658	NR	NR	
							M:51.1	M:55.6				
[31]	125	Pneumonia	S/D	63	COL	62	62	40	NR	86	61	NR
						M:19		M:32	0.0935 ¶			

VAP = Ventilator-associated pneumonia; B = bacteraemia; A/S = ampicillin/sulbactam; C/S = Cefoperazone/sulbactam; CARB = Carbapenem; I/C = imipenem/Cilastatin; COL = Colistin; nCOL = nebulised Colistin; MR= meropenem; TG = tigecycline; L = Levofloxacin; V = Various, i.e., 68.6% Carbapenem, 8.7% cephalosporins, 3.5% Fluoroquinolones; M = mortality; * = comparison between C/S and TG; ** = comparison between TG and C/S+TG; aOR = adjusted Odds Ratio; NR = not reported; ¶ = log rank p.

CRAB-ESCMID 2022 Rehber Önerileri-Polimiksin&TGC

- Çoğu VAP olgusu dahil edilmiş ve polimiksin (kolistin) ve TGC'nin, farklı antibiyotiklerle kombine edildiği 4 retrospektif gözlemsel çalışmada;
- Biri hariç tümünde **TGC kolunda yüksek mortalite ve düşük klinik cevap** görülmüş, bir çalışmada TGC'nin mikrobiyolojik başarısı daha yüksek bulunmuş
- Diğer 3 çalışmada nefrotoksisite kolistin grubunda daha yüksek imiş
- TGC dozu sıklıkla 50 mg/günde 2 kez ama, iki katı dozlar da uygulanabilir

CRAB-ESCMID 2022 Rehber Önerileri-TGC&Sulbaktam

- 5 retrospektif kohort çalışması irdelenmiş;
- Taiwan 386 olgu, sulbakt… …rbapenem veya diğer beta laktamlarla kombine edilmiş. 3… …**nda daha düşük klinik-mikrobiyolojik**
- Taiwan, 86 VAP… …grup arasında; mikrobiyolojik y… …**ubunda daha yüksek**
- Taiwan, sulbaktam m… …an 84 olgu arasında **ICU-mortalitesi ve tedavi başarı**… …**k** bulunmuş
- Çin, 210 BSI, CS ile TGC karşılaştırılmış (Her iki kola kombinasyon yapılmış) ve **28 günlük mortalite CS grubunda anlamlı düşük** bulunmuş
- Çin, 274 MDR-AB BSI olgusu, CS&TGC karşılaştırılmış, **CS kolunda mortalite daha düşük**

Sulbaktam bazlı terapilerin,

TGC bazlı olanlardan avantajlı

olduğu (düşük kanıt düzeyi)

CRAB-ESCMID 2022 Rehber Önerileri-Sefiderokol

- Gram negatiflere etkili **siderofor SS,** kimyasal olarak sefepim ve seftazidime benzer
- Demir iyon kanalları olan k… …llanarak bakteri içine girer
- İYE, VİP tedavi…
- **CREDIBLE** …laviler karşılaştırılmış. **28 günlük m…** …%18. Ayrıca **sefiderokol…**
- **APEKS-NP RCT:** Se… …zyonu, **farklılık yok**
- **Böbrek doz ayarı gerekli,** KC doz ayarına gerek yok

Sefiderokol bazlı terapiler, CRAB tedavisinde diğer ajanlara benzer (düşük kanıt düzeyi)

Table 2. Summary of comparative studies examining efficacy of cefiderocol in patients with *A. baumannii* infections.

Study (Year)	No. of Evaluable	Infection ¶	Antibacterial Regimens No. Pts				Cure and/or Improvement (%) Mortality (%)			Bacteriological Eradication (%)		
			Comparator 1		Comparator 2		Comparator 1	Comparator 2	*p*-Value	Comparator 1	Comparator 2	*p*-Value
[33]	47	Pneumonia	CFD	23	MR	24	52	58	NS	39	33	NS
							M:19	M:22	NS			
[34]	54	Pneumonia/B/UTI	CFD	37	BAT	17	43	53	NS	27	29	NS
							M:49	M:18	NR			
[36]	107	B:27 LRTI:14 ALL COVID-19	CFD	42	COL−R	65	40	36	0.45	28	21	0.24
							M:55	M:58	0.70			
[37]	124	B:79 VAP:35	CFD−R	47	COL−R	28	NR	NR				
							M:34%	M:55.8	0.018 *	82.6	93.2	0.079
[38]	111	B:53 P:47	CFD−R	60	COL−R	51	73	67	0.44	43	41	0.82
							M:51	M:37				
[39]	118	B	CFD−R	43	COL−R	75	NR	NR		NR	NR	
							M:40	M:59	0.045			
[40]	121	VAP ALL COVID-19	CFD−R	55	NON CFD−R	66	NR	NR		47	69	0.038
							M:44	M:67	0.011			
[41]	90	VAP	CFD+Ncol	40	COL+nCOL	50	75	52	0.02	70	40	0.003
							M:35	M:52	NS			
[42]	73	Bacteremic VAP ALL COVID-19	CFD−R	19	COL−R	54	NR	NR		NR	NR	
							M:31.5	M:98.1	<0.001			

Abbreviations: No. = number; Pts = patients; M = mortality; ¶ = numbers in the infection column are absolute numbers of patients with the specific type of infection mentioned; VAP = Ventilator-associated pneumonia; *p* = pneumonia; LRTI = lower respiratory tract infection; B = bloodstream infection; CFD = cefiderocol; CFD-R = cefiderocol-containing regimen; COL-R = colistin-containing regimens, i.e., combination regimens ± monotherapy; COL = Colistin; nCOL = nebulised colistin; * = regarding mortality of bacteraemia only; MR= meropenem; BAT = best available treatment; NR = not reported; NS = non-significant.

CRAB-ESCMID 2022 Rehber Önerileri-Eravasiklin

- Yeni TS grubu sentetik ajan, florosiklin,
- CRAB'a karşı TGC'den 2-8 kat daha düşük MİK değerlerine sahip
- **IGNITE-1 ve IGNITE-4 RCT:** cIAI olguları, Eravasiklin&ertapenem eravasiklin&MEM karşılaştırıldığı faz-3 ilaç çalışmalarında eravasiklinin invitro potansiyel aktif olduğu halde **CRAB enfeksiyonlarında klinik etkinliğine dair veri yok!**

CRAB-ESCMID 2022 Rehber Önerileri-Diğer ABler

- Retrospektif küçük çaplı klinik çalışmalar,
- MDR GN ve CRAB'a karşı **Tobramisin** ve TGC dışı **diğer TS'lerle** yapılmış
- Çalışmalar küçük ve sonuçlar yeterli değil

CRAB-ESCMID 2022 Rehber Önerileri-Mono-Kombine Terapi

- CRAB için kombinasyon tedavisi, polimiksinlerin karbapenem, RIF, VA, diğer AB'ler ve AB dışı bileşiklerle yapılmış sinerjistik etkileşimi gösteren invitro çalışmalara dayansa da klinik çalışmalarla desteklenmesi gerekir
- **AIDA RCT:** CR-GNB ilişkili 406 VAP/BSI olgusu, 312'si CRAB; ana grup ve CRAB alt grubunda kolistin&kolistin+MEM kollarında **sonuçlar arasında farklılık yok**
- **OVERCOME RCT:** CR-GNB ilişkili 165 VAP/BSI olgusu (çoğu CRAB), **mortalite oranları** kolistin&kolistin+MEM kolunda **benzer**
- **Kolistin+RIF kombinasyonu:** 209 çoğu CRAB ilişkili VAP olgusu, 30 günlük mortalitede kombine tedavinin **monoterapiye üstünlüğü gösterilmemiş,** sadece mikrobiyolojik kür daha yüksek
- **Kolistin+VA kombinasyonu:** 57 çoğu CRAB ilişkili VAP olgusu, yatış süresi ve mortalite açısından **fark yok,** kombinasyon grubunda **nefrotoksisite daha yüksek**
- **Kolistin+fosfomisin kombinasyonu:** 94 CRAB ilişkili VAP olgusu, fosfomisin Rli, mikrobiyolojik kür dışında iki grup arasında **fark yok**

CRAB-ESCMID 2022 Rehber Önerileri-Mono-Kombine Terapi

- **Aslında kombine tedavilerin monoterapiye üstünlüğü yok!**
- **Polimiksin+MEM** veya **Polimiksin+RIF** kombinasyonu **kesinlikle önerilmiyor!** (Güçlü öneri, yüksek kanıt düzeyi)
- Ciddi ve yüksek riskli CRAB enfeksiyonlarında invitro aktif **2 ilaçla kombine tedavi** (Düşük kanıt düzeyi)
  - Polimiksin
  - AG
  - TGC
  - Sulbaktam kombinasyonları
- **MEM MİK< 8 mg/L ise** karbapenemle kombine tedavi (Yüksek doz uzamış karbapenem infüzyonu)

Clinical Infectious Diseases
IDSA GUIDELINES

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

Pranita D. Tamma,[1,©] Samuel L. Aitken,[2] Robert A. Bonomo,[3] Amy J. Mathers,[4,5] David van Duin,[6] and Cornelius J. Clancy[7]

IDSA 2023 Rehber Önerileri

- CRAB tedavisi çeşitli zorluklar içeriyor, **en iyi tedavi seçeneği hala belirsiz!**
- Solunum örnekleri ve yaralarda kolonize olduğundan **enfeksiyon/kolonizasyon ???**
- Ciddi CR (OXA-24/40, OXA-23 ve farklı MBL ile ilişkili beta laktam R)
- Aminoglikozid R ve akciğer dokusuna nebülizer formda bile iyi geçememeleri, plazomisin dahil AG seçeneğini elemekte, florokinolon R
- Genel öneri; **yüksek doz SAM (6-9 gr/gün S) + önerilen bir ajan ile kombinasyon (polimiksin, tigesiklin, sefiderokol)**
- SAM dirençli olsa da yüksek dozda kullanılmalı

https://doi.org/10.1093/cid/ciad428

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

Pranita D. Tamma,[1,©] Samuel L. Aitken,[2] Robert A. Bonomo,[3] Amy J. Mathers,[4,5] David van Duin,[6] and Cornelius J. Clancy[7]

IDSA 2023 Rehber Önerileri

- CRAB tedavisinde **MEM/IMP önerilmiyor!**
- **Nebulize antibiyotikler** de **önerilmiyor!** (Ciddi YE ve faydasız oluşları sebebiyle)
- **Fosfomisin veya RIF** kombinasyon tedavisinde **önerilmiyor!**
- Kombinasyon tedavisinde düşünülebilecek diğer ajanlar:
  - **Polimiksin B**
  - **Minosiklin**
  - **TGC**
  - **Sefiderokol**

https://doi.org/10.1093/cid/ciad428

CRAB Tedavisinde Monoterapi & Kombine Terapi

Monoterapi	Kombine terapi	n	Enfeksiyon	Sonuç
Kolistin	Kolistin + RIF	210	İnvaziv enf.	Fark yok
Kolistin	Kolistin + RIF	43	Pnömoni	Fark yok
Kolistin	Kolistin + RIF	9	Pnömoni	Fark yok
Kolistin	Kolistin + Fosfomisin	94	Çeşitli enf.	Fark yok
Kolistin	Kolistin + MEM	312	Pnömoni, BSI, UTI	Fark yok
Kolistin	Kolistin + MEM	329	Pnömoni, BSI	Fark yok
MEM + Kolistin	MEM + SAM	47	Pnömoni	Fark yok
Kolistin	**Kolistin + Sulbaktam**	**39**	**Pnömoni**	**Kombine tedavi avantajlı***

5.Günde mortalite %70 & %16

Çalışmaların hiçbirinde Polimiksin B kullanılmamış (Daha avantajlı olduğu halde)

Clinical Infectious Diseases

IDSA GUIDELINES

IDSA 2023 Rehber Önerileri-SAM

- 1835 olguluk 18 çalışmanın verisine göre, ikinci aktif bir ajanla kombine edilen minimum 6 gr/gün SAM, **en etkili, nefrotoksisitesi en düşük ve mortaliteyi azaltan rejim**
- 2118 olguluk 23 çalışma sonucuna göre SAM bazlı rejimler **mortaliteyi en çok azaltan** rejim. Nefrotoksiste değerlendirilmemiş
- **Kolistin ve SAM monoterapisinin** irdelendiği 28 olguluk bir çalışmada 28 günlük mortalite ve klinik cevap farkı saptanmamış ama, **nefrotoksisite SAM kolunda daha ↓**
- SAM **dirençli olsa da** yüksek dozda **kullanılmalı!**

https://doi.org/10.1093/cid/ciad428

IDSA 2023 Rehber Önerileri-Sulbaktam-Durlobaktam

- FDA onayı aldı (CRAB VAP/HAP, Mayıs 2023)
- CRAB izolatlarına bakterisidal etkili bir BL/BLI kombinasyonu
- Durlobaktam potent bir Ambler A, C, D beta laktamaz inhibitörü
- **Durlobaktam,** sulbaktamın PBP'lere daha düşük dozlarda ulaşmasını sağlayan **koruyucu etkisiyle sulbaktamın CRAB izolatlarına etkinliğini arttırmakta**

https://doi.org/10.1093/cid/ciad428

IDSA 2023 Rehber Önerileri-Polimiksinler

- Polimiksin bazlı rejimlere **Polimiksin B önerilmekte** (Kolistine kıyasla daha iyi PK özellikleri sebebiyle)
- Polimiksin MİK değeriyle ilgili CLSI'da veri yok ancak etkinliği MİK >2 mg/L iken azalmakta
- Rehber polimiksin **monoterapisini önermemekte:**
  - Polimiksin kan düzeyleri efektif bakterisidal etki için istenen düzeyin altında kalmakta
  - Tedavi edici aralıkta nefrotokisite riski de var!
  - Pulmoner epiteldeki etkinliği suboptimal düzeyde
  - Ayrıca yetersiz klinik cevap ve monoterapiyle R bildiren çalışmalar mevcut

https://doi.org/10.1093/cid/ciad428

IDSA 2023 Rehber Önerileri-Tetrasiklin Deriveleri

- **Yüksek doz minosiklin veya yüksek doz TGC,** en az bir aktif ajanla **kombinasyon şeklinde önerilmekte**
- Minosiklin ilişkili klinik deneyim ve CLSI verisi mevcut ancak, TGC de makul bir seçenek
- Rehber 200 mgx2 İV/oral minosiklini önermekte
- TGC, MİK değerleri belirsiz, yüksek doz (200 mg İV yükleme ve 100x2 idame) ve bir aktif ajanla kullanımını öneriyor, TGC monoterapisi yüksek mortaliteyle ilişkili
- **Eravasiklin** MİK değerleri diğer TS'lerden 2-8 kat daha düşük ama, CLSI MİK önerisi yok
- 27'si eravasiklin alan 93 olguluk çalışmada eravasiklin grubunda mortalite ve klinik yanıtsızlık anlamlı olarak yüksek bulunmuş, 4 BSI olgusu ex, mekanik ventilasyon süresi uzamış
- **Rehber eravasiklini** diğer TS derivelerinin uygun olmadığı **sınırlı durumlarda kullanılmasını** öneriyor
- Rehber yetersiz veri sebebiyle **omadasiklini önermiyor**

https://doi.org/10.1093/cid/ciad428

IDSA 2023 Rehber Önerileri-Sefiderokol

- Rehber, sefiderokol diğer ajanların uygun olmadığı **sınırlı durumlarda kombinasyon şeklinde** kullanılmasını öneriyor
- CLSI: Duyarlılık sınırı < 4 mg/L
- **CREDIBLE-CR RCT:** 150 olgu, 101'i sefiderokol alıyor, 85'i monoterapi şeklinde, 54 olguda CRAB izole edilmiş. Sefiderokol kolunda ölüm oranı %34, diğer kolda %18. CRAB izole edilenlerde ölüm oranı %49
- **APEKS-NP RCT:** Sefiderokol ve yüksek doz uzamış MEM karşılaştırılıyor, **sonuçlar benzer**
- Sefiderokol&Kolistin karşılaştırıldığı başka bir çalışmada ise 30 günlük mortalite %34 ve %56; rekürren CRAB enfeksiyon oranları %17 ve %7

https://doi.org/10.1093/cid/ciad428

IDSA 2023 Rehber Önerileri-Uzamış MEM/IMP

- **Rehber, MEM veya IMP tedavisini önermiyor!**
- İnvitro çalışmaların aksine, MEM/IMP kombinasyonunun kolistin tedavisine sinerjik bir etkisi gösterilmemiş
- SAM, CRAB tedavisinde etkin bir ajan olarak önerildiği için CRAB tedavisinde ek bir beta laktam toksisitesi riski nedeniyle önerilmemekte

IDSA 2023 Rehber Önerileri-RIF

- **Rehber, RIF tedavisini önermiyor!** (rifabutin veya diğer rifamisinler dahil)
- 3 klinik çalışma kolistin monoterapisi ile RIF ile kombinasyonu arasında tedavi sonuçları açısından farklılık olmadığını göstermiştir

https://doi.org/10.1093/cid/ciad428

IDSA 2023 Rehber Önerileri-Nebülize AB'ler

- **Rehber, respiratuvar CRAB enfeksiyonlarında nebülize AB'leri önermiyor!**
- Kolistin, amikasin, fosfomisin nebül denenmiş ancak, faydasız olmaları yanında ciddi bronkokonstriksiyon YE!
- 3 klinik çalışma, sistemik AB'ler de kullanılmış
- Nebülize kolistin &plasebo; nebülize amikasin/fosfomisin & plasebo ve nebülize amikasin & plasebo; toplamda 750 olguda **nebülize AB'lerin ek faydası gösterilmemiş**
- 13 klinik çalışma ve 1733 olguluk bir meta-analizde hayatta kalma, YBÜ yatış süresi veya ventilatör gününe düzeltici etkisi gösterilmemiş

https://doi.org/10.1093/cid/ciad428

TABLE 1 | Nebulizer characteristics.

	Aerosol generation
Ultrasonic	High frequency piezo-e Crystal in drug solution
Jet	Venturi effect on comp gas
Vibrating mesh	High frequency mesh v drug solution

TABLE 2 | New studies of inhaled antibiotics for ICU pneumonia.

Parameter	Phase II Inhaled amikacin trial (22)	Amikacin/Fosfomycin trial (2)	Inhaled vs. aerosol adjunctive amikacin (23)	INHALE trial [(3), NCT01799993]
Design	Multicenter, randomized, double-blind, placebo-controlled	Multicenter, randomized, double-blind, placebo-controlled	Single-center randomized, controlled, not blinded	Multicenter, randomized, double-blinded, placebo-controlled
Number enrolled	69	143	133 post cardiac surgery patients	712
Intervention therapy	Inhaled amikacin 400 mg bid (n = 21), inhaled amikacin 400 mg daily (n = 26), inhaled placebo (n = 22) for 7–14 days; standard of care systemic antibiotics	Inhaled amikacin 300 mg/fosfomycin 120 mg bid (n = 71) vs. Placebo (n = 72) for 10 days, with intravenous meropenem or imipenem	Inhaled amikacin 400 mg bid plus systemic piperacillin-tazobactam (n = 86) vs. intravenous amikacin 20 mg/kg daily plus systemic piperacillin-tazobactam (n = 47). Duration dependent on patient response	Inhaled amikacin 400 mg bid (n = 354) vs. Inhaled placebo (n = 358) for 10 days; standard of care systemic antibiotics
Delivery device	Vibrating mesh nebulizer with PDDS system, distal to Y connector	Vibrating mesh nebulizer, used continuously, proximal to Y connector	Pneumatic nebulizer for ventilated patients; ultrasonic nebulizer for non-ventilated patients	Vibrating mesh nebulizer with PDDS system, distal to Y connector
Adjunctive vs. Salvage	Adjunctive, with high suspicion of gram-negatives	Adjunctive, with high suspicion of gram-negatives	Adjunctive aerosol vs. adjunctive IV	Adjunctive in patients with high suspicion of gram-negatives
Primary endpoint	Percent achieving tracheal amikacin concentration >6,400 mcg/ml	Change of CPIS from baseline, during therapy in patients with proven gram-negative infection	Clinical cure on day 7 of therapy	Mortality 28–32 days post start of therapy
Findings	50% achieved primary endpoint with amikacin 400 mg bid	No difference in CPIS during therapy (p = 0.7)	Higher clinical cure rate with nebulized therapy (91.8 vs. 70.2%) (p = 0.002)	No difference in mortality
Other findings	Reduced mean number of antibiotics per patient per day, at end of aerosol therapy; 0.9 with q12h, 1.3 with q24h, and 1.9 with placebo (p = 0.02)	No difference in mortality, clinical cure; higher rate of negative tracheal cultures for gram-negatives at day 3 and 7 with aerosol therapy	Nebulized therapy with: shorter time to clinical cure, shorter length of stay, less nephrotoxicity, less duration of amikacin, NO change in mortality	No difference in percent with early clinical response, days on ventilation, days in ICU, adverse events. More bronchospasm with inhaled therapy.

Post NRŞ Menenjit-İV/İT Polimiksin

European Journal of Clinical Microbiology & Infectious Diseases
https://doi.org/10.1007/s10096-024-04794-y

ORIGINAL ARTICLE

Intraventricular or intrathecal polymyxin B for treatment of post-neurosurgical intracranial infection caused by carbapenem-resistant gram-negative bacteria: a 8-year retrospective study

Yangmin Hu[1] · Danyang Li[2] · Gensheng Zhang[2] · Yunjian Dai[1] · Meng Chen[1] · Huifang Jiang[1] · Wei Cui[2]

- Post NRŞ menenjitlerde mortalite yüksek (%29)
- CRKP ilişkili post NRŞ menenjit CRAB'a kıyasla DTR
- İV/İT polimiksin B, retrospektif bir çalışma, Çin
- 114 olgu, 72'si sistemik PB ile beraber İV/İT PB alırken 42 olgu sadece sistemik PB alıyor

- 7. günde CSF sterilizasyon oranı İV/İT PB alan grupta çok yüksek, 30 günlük mortalite anlamlı derecede düşük saptanmış
- İV/İT PB süresi, 30 günlük mortaliteye etkili bağımsız değişken olarak bildirilmiş

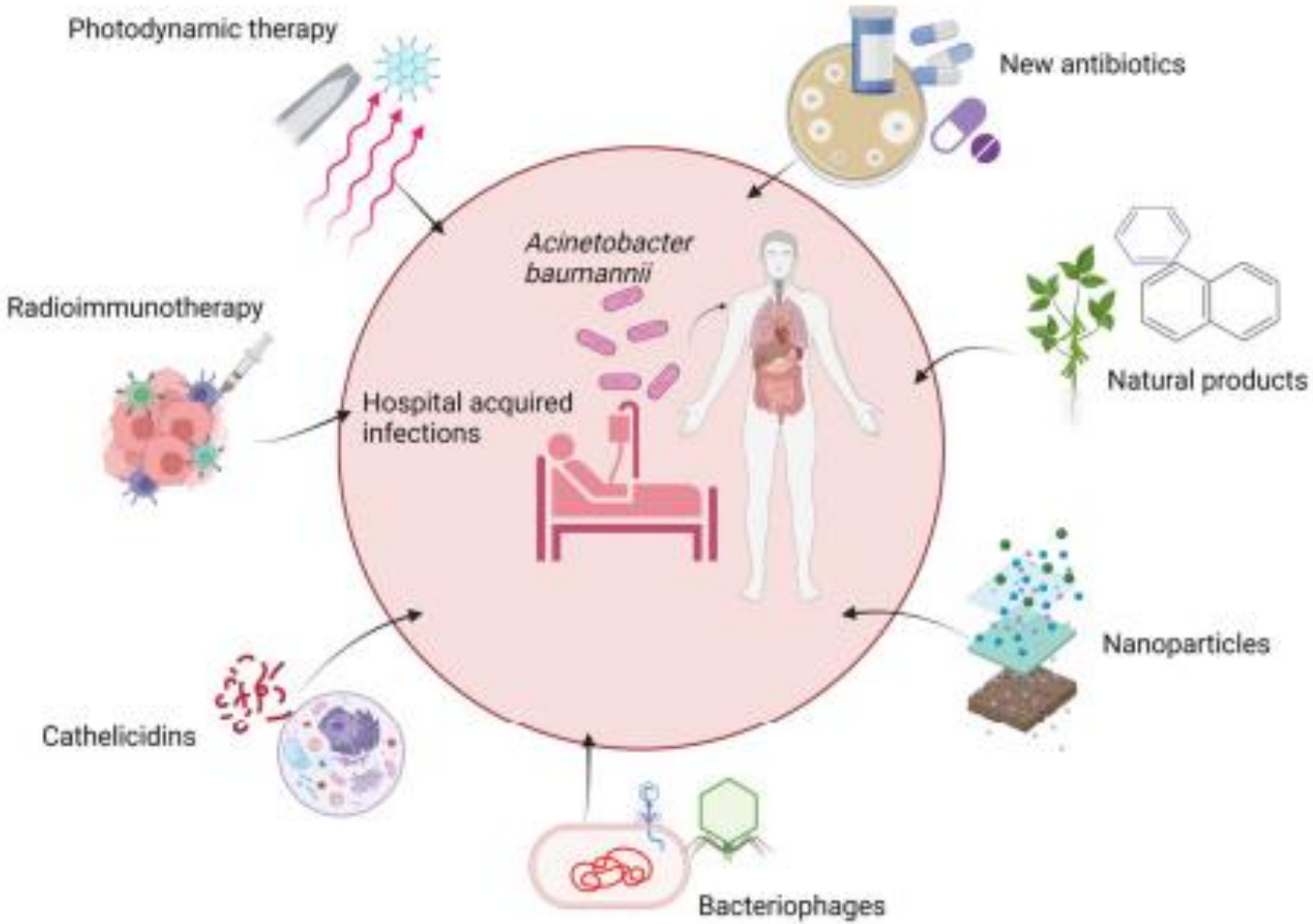


Figure 3. Possible future therapies for *A. baumannii* infection. The figure was made with www.biorender.com (accessed on 25 July 2022).

Table 3 Antimicrobial treatment alternatives with their mechanisms of action. (Modified from Bassetti et al. [3])

Treatment	Mechanism of action
Antimicrobial peptides (AMP)	Mainly cellular membrane damage
Phage therapy	Use of lytic phages to kill bacteria
Eligobiotics	System injected by a phage
Phage endolysins	Use of a phage endolysin instead of the whole phage
Anti-virulence factors	Adjuvants or adjunct therapies to complement the use of antibiotics
Phytochemicals	Multiple actions
Metallo-antibiotic	Increased spectrum of conventional antibiotic action
Efflux pump inhibitor	Molecules to inhibit the active protein pump in the bacterial cell
Lipo-polysaccharide (LPS) inhibitors	Inhibitor of an enzyme important in LPS pathway

Intensive Care Med (2018) 44:189–196
https://doi.org/10.1007/s00134-017-5036-1

4.2. Natural Products

With the rise of drug resistance observed in the late 1970s, there was a dearth of drugs against various diseases caused by microorganisms. By the late 1990s, the effective and operative drug left to us was carbapenem, which also joined the drug resistance assemblage and made treatment challenging. Subsequently, having no innovative growth of drugs to counter the carbapenem-resistant strains, it has become necessary to emphasize the use of traditional medicine. The secondary metabolites mainly account for the antimicrobial activity of plants. There are several studies using plant extracts for evaluating the antimicrobial effect against drug-resistant pathogens. Some of the plants and their active compounds are listed in Table 2.

Table 2. List of natural products used against *A. baumannii*.

Plant's Name	Active Compounds	References
Lythrum salicaria	Hexahydroxy diphenoyl ester vescalagin	[81]
Rosa rugosa	Ellagic acid	[82]
Terminalia chebula	Terchebulin, Chebulagic acid, Chebulinic acid, Corilagin	[82]
Scutellaria baicalensis	Norwogonin, Baicalin, Baicalein	[82]
Syzygium aromaticum	Eugenol	[83]
Cinnamomum zeylanicum	Trans-cinnamaldehyde	[84]
Oreganum vulgare	Carvacrol	[83,84]
Green tea *Camellia sinensis*	Epigallocatechin gallate (EGCG)	[85]
	Epicatechin	[86]
	Theaflavin	[86]
Lyciumchinense Mill.	(+)-Lyoniresinol-3 alpha-O-beta-D-glucopyranoside	[87]
Paeonia suffruticosa Andr.	Paeonol	[87]
Coptidischinensis Franch.	Berberine	[87]
Green tea (*Camellia sinesis*)	polyphenol, (−)-epigallocatechin-3-gallate (EGCG)	[88]
Pantoea agglomerans	*Pantoea* Natural Product 3 (PNP-3).	[89]

antibiotics

MDPI

Review

Next-Generation Polymyxin Class of Antibiotics: A Ray of Hope Illuminating a Dark Road

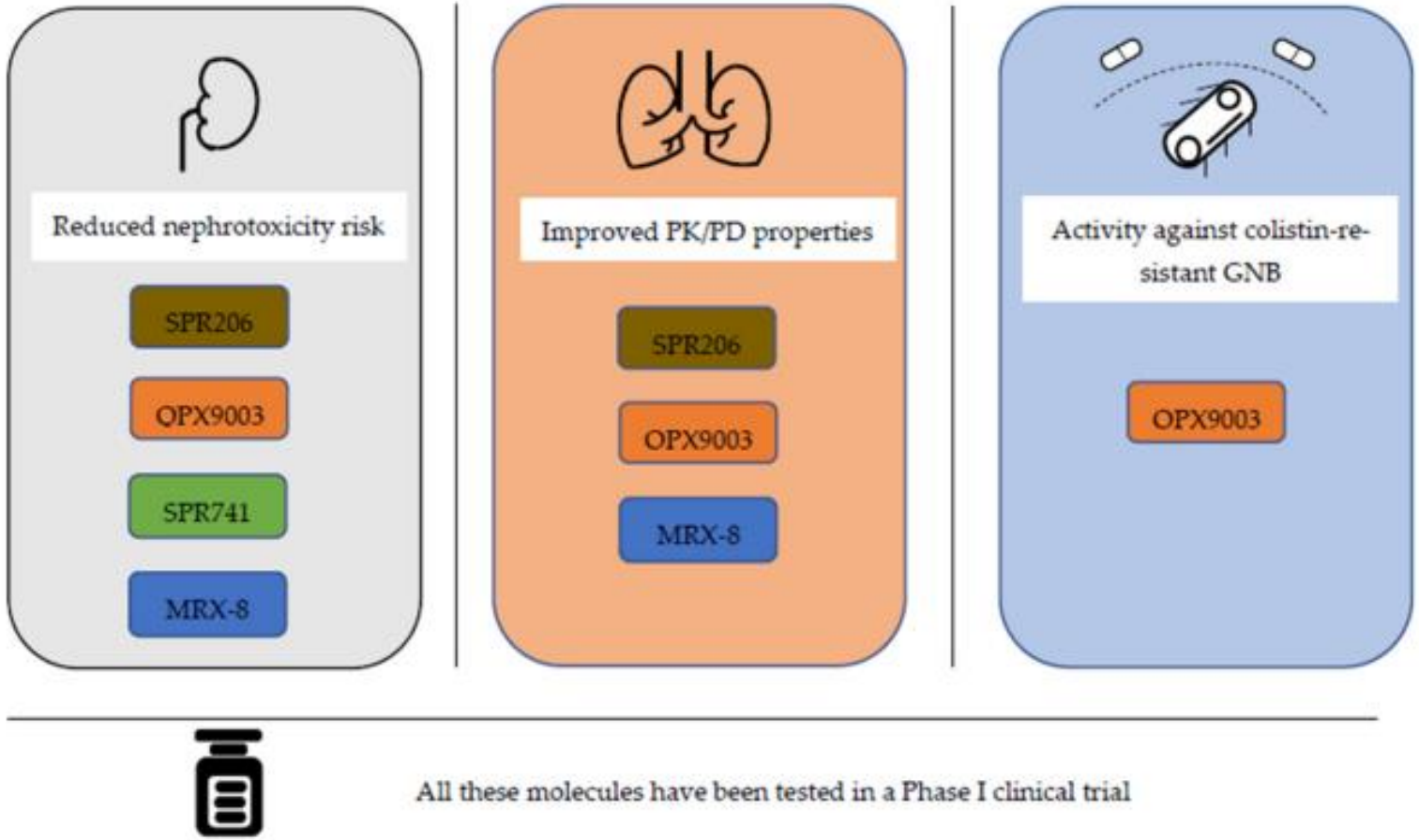
Abdullah Tarık Aslan [1,2,*], Murat Akova [3] and David L. Paterson [2,4]

Antibiotics **2022**, *11*, 1711

Table 1. The structure of colistin, polymy

Compound	R1	R2	R3	R4	R5	R6	R7
Colistin	-Dab	-Thr	-Dab	-Dab	-Dab	-DLeu	-Leu
PMB	-Dab	-Thr	-Dab	-Dab	-Dab	-DPhe	-Leu
SPR206	-	-Thr	-Dab	-Dab	-Dab	-DPhe	-Leu
MRX-8	-Dab	-Thr	-Dab	-Dab	-Dab	-DPhe	-Leu
SPR741	-	-Thr	-DSer	-Dab	-Dab	-DPhe	-Leu
QPX9003	-Dab	-Thr	-Dap	-Dab	-Dab	-DLeu	-Abu

PMB, polymyxin B; Dab, diaminobutyric acic
serine; Leu, leucine; Phe, phenylalanine; Thr, t



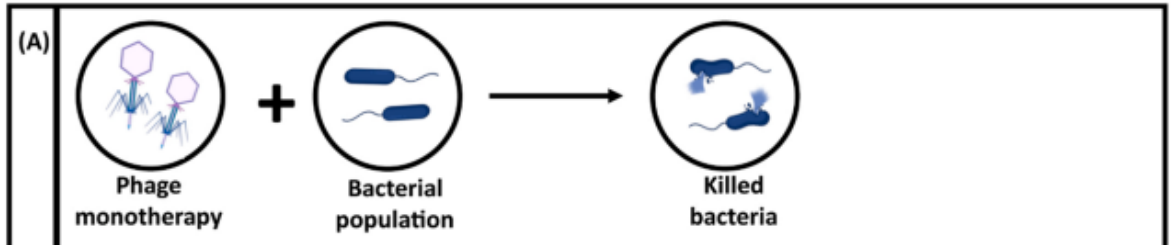
ANTIBIOTIC RESISTANCE

Repurposing a neurodegenerative disease drug to treat Gram-negative antibiotic-resistant bacterial sepsis

David M. P. De Oliveira[1], Lisa Bohlmann[1], Trent Conroy[2], Freda E.-C. Jen[2], Arun Everest-Dass[2], Karl A. Hansford[3], Raghu Bolisetti[3], Ibrahim M. El-Deeb[2], Brian M. Forde[1,4], Minh-Duy Phan[1], Jake A. Lacey[5], Aimee Tan[5], Tania Rivera-Hernandez[1,6], Stephan Brouwer[1], Nadia Keller[1], Timothy J. Kidd[1], Amanda J. Cork[1], Michelle J. Bauer[4], Gregory M. Cook[7], Mark R. Davies[5], Scott A. Beatson[1], David L. Paterson[4], Alastair G. McEwan[1], Jian Li[8], Mark A. Schembri[1], Mark A. T. Blaskovich[3], Michael P. Jennings[2], Christopher A. McDevitt[5]*, Mark von Itzstein[2]*, Mark J. Walker[1]*†

The emergence of polymyxin resistance in carbapenem-resistant and extended-spectrum β-lactamase (ESBL)–producing bacteria is a critical threat to human health, and alternative treatment strategies are urgently required. We investigated the ability of the hydroxyquinoline analog ionophore PBT2 to restore antibiotic sensitivity in polymyxin-resistant, ESBL-producing, carbapenem-resistant Gram-negative human pathogens. PBT2 resensitized *Klebsiella pneumoniae*, *Escherichia coli*, *Acinetobacter baumannii*, and *Pseudomonas aeruginosa* to last-resort po myxin class antibiotics, including the less toxic next-generation polymyxin derivative FADDI-287, in vitro. W unable to select for mutants resistant to PBT2 + FADDI-287 in polymyxin-resistant *E. coli* containing a borne *mcr-1* gene or *K. pneumoniae* carrying a chromosomal *mgrB* mutation. Using a highly invasive *K. p* strain engineered for polymyxin resistance through *mgrB* mutation, we successfully demonstrated th PBT2 + polymyxin (colistin or FADDI-287) for the treatment of Gram-negative sepsis in immunocomp In comparison to polymyxin alone, the combination of PBT2 + polymyxin improved survival and reduc dissemination to the lungs and spleen of infected mice. These data present a treatment modality to brea resistance in high-priority polymyxin-resistant Gram-negative pathogens.

PBT-2: Faz 2 aşamadaki Alzheimer ilacı, Zinc ile kombinasyonu CRAB dahil dirençli GN'leri kolistine karşı resensitize edici özelliğe sahip



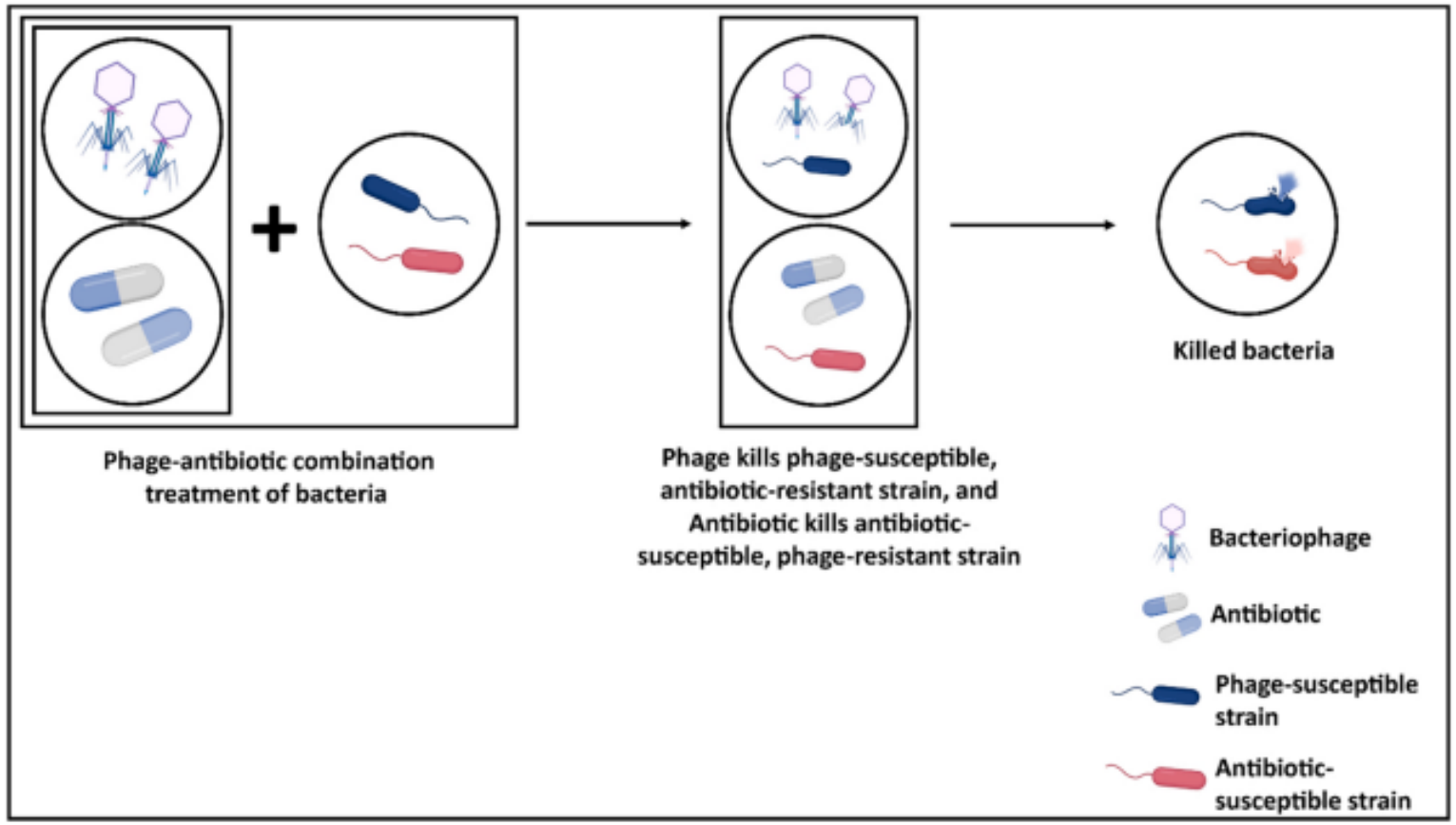


Fig. 2. Development of phage-antibiotic combination treatments is a good approach in combatting infections of *A. baumannii*.

Fig. 1. Potential of bacteriophage and bacteriophage cocktails for the treatment of infections of *A. baumannii*. (A) In the absence of phage-resistant strains, phage monotherapy can result in the complete clearance of bacteria. (B) The use of a single phage type may increase the chance of resistance generation during treatment. (C) Phage cocktails may reduce the chance of resistance during treatment.

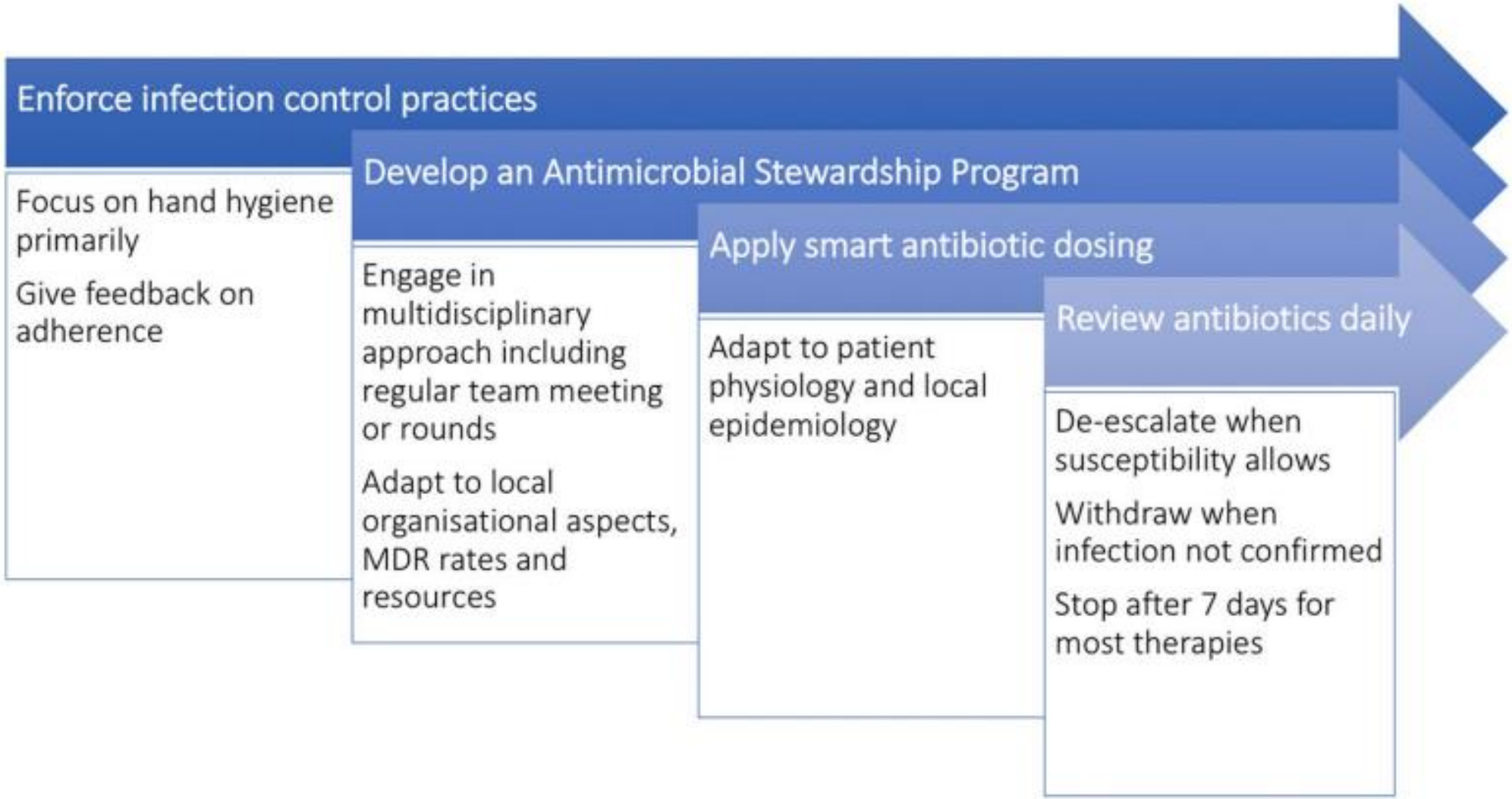


Fig. 3 Simple, immediately actionable interventions to tackle AMR in the ICU

Intensive Care Med (2018) 44:189–196
https://doi.org/10.1007/s00134-017-5036-1

- Dirençten esas sorumlu sınıf D karbapenemazlar (OXA-23, OXA 24/40 ve OXA-58), ancak A-D BL'ları da var
- DTR-GN'lerin en sık sebebi (BSI suşlarının %18'i DTR, *Pseudomonas* için bu oran %2,3 *Klebsiella* için %1,7)
- Birinci kuşak ilaçlar I/R (karbapenem, SS, FQ), diğer ilaçlar etkinliği ↓/dokuya geçemiyor/ toksisitesi↑
- Polimiksinler hala tedavinin omurgasını oluşturmakta
- Ciddi CRAB enfeksiyonlarında ikili hatta üçlü kombine terapiler (yüksek doz TGC, AG'ler, fosfomisin)
- SAM invitro duyarlıysa hala iyi bir seçenek, gerekirse yüksek doz-uzamış infüzyon şeklinde
- Sefiderokol ruhsat çalışmasındaki yüksek mortalite oranıyla hayal kırıklığı yaratsa da, bilhassa CRAB ilişkili BSI için umut verici
- Eravasiklin invitro çok iyi görünse de klinik sonuçlar alternatif bir seçenek olması için henüz yetersiz

CRAB ve son söz...

“It Takes All the Running You Can Do, to Keep in the Same Place»

Through the Looking-Glass-Lewis Carroll ,1871