Antimikrobiyal Direnç ile Mücadelede Yeni Bakış, Yeni Başlangıç

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İÜC-CTF
Klinik Mikrobiyoloji Enfeksiyon Hastalıkları AD

Çoklu Dirençli Gram (-) Enfeksiyonların Yönetimi

- Direnç sorunu (Global/lokal)
- Akılcı Antibiyotik Tedavisi yaklaşım

  * Ampirik tedavi

  ** Karbapenem direncinde tedavi
- CAZ/AVI laboratuvardan kliniğe
- SONUÇ

GÜNCEL SORUN

WHO

WHO priority pathogens list for R&D of new antibiotics

Priority 1: CRITICAL

- *Acinetobacter baumannii*, carbapenem-resistant
- *Pseudomonas aeruginosa*, carbapenem-resistant
- *Enterobacteriaceae*, carbapenem-resistant, ESBL-producing

Priority 2: HIGH

- *Enterococcus faecium*, vancomycin-resistant
- *Staphylococcus aureus*, methicillin-resistant, vancomycin-intermediate and resistant
- *Helicobacter pylori*, clarithromycin-resistant
- *Campylobacter* spp., fluoroquinolone-resistant
- *Salmonellae*, fluoroquinolone-resistant
- *Neisseria gonorrhoeae*, cephalosporin-resistant, fluoroquinolone-resistant

Priority 3: MEDIUM

- *Streptococcus pneumoniae*, penicillin-non-susceptible
- *Haemophilus influenzae*, ampicillin-resistant
- *Shigella* spp., fluoroquinolone-resistant

USA/CDC

Urgent Threats

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

Serious Threats

- Drug-resistant *Campylobacter*
- Drug-resistant *Candida*
- Extended-spectrum beta-lactamase (ESBL)-producing Enterobacteriaceae
- Vancomycin-resistant *Enterococci* (VRE)
- Multidrug-resistant *Pseudomonas aeruginosa (P. aeruginosa)*
- Drug-resistant nontyphoidal *Salmonella*

Hipervirulan ve dirençli kökenler!

frontiers in Cellular and Infection Microbiology

REVIEW
published: 21 November 2017
doi: 10.3389/fcimb.2017.00483

Antimicrobial Resistance of Hypervirulent *Klebsiella pneumoniae*: Epidemiology, Hypervirulence-Associated Determinants, and Resistance Mechanisms

Chang-Ro Lee,[1,†] Jung Hun Lee,[1,†] Kwang Seung Park,[1,†] Jeong Ho Jeon,[1] Young Bae Kim,[2] Chang-Jun Cha,[3] Byeong Chul Jeong,[1] and Sang Hee Lee[1,*]

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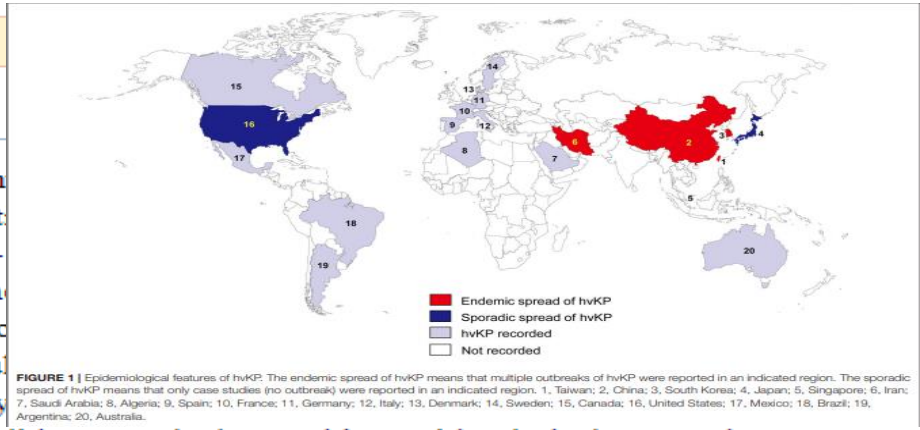
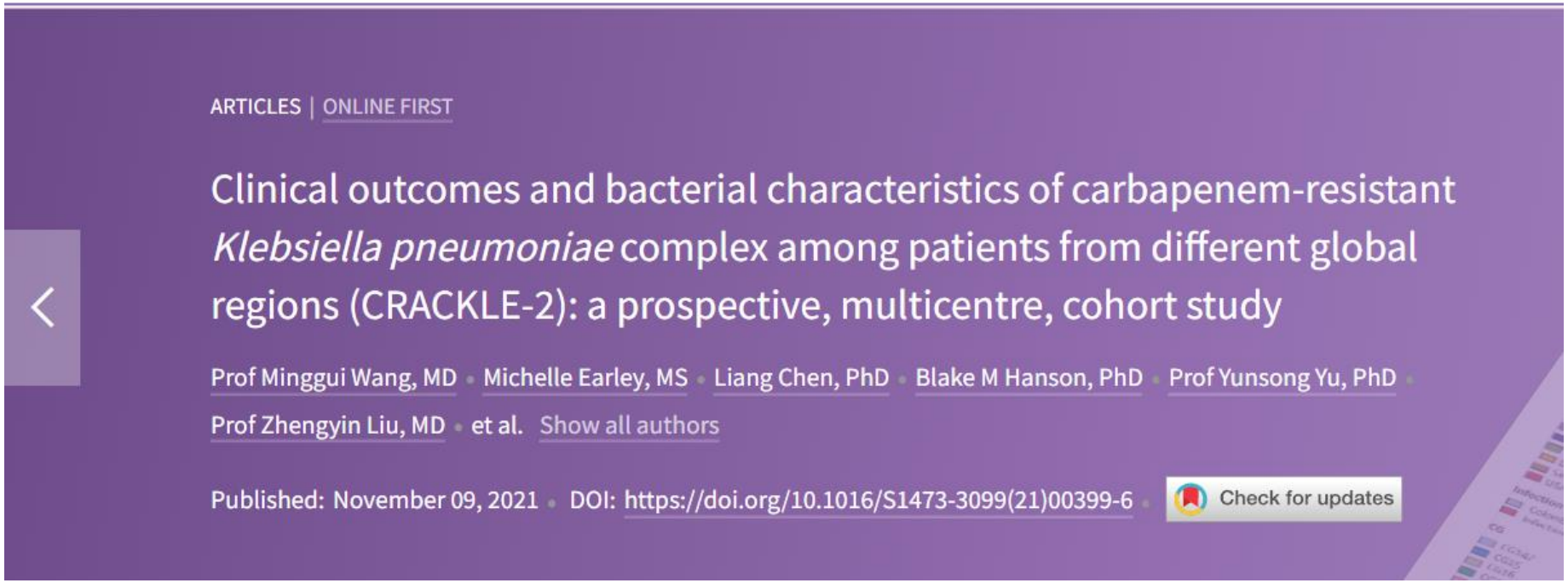


FIGURE 1 | Epidemiological features of hvKP. The endemic spread of hvKP means that multiple outbreaks of hvKP were reported in an indicated region. The sporadic spread of hvKP means that only case studies (no outbreak) were reported in an indicated region. 1, Taiwan; 2, China; 3, South Korea; 4, Japan; 5, Singapore; 6, Iran; 7, Saudi Arabia; 8, Algeria; 9, Spain; 10, France; 11, Germany; 12, Italy; 13, Denmark; 14, Sweden; 15, Canada; 16, United States; 17, Mexico; 18, Brazil; 19, Argentina; 20, Australia.

Abstract

Klebsiella pneumoniae is one of the most clinically relevan
responsible for community-acquired and nosocomial infect
infections, bacteremias, and liver abscesses. Since the mid-
associated with the hypermucoviscosity phenotype, has em
responsible for serious disseminated infections, such as pyo
endophthalmitis, in a generally younger and healthier popu
were primarily found in East Asia and now are increasingly
hypervirulent *K. pneumoniae* isolates are antibiotic-susceptible, some isolates with combined virulence and resistance, such as the carbapenem-resistant hypervirulent *K. pneumoniae* isolates, are increasingly being detected. The combination of multidrug resistance and enhanced virulence has the potential to cause the next clinical crisis. To better understand the basic biology of hypervirulent *K. pneumoniae*, this review will provide a summarization and discussion focused on epidemiology, hypervirulence-associated factors, and antibiotic resistance mechanisms of such hypervirulent strains. Epidemiological analysis of recent clinical

THE LANCET
Infectious Diseases



ARTICLES | ONLINE FIRST

Clinical outcomes and bacterial characteristics of carbapenem-resistant *Klebsiella pneumoniae* complex among patients from different global regions (CRACKLE-2): a prospective, multicentre, cohort study

Prof Minggui Wang, MD • Michelle Earley, MS • Liang Chen, PhD • Blake M Hanson, PhD • Prof Yunsong Yu, PhD • Prof Zhengyin Liu, MD • et al. Show all authors

Published: November 09, 2021 • DOI: https://doi.org/10.1016/S1473-3099(21)00399-6 • Check for updates

Interpretation

Global CRKP epidemics have important regional differences in patients' baseline characteristics and clinical outcomes, and in bacterial characteristics. Research findings from one region might not be generalisable to other regions.

ÇİD-Türkiye

Journal of Hospital Infection 94 (2016) 381–385

Available online at www.sciencedirect.com

Journal of Hospital Infection

journal homepage: www.elsevierhealth.com/journals/jhin

Short report

Healthcare-associated Gram-negative bloodstream infections: antibiotic resistance and predictors of mortality

Ö. Ergönül[a,*], M. Aydin[b], A. Azap[c], S. Başaran[d], S. Tekin[a], Ş. Kaya[e], S. Gülsün[e], G. Yörük[f], E. Kurşun[g], A. Yeşilkaya[h], F. Şimşek[i], E. Yılmaz[j], H. Bilgin[k], Ç. Hatipoğlu[l], H. Cabadak[m], Y. Tezer[m], T. Togan[n], İ. Karaoğlan[o], A. İnan[p], A. Engin[q], H.E. Alışkan[g], S.Ş. Yavuz[d], Ş. Erdinç[i], L. Mulazimoglu[k], Ö. Azap[h], F. Can[a], H. Akalın[j], F. Timurkaynak[b], Turkish Society of Clinical Microbiology and Infectious Diseases, Healthcare-Related Infections Study Group

Antibiotic resistance rates in healthcare-associated Gram-negative bloodstream infections

Bacteria	Carbapenems N (%)	Fluoroquinolones N (%)	Third-generation cephalosporins N (%)	Aminoglycosides N (%)	Colistin N (%)
Acinetobacter baumannii	239 (94)	240 (94)	247 (97)	187 (73)	15 (6)
Klebsiella pneumoniae	88 (40)	130 (60)	159 (72)	56 (25)	14 (6)
Escherichia coli	13 (6.4)	128 (63)	143 (71)	47 (23)	0
Pseudomonas aeruginosa	32 (43)	36 (49)	37 (51)	19 (26)	1 (1)
Enterobacter cloacae	5 (16)	6 (19)	16 (53)	5 (16)	0

Journal of Hospital Infection 98 (2018) 260–263

Available online at www.sciencedirect.com

Journal of Hospital Infection

journal homepage: www.elsevier.com/locate/jhin

Rapid emergence of colistin resistance and its impact on fatality among healthcare-associated infections

M. Aydın[a,*], Ö. Ergönül[b], A. Azap[c], H. Bilgin[d], G. Aydın[c,e], S.A. Çavuş[f], Y.Z. Demiroglu[g], H.E. Alışkan[h], O. Memikoglu[c], Ş. Menekşe[i], Ş. Kaya[j], N.A. Demir[k], I. Karaoglan[l], S. Başaran[m], Ç. Hatipoglu[n], Ş. Erdinç[n], E. Yılmaz[o], A. Tümtürk[p], Y. Tezer[p], H. Demirkaya[q], Ş.E. Çakar[r], Ş. Keske[b], S. Tekin[b], C. Yardımcı[s], Ç. Karakoç[t], P. Ergen[u], Ö. Azap[q], L. Mülazımoglu[d], O. Ural[k], F. Can[v], H. Akalın[o], Turkish Society of Clinical Microbiology and Infectious Diseases, Healthcare-related Infections Study

...scribes the emergence of resistance and predictors of fatality for 1556 cases ... associated Gram-negative bloodstream infection in 2014 and 2015. The colistin resistance rate in *Klebsiella pneumoniae* was 16.1%, compared with 6% in 2013. In total, 660 (42.4%) cases were fatal. The highest fatality rate was among patients with *Acinetobacter baumannii* bacteraemia (58%), followed by *Pseudomonas aeruginosa* (45%), *Klebsiella pneumoniae* (41%), *Enterobacter cloacae* (32%) and *Escherichia coli* (28%). On multi-variate analysis, the minimum inhibitory concentrations for carbapenems [odds ratio (OR) 1.02, 95% confidence interval (CI) 1.01–1.04; $P = 0.002$] and colistin (OR 1.1, 95% CI 1.03–1.17; $P = 0.001$) were found to be significantly associated with fatality.

ÇİD-CTF

- Karbapenem ve Kolistin dirençli Klebsiella
- ÇİD Pseudomonas !
- XDR A.baumannii

- Kolistin dirençli GNÇ

(Serratia, Proteus)

› Eur J Clin Microbiol Infect Dis. 2021 Oct;40(10):2161-2170. doi: 10.1007/s10096-020-04124-y. Epub 2021 May 8.

Colistin resistance increases 28-day mortality in bloodstream infections due to carbapenem-resistant Klebsiella pneumoniae

Ilker Inanc Balkan [1], Mustafa Alkan [2], Gökhan Aygün [2], Mert Kuşkucu [2], Handan Ankaralı [2], Alper Karagöz [2], Sümeyye Şen [2], Hatice Yaşar Arsu [2], Mehtap Biçer [2], Sibel Yıldız Kaya [2], Rıdvan Karaali [2], Bilgül Mete [2], Neşe Saltoğlu [2], Fehmi Tabak [2]

Affiliations + expand

PMID: 33963928 DOI: 10.1007/s10096-020-04124-y

Abstract

Mortality due to K. pneumoniae bacteremia is on rise, particularly in regions with high rates of carbapenem and colistin resistance. We aimed to define risk factors for colistin resistance and its impact on mortality. Patients diagnosed with "carbapenem-resistant K. pneumoniae (CRKp)" bacteremia between 2014 and 2018 were divided into two groups as "colistin susceptible (ColS)" and "colistin resistant (ColR)" based on broth microdilution method. Retrospective case-control study was conducted to compare characteristics and outcomes. Multiple logistic regression model was used to define independent risk factors for acquired colistin resistance and Cox proportional hazard model for 28-day mortality. A total of 82 patients (39 ColS and 43 ColR) were included. Mean age was 61.5 years, and 50 (61%) were male. Colistin resistance was significantly increased with duration of hospital stay ($p = 0.007$) and prior colistin use ($p = 0.007$). Overall, the 28-day mortality rate was 66%. Age ($p = 0.014$) and colistin resistance significantly increased 28-day ($p = 0.009$) mortality. Microbiological response to treatment within 7 days favors survival. PFGE analysis revealed an outbreak with K. pneumoniae ST78 and ST45 clones. Patients treated with combined antimicrobials had significantly lower 28-day mortality ($p = 0.045$) in comparison to monotherapy. However, types of combinations did not show significant superiority on each other. Colistin resistance increases 28-day mortality in

Akılcı antibiyotik tedavisi?

- Antibiyotik verme !!!

*Riskleri ortadan kaldırmaya çalış !

**Enfeksiyon dışı olasılıkları hatırla

***Kolonizasyonu tedavi etme

- Uygun ampirik tedavi !
- Tedavi sürecini etkin hale getir (Doz, FK/FD)
- Antibiyotikleri –zamanında- kes !

- Laboratuvar verilerini dikkatle izle !

Clinical Infectious Diseases
IDSA FEATURES

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

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

- Ampirik Tedavi:

  Son 6 aylık etken profili

  Son 30 gün antibiyotik hikayesi

  Hastanın özellikleri (immunsupresyon)

  Enfeksiyon odağı (sistit vs VIP)

Uygun ampirizm: Kültür kültürü

Lokal verilere dayanmalı !!!

- Laboratuvarlar uygun yöntemle

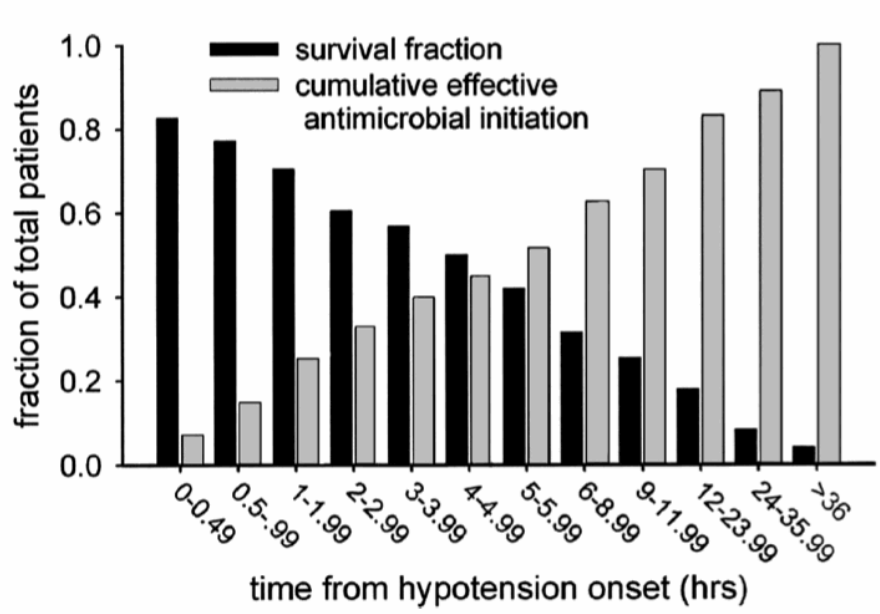
  zamanında (antibiyotik öncesi)

  örnek alınmasını sağlamalıdır !!!
- Laboratuvarlar standartlara uygun , kalite kontrolleri olan bir yöntemle çalışmalıdır.
- Etkin bir iletişim ortamı oluşturmalıdır
- En kısa zamanda sonuç (etken, direnç, karbapenemaz)

Comparative Study > Crit Care Med. 2014 Aug;42(8):1749-55.
doi: 10.1097/CCM.0000000000000330.

Empiric antibiotic treatment reduces mortality in severe sepsis and septic shock from the first hour: results from a guideline-based performance improvement program

Ricard Ferrer [1], Ignacio Martin-Loeches, Gary Phillips, Tiffany M Osborn, Sean Townsend, R Phillip Dellinger, Antonio Artigas, Christa Schorr, Mitchell M Levy



> Lancet Infect Dis. 2021 Feb;21(2):241-251. doi: 10.1016/S1473-3099(20)30477-1. Epub 2020 Sep 8.

Inappropriate empirical antibiotic therapy for bloodstream infections based on discordant in-vitro susceptibilities: a retrospective cohort analysis of prevalence, predictors, and mortality risk in US hospitals

Sameer S Kadri [1], Yi Ling Lai [2], Sarah Warner [3], Jeffrey R Strich [4], Ahmed Babiker [5], Emily E Ricotta [2], Cumhur Y Demirkale [3], John P Dekker [6], Tara N Palmore [7], Chanu Rhee [8], Michael Klompas [8], David C Hooper [9], John H Powers 3rd [10], Arjun Srinivasan [11], Robert L Danner [3], Jennifer Adjemian [12],
forming the National Insititutes of Health Antimicrobial Resistance Outcomes Research Initiative (NIH-ARORI)

Findings: 21 608 patients with bloodstream infections received empirical antibiotic therapy on the day of first blood culture collection. Of these patients, 4165 (19%) received discordant empirical antibiotic therapy. Discordant empirical antibiotic therapy was independently associated with increased risk of mortality (adjusted odds ratio 1·46 [95% CI, 1·28-1·66]; p<0·0001), a relationship that was unaffected by the presence or absence of resistance or sepsis or septic shock. Infection with antibiotic-resistant species strongly predicted receiving discordant empirical therapy (adjusted odds ratio 9·09 [95% CI 7·68-10·76]; p<0·0001). Most incidences of discordant empirical antibiotic therapy and associated deaths occurred among patients with bloodstream infections caused by Staphylococcus aureus or Enterobacterales.

Hızlı sonuç

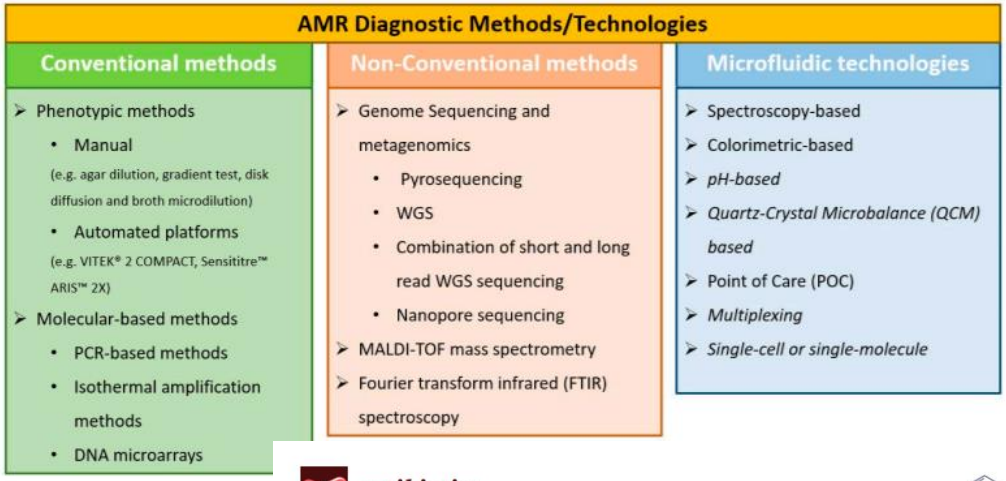
- EUCAST hızlı AB
- MALDI-TOF MS tanımlama ve ötesi

  Etken (HK şişesi, İdrar,…)

  Direnç

- Moleküler biyoloji

  Etken ve direnç



antibiotics
MDPI

Review

Rapid Methods for Antimicrobial Resistance Diagnostics

Georgia D. Kaprou [1,2,*], Ieva Bergšpica [1,3], Elena A. Alexa [1], Avelino Alvarez-Ordóñez [1,4] and Miguel Prieto [1,4]

Cochrane Library

Cochrane Database of Systematic Reviews

Rapid versus standard antimicrobial susceptibility testing to guide treatment of bloodstream infection (Review)

Anton-Vazquez V, Hine P, Krishna S, Chaplin M, Planche T

Main results

We included six trials, with 1638 participants. For rapid antimicrobial susceptibility testing compared to conventional methods, there was little or no difference in mortality between groups (RR 1.10, 95% CI 0.82 to 1.46; 6 RCTs, 1638 participants; low-certainty evidence). In subgroup analysis, for rapid genotypic or molecular antimicrobial susceptibility testing compared to conventional methods, there was little or no difference in mortality between groups (RR 1.02, 95% CI 0.69 to 1.49; 4 RCTs, 1074 participants; low-certainty evidence). For phenotypic rapid susceptibility testing compared to conventional methods, there was little or no difference in mortality between groups (RR 1.37, 95% CI 0.80 to 2.35; 2 RCTs, 564 participants; low-certainty evidence).

In qualitative analysis, rapid susceptibility testing may make little or no difference in time-to-discharge (4 RCTs, 1165 participants; low-certainty evidence). In qualitative analysis, rapid genotypic susceptibility testing compared to conventional testing may make little or no difference in time-to-appropriate antibiotic (3 RCTs, 929 participants; low-certainty evidence). In subgroup analysis, rapid phenotypic susceptibility testing compared to conventional testing may improve time-to-appropriate antibiotic (RR -17.29, CI -45.05 to 10.47; 2 RCTs, 564 participants; low-certainty evidence).

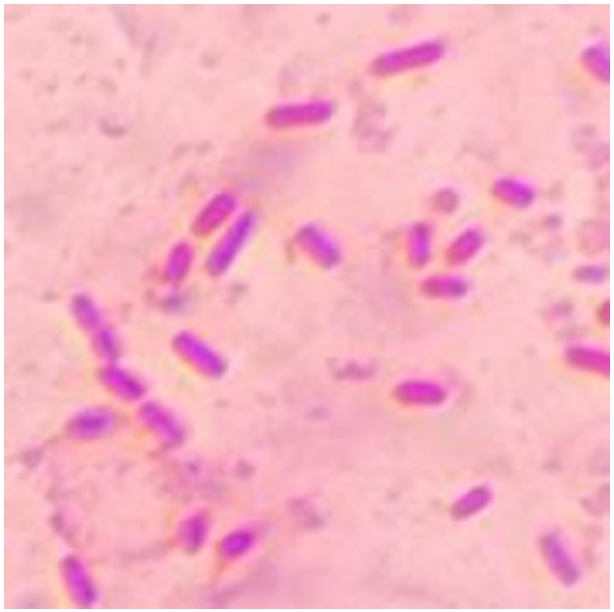
Authors' conclusions

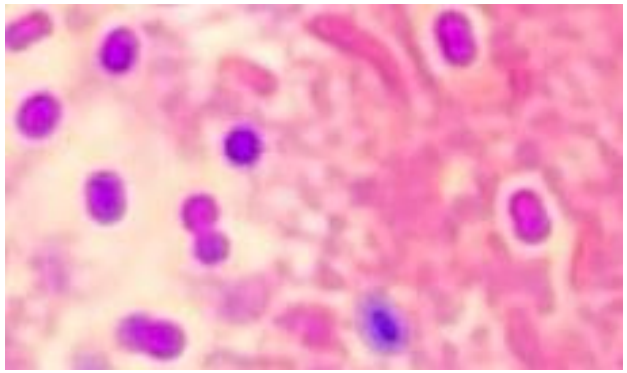
The theoretical benefits of rapid susceptibility testing have not been demonstrated to directly improve mortality, time-to-discharge, or time-to-appropriate antibiotic in these randomized studies. Future large prospective studies should be designed to focus on the most clinically meaningful outcomes, and aim to optimize blood culture pathways.

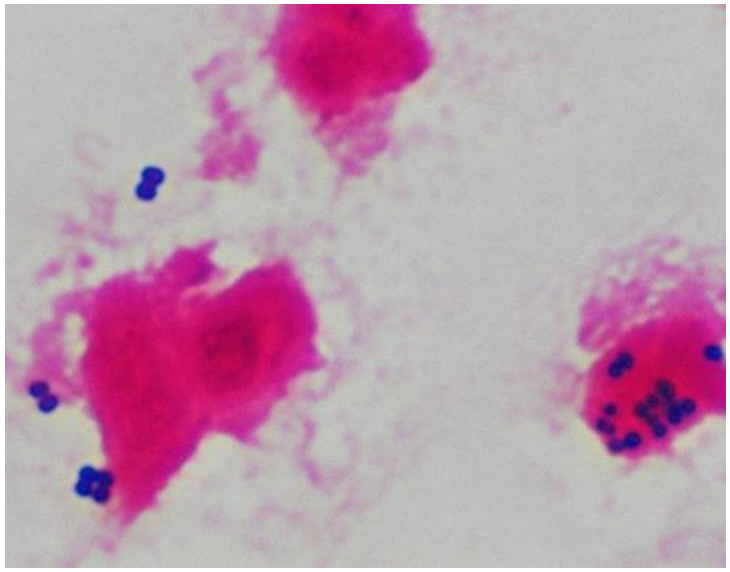
CTF YBÜ antibiyotik tedavi

- Hızlı tedavi: MALDI-TOF ve genotipik testler yok
- Sabah: YBÜ viziti…AMPİRİK AB
- Saat 14-16 arası tüm olası odak örneklerinden (BAL/ETA, idrar, apse,…) GRAM
- GRAM sonucuna göre AB revizyonu
- Gerekliyse kromojenik besiyerine ekim

ETA-Gram







CTF YBÜ antibiyotik tedavi

- HK sinyal verdi
- Gram boyama
- Gram-negatif çomak …hızlı AB
- Kromojenik by pasaj (AB? PS? KES?)
- KES ya da PS ise rutin AB + CAZ/AVI

(CAZ/AVI YBÜ ve Hematoloji olgularında)

Hızlı Karbapenem direnci

Carbapenemase-producing Enterobacteriaceae

Importance of detection of resistance mechanism	
Required for clinical antimicrobial susceptibility categorization	No
Infection control purposes	Yes
Public health purposes	Yes

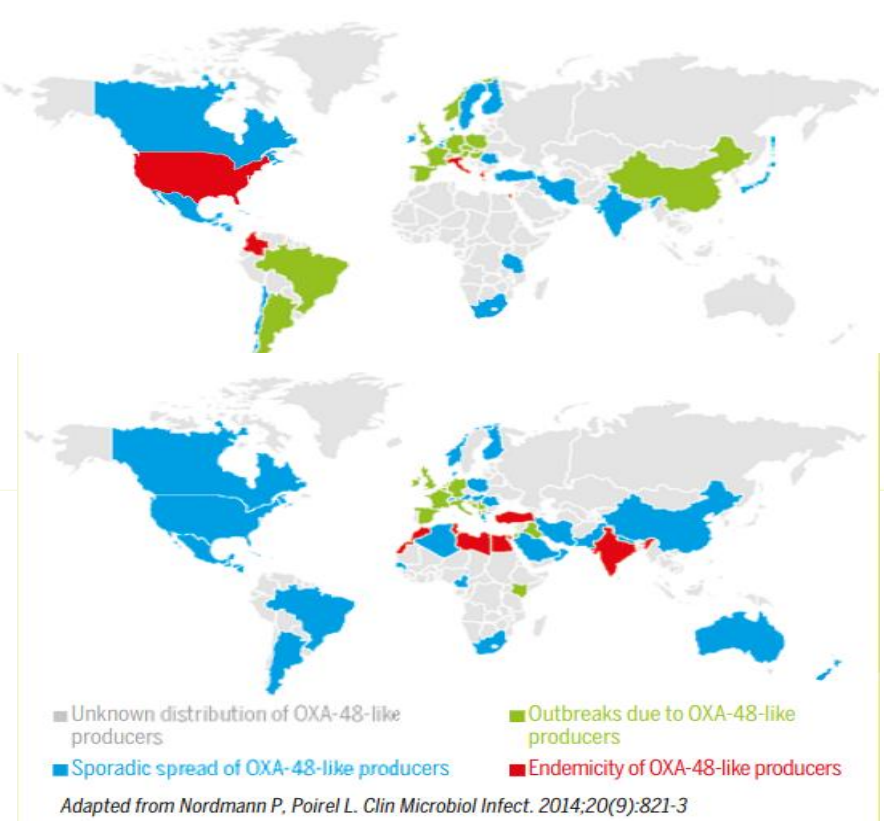
Carbapenem	MIC (mg/L)		Disk diffusion zone diameter (mm) with 10 µg disks	
	S/I breakpoint	Screening cut-off	S/I breakpoint	Screening cut-off
Meropenem[1]	≤2	>0.125	≥22	<28[2]
Ertapenem[3]	≤0.5	>0.125	≥25	<25

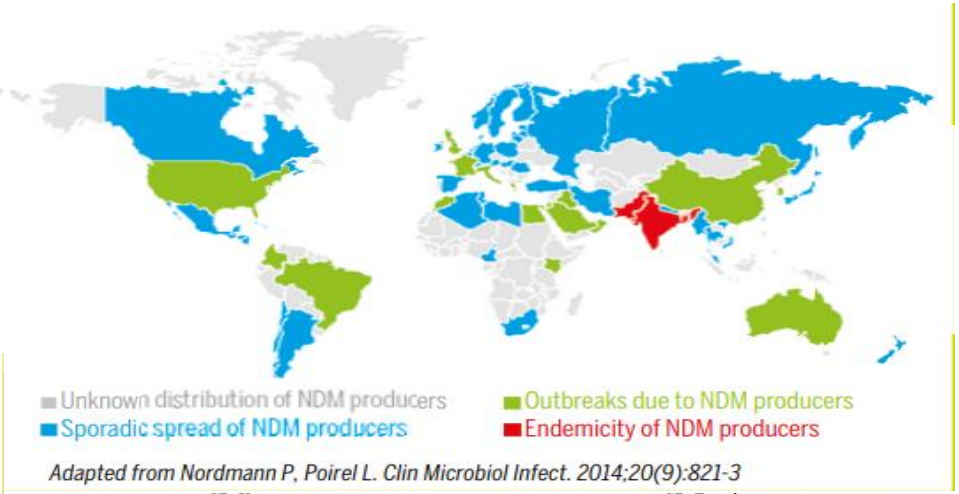
[1]Best balance of sensitivity and specificity

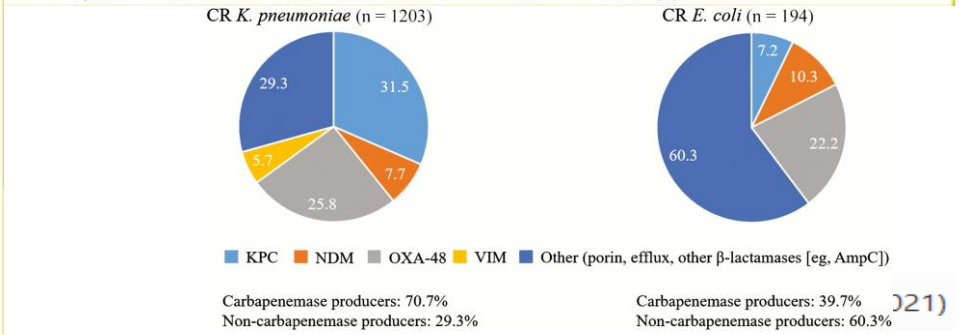
[2]Isolates with 25-27 mm only need to be investigated for carbapenemase-production if they are resistant to piperacillin-tazobactam and/or temocillin (temocillin contributes more to the specificity). Investigation for carbapenemases is always warranted if zone diameter of meropenem is <25 mm.

[3]High sensitivity but low specificity. Can be used as an alternative screening agent, but isolates with ESBL and AmpC may be resistant without having carbapenemases.

Enterobacterales
Karbapenem direnci= ÇİD







Özgün Çalışma/Original Article Mikrobiyol Bul 2021;55(1):1-16/doi: 10.5578/mb.20124

Geliş Tarihi (Received): 25.05.2020 • Kabul Ediliş Tarihi (Accepted): 19.11.2020

Türkiye'de 2019 Yılı İçinde İzole Edilen *Escherichia coli* ve *Klebsiella pneumoniae* İzolatlarında Karbapenemaz Epidemiyolojisi

The Epidemiology of Carbapenemases in *Escherichia coli* and *Klebsiella pneumoniae* Isolated in 2019 in Turkey

Serap SÜZÜK YILDIZ[1](ID), Hüsniye ŞİMŞEK[1](ID), Zekiye BAKKALOĞLU[1](ID), Yasemin NUMANOĞLU ÇEVİK[1](ID), Can Hüseyin HEKİMOĞLU[1](ID), Selçuk KILIÇ[1](ID), Emine ALP MEŞE[2](ID), Ulusal Karbapenemaz Sürveyans Çalışma Grubu*

- 207 karbapenemaz geni

108-OXA-48

34-KPC

31-NDM

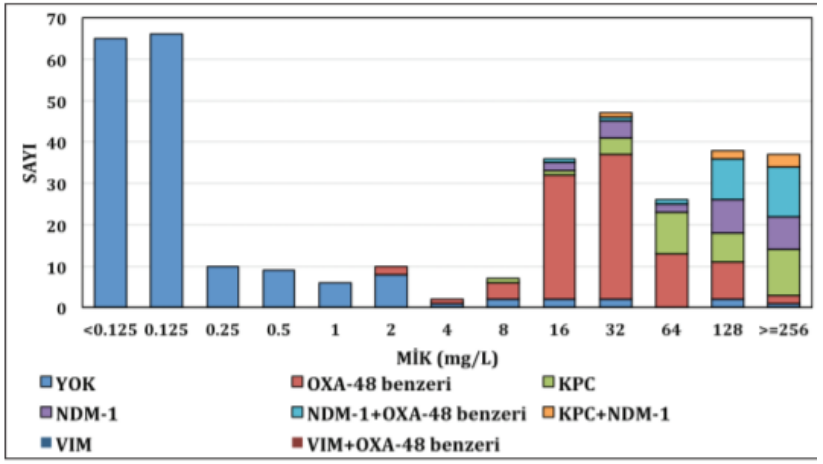
1-VIM

26 OXA + NDM

6 KPC+NDM

1 OXA-48 + VIM

MBL …. 65/207 (% 31.4)



Şekil 6. K.pneumoniae izolatlarının meropenem MİK dağılımlarına göre karbapenemaz enzin tipinin dağılımı.

Karbapenemazlar(Nonfermentatif)

- P.aeruginosa !

VIM, GES, IMP (NDM !)…

Fenotipik testler sorunlu olabiliyor !

Asıl sorun porin defekti, pompa sistemleri

IMP R/MEM S ya da IPM S /MEM R !

- Acinetobacter baumannii

OXA – 23, 58, 24/40, 143, 235

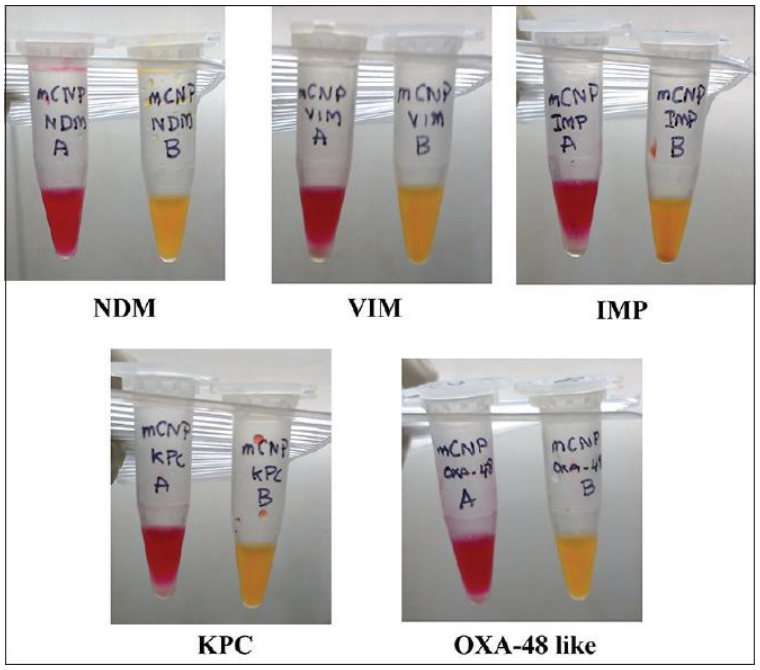
Genotipik metodlar ile ayrım !!!

Karbapenemaz ?

- **Carba NP**

2 saat içinde sonuç !

- Bazı mukoid Klebsiella ve OXA-48 için sorunlu !



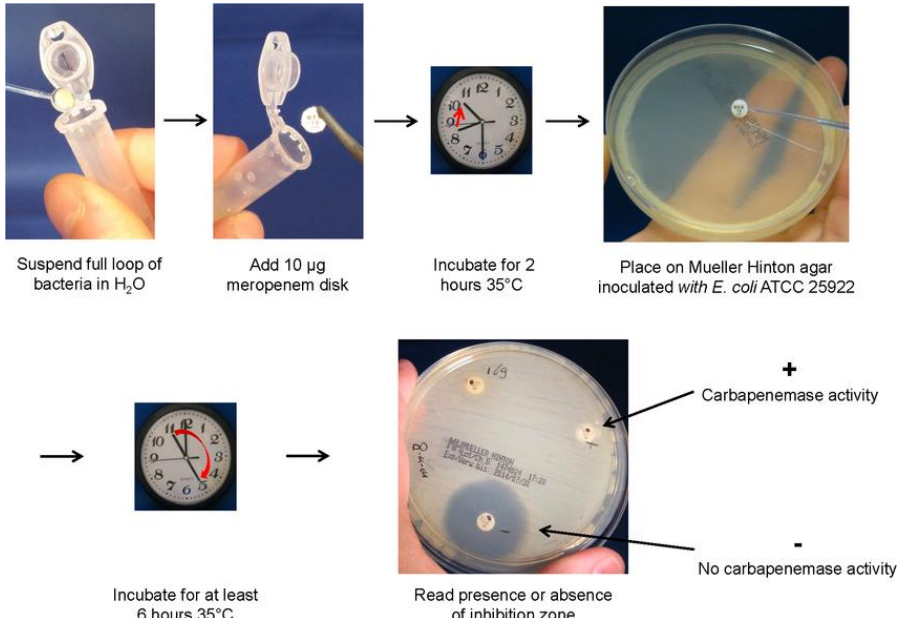
Karbapenemaz ?

- **CIM (Carbapenemase inactivation method)**

8-18 saat gerekli

Negatif prediktif değeri tam bilinmiyor.

Uygun bir alternatif !



Hangi karbapenemaz ?

B-lactamase	Synergy observed as increase in zone diameter (mm) with 10 µg meropenem disk/tablet				Temocillin MIC >128 mg/L or zone diameter <11 mm
	DPA/EDTA	APBA/PBA	DPA+APBA	CLX	
MBL	+	-	-	-	Variable[1]
KPC	-	+	-	-	Variable[1]
MBL + KPC[2]	Variable	Variable	+	-	Variable[1]
OXA-48-like	-	-	-	-	Yes
AmpC + porin loss	-	+	-	+	Variable[1]
ESBL + porin loss	-	-	-	-	No

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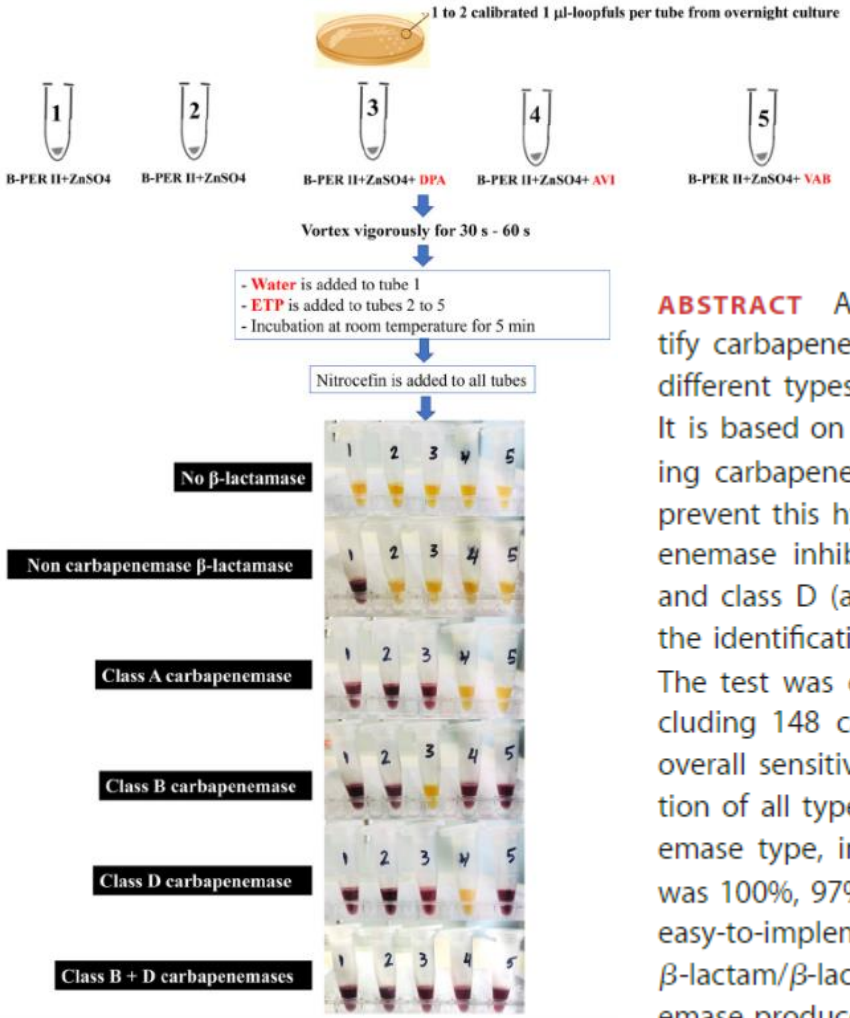
BACTERIOLOGY

NitroSpeed-Carba NP Test for Rapid Detection and Differentiation between Different Classes of Carbapenemases in *Enterobacterales*



ABSTRACT A biochemical test (NitroSpeed-Carba NP test) was developed to identify carbapenemase production in *Enterobacterales* and to discriminate between the different types of clinically significant carbapenemases (Ambler classes A, B, and D). It is based on two main features, namely, the hydrolysis by all β-lactamases, including carbapenemases of the nitrocefin substrate, and the capacity of ertapenem to prevent this hydrolysis for all β-lactamases except carbapenemases. Specific carbapenemase inhibitors of class A (avibactam, vaborbactam), class B (dipicolinic acid), and class D (avibactam) were used to inhibit the nitrocefin hydrolysis and to allow the identification of the carbapenemase types with a turnaround time of ca. 30 min. The test was evaluated with a collection of 248 clinical enterobacterial isolates, including 148 carbapenemase producers and 100 non-carbapenemase producers. Its overall sensitivity and specificity were 100% and 97%, respectively, including detection of all types of OXA-48-like carbapenemases. For the detection of the carbapenemase type, including strains that produce double carbapenemases, the sensitivity was 100%, 97%, and 100% for the detection of classes A, B, and D, respectively. This easy-to-implement test may contribute to optimization of the choice of the β-lactam/β-lactamase inhibitor combinations for treating infection due to carbapenemase producers.

Clinical and laboratory considerations for the rapid detection of carbapenem-resistant Enterobacteriaceae

Ritu Banerjee & Romney Humphries

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Table 1.

Test (Manufacturer)	Specimen Type	Carbapenemase Gene(s) Detected	Regulatory Status	References
FilmArray® Blood Culture Identification Panel (BioFire)	Positive Blood Culture Broth	bla_{KPC}	US. FDA Cleared CE-IVD	19-22
Verigene® Gram-negative blood culture test (Nanosphere)	Positive Blood Culture Broth	bla_{KPC} bla_{IMP} bla_{VIM} bla_{NDM} bla_{OXA-48}	US. FDA Cleared CE-IVD	23-24
Unyvero® P55 (Curetis AG)	Respiratory secretions	bla_{KPC} bla_{IMP} bla_{VIM} bla_{NDM} bla_{OXA-48}	CE-IVD	25
GeneXpert Carba-R (Cepheid)	Rectal swabs	bla_{KPC} bla_{IMP} bla_{VIM} bla_{NDM} bla_{OXA-48}	US. FDA Cleared CE-IVD	26

Note. US. FDA, United States Food and Drug Administration; CE-IVD, Conformite Europeene *In Vitro* Diagnostic.

Elimizdekiler

- Yüksek doz/Dual karbapenem
- Kolistin/Polimiksin-B
- Fosfomisin
- Tigesiklin
- Aminoglikozit (Amikasin)

- Seftazidim-Avibaktam

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

ESBL – Extended spectrum beta-lactamase

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

KPC - Klebsiella pneumoniae carbapenemase

OXA - Oxacillin carbapenemase number 48

NDM - New Delhi metallo-beta-lactamase

P. aeruginosa'ya karşı etkinlik

Mekanizmalar	Ceftazidime	Cefepime	Imipenem	Meropenem	Ceftazidime-avibactam
AmpC	R	S	S	S	S
Efflux	S/I	I/R	S/I	I/R	S/I
Porin OprD	S	S	R	S	S
+ ESBL (GES, PER…)	R	R	S	S	S
+ ESBL (OXA)	R	R	S	S	S
GES carbapenemases	R	R	R	R	S
+ MBL (VIM, IMP…)	R	R	R	R	R

ESBL, extended-spectrum β-lactamase, intermediate; R, resistant; S, susceptible
Adapted from Livermore D et al. *J Antimicrob Chemother*. 2018;73:648-57

ÇİD Tedavisi Seçenekler

- Kolsitin : BMD/ Disk elüsyon !
- Fosfomisin: Agar Dilüsyon
- Tigesiklin : (E.coli için DD, diğerlerine MİK)
- CAZ-AVİ: Disk difüzyon !!!

	Enterobacteriacea		Pseudomonas aeruginosa	
Disk Difüzyon EUCAST (10/4)	≥13	<13	≥17	17
Disk Difüzyon CLSI (30/20)	≥21	<20		
Broth Dilüsyon MİK	≥8	<8	≥8	<8
E Test	≥8	<8	≥8	<8

GLASS
The detection and reporting of colistin resistance
Second edition

Global Antimicrobial Resistance and Use Surveillance System (GLASS)

World Health Organization

CLSI has recently included two additional methods, Colistin Broth Disk Elution (CBDE) and Colistin Agar Test (CAT) as acceptable for detection of colistin resistance *(59)*. Broth microdilution remains the only approved and recommended method for polymyxin B.

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BACTERIOLOGY

Two-Site Evaluation of the Colistin Broth Disk Elution Test To Determine Colistin *In Vitro* Activity against Gram-Negative Bacilli

Patricia J. Simner,[a] Yehudit Bergman,[a] Marisol Trejo,[b] Ava A. Roberts,[a] Remy Marayan,[a] Tsigereda Tekle,[a] Shelley Campeau,[c] Abida Q. Kazmi,[a] Drew T. Bell,[a] Shawna Lewis,[a] Pranita D. Tamma,[d] Romney Humphries,[c] Janet A. Hindler[b,e]

4 μg/ml on repeat testing. The results for all other isolates were in CA with those of BMD. CBDE versus BMAD had an EA of 100% and a CA of 100%. Compared to currently used techniques, CBDE is an easy and practical method to perform colistin MIC testing. Some *mcr-1*-producing isolates yielded MICs of 2 μg/ml by CBDE and 4 μg/ml by BMD. As such, the results for isolates with colistin MICs of 2 μg/ml by CBDE should be confirmed by the reference BMD method, and isolates with MICs of ≥2 μg/ml should be evaluated for the presence of *mcr* genes.

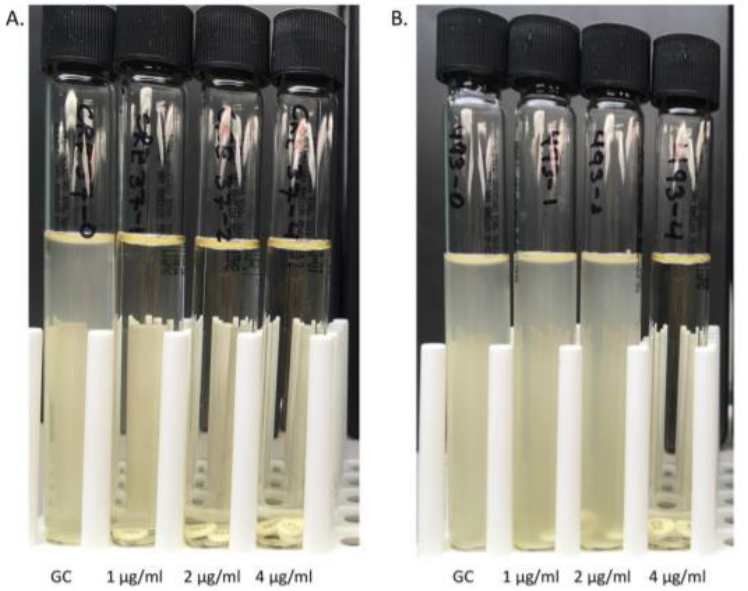


FIG 1 Colistin broth disk elution method. CBDE is performed with four 10-ml cation-adjusted Mueller-Hinton broth tubes per isolate, to which 0, 1, 2, and 4 colistin disks (10 μg) are added, generating fina concentrations of 0 (growth control [GC]), 1, 2, and 4 μg/ml, respectively. (A) Tubes for a non-carbapenemase-producing carbapenem-resistant *Klebsiella pneumoniae* isolate with a colistin MIC o ≤1 μg/ml. (B) Tubes for an *mcr-1*-producing *Escherichia coli* isolate (CDC AR Bank accession number 493 with a colistin MIC of 4 μg/ml.

NDM vs CAZ/AVI

- ÜSE etkenlerinde karbapenem direnci

3242 Enterobacterales 150 CRE (%5)

46 ileri inceleme (45/46 CAZ/AVI S)

OXA-48,NDM,VIM,IMP KPC bakıldı

OXA-48….25

NDM-….12

OXA-48 +NDM….6

3 kökende rezistogram….OXA-534
KPC-3

- NDM !!!
- CAZ/AVI duyarlı?

- Ayrıntılı inceleme yapıldığında bir çok yeni direnç geni saptanabiliyor

Uzmanlık Tezi (2021)

Münevver S. Güler

Zhang et al. Antimicrobial Resistance and Infection Control (2018) 7:142
https://doi.org/10.1186/s13756-018-0435-9

Antimicrobial Resistance and Infection Control

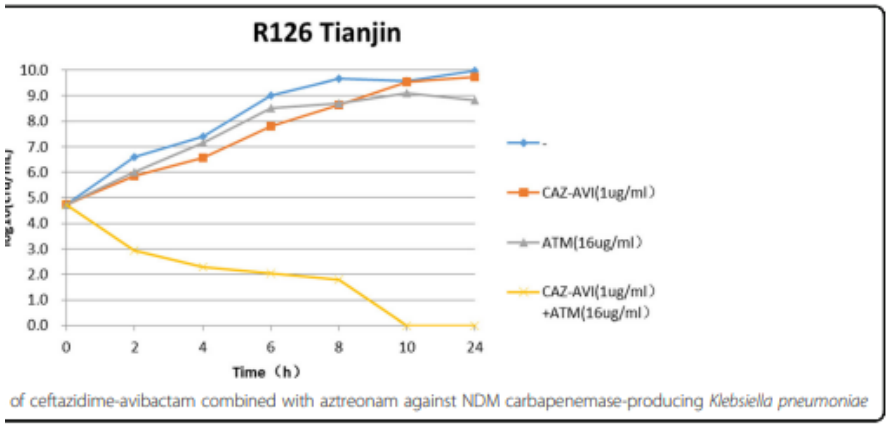
RESEARCH Open Access

In vitro and in vivo bactericidal activity of ceftazidime-avibactam against Carbapenemase–producing *Klebsiella pneumoniae*

Wenxia Zhang[1,2†], Yan Guo[1,4†], Jiayin Li[3†], Yiyuan Zhang[3], Yang Yang[1,4], Dong Dong[1,4], Demei Zhu[1,4], Ping He[3*] and Fupin Hu[1,4*]

Table 2 Results of MIC and antimicrobial susceptibility testing of ceftazidime-avibactam single dosing and combined with aztreonam against NDM + KPC-2 carbapenemase-producing *Klebsiella pneumoniae* in 30 strains

Strain no.	Bacteria	β-lactamase	MIC(mg/L) single dosing		MIC(mg/L) Combined dosing		FIC value	Associated β-lactamase
			ATM	CAZ-AVI	ATM	CAZ-AVI	ATM + CAZ-AVI	
R078 Anhui	*K. pneumoniae*	NDM	256	32	8	1	0.06	SHV-28, DHA-1, CTX-M-15
R080 Hainan	*K. pneumoniae*	NDM	128	4	32	0.25	0.31	SHV-11, DHA-1, CTX-M-14
R081 Hainan	*K. pneumoniae*	NDM	1024	8	64	2	0.31	SHV-11, DHA-1, CTX-M-14
R082 Hainan	*K. pneumoniae*	NDM	256	64	16	1	0.08	SHV-11, DHA-1, CTX-M-15, CTX-M-14
R083 Hainan	*K. pneumoniae*	NDM	128	64	32	0.5	0.26	SHV-12, DHA-1, CTX-M-15
R084 Hainan	*K. pneumoniae*	NDM	512	64	16	1	0.05	SHV-12, DHA-1
R085 Hainan	*K. pneumoniae*	NDM	1024	128	32	2	0.05	SHV-12, DHA-1, CTX-M-15
R086 Hainan	*K. pneumoniae*	NDM	128	64	16	0.5	0.13	SHV-12, DHA-1, CTX-M-15
R088 Hainan	*K. pneumoniae*	NDM	32	2	4	0.5	0.38	SHV-11, DHA-1, CTX-M-14
R093 Hebei	*K. pneumoniae*	NDM	32	64	4	0.5	0.13	SHV1, DHA-1, CTX-M-14
R094 Hebei	*K. pneumoniae*	NDM	32	64	8	0.25	0.25	SHV-12, DHA-1, CTX-M-14
R095 Hebei	*K. pneumoniae*	NDM	32	2	8	0.25	0.38	SHV-12, DHA-1, CTX-M-15
R096 Henan	*K. pneumoniae*	NDM	16	64	16	0.5	1.01	SHV1, DHA-1, CTX-M-15
R097 Henan	*K. pneumoniae*	NDM	8	256	4	128	1.00	SHV1, DHA-1, CTX-M-14
R098 Henan	*K. pneumoniae*	NDM	256	64	32	1	0.14	DHA-1
R100 Shanxi	*K. pneumoniae*	NDM	8	32	4	32	1.50	SHV-78, DHA-1, CTX-M-14
R101 Shanxi	*K. pneumoniae*	NDM	256	128	16	1	0.07	SHV-78, DHA-1, CTX-M-14
R102 Shanxi	*K. pneumoniae*	NDM	32	256	4	1	0.13	SHV-78, DHA-1, CTX-M-14
R103 Shanxi	*K. pneumoniae*	NDM	128	64	32	0.25	0.25	SHV1, DHA-1, CTX-M-15
R106 Sanxi	*K. pneumoniae*	NDM	128	64	8	1	0.08	SHV-12, DHA-1
R110 Sanxi	*K. pneumoniae*	NDM	128	256	8	1	0.07	SHV-12, DHA-1
R113 Sanxi	*K. pneumoniae*	NDM	128	64	16	0.5	0.13	SHV-12, DHA-1
R122 Tianjin	*K. pneumoniae*	NDM	32	1	4	0.25	0.38	SHV-12, DHA-1, CTX-M-14
R126 Tianjin	*K. pneumoniae*	NDM	512	64	16	1	0.05	SHV-12, DHA-1, CTX-M-14
R127 Tianjin	*K. pneumoniae*	NDM	256	128	32	1	0.13	SHV2, DHA-1
R128 Zhejiang	*K. pneumoniae*	NDM	128	256	8	2	0.07	SHV1, DHA-1
R129 Zhejiang	*K. pneumoniae*	NDM	4	0.5	0.5	0.125	0.38	SHV-12, DHA-1, CTX-M-15
R136 Zhejiang	*K. pneumoniae*	NDM	256	64	16	1	0.08	SHV-12, DHA-1
R148 Tianjing	*K. pneumoniae*	KPC-2,NDM	2048	8	256	2	0.38	SHV-12, DHA-1, CTX-M-14
R153 Henan	*K. pneumoniae*	KPC-2,NDM	2048	128	128	8	0.13	SHV-12, DHA-1



of ceftazidime-avibactam combined with aztreonam against NDM carbapenemase-producing *Klebsiella pneumoniae*

J Antimicrob Chemother. 2020 Apr 1;75(4):997-1005. doi: 10.1093/jac/dkz532.

Metallo-β-lactamase resistance in Enterobacteriaceae is an artefact of currently utilized antimicrobial susceptibility testing methods

Tomefa E Asempa [1], Kamilia Abdelraouf [1], David P Nicolau [1 2]

Conclusions: Results indicate that meropenem in vivo efficacy is best represented by the pharmacodynamic profile generated using MICs determined in zinc-depleted media for MBL-producing Enterobacteriaceae. These translational data suggest that the use of conventional CAMHB for MBL susceptibility testing is inappropriate in distinguishing meaningful in vivo resistance given that zinc concentrations are supraphysiological in conventional CAMHB and negligible at infection site

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MINIREVIEW
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Activity of β-Lactam Antibiotics against Metallo-β-Lactamase-Producing *Enterobacterales* in Animal Infection Models: a Current State of Affairs

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[b]Division of Infectious Diseases, Hartford Hospital, Hartford, Connecticut, USA

ABSTRACT Metallo-β-lactamases (MBLs) result in resistance to nearly all β-lactam antimicrobial agents, as determined by currently employed susceptibility testing methods. However, recently reported data demonstrate that variable and supraphysiologic zinc concentrations in conventional susceptibility testing media compared with physiologic (bioactive) zinc concentrations may be mediating discordant *in vitro-in vivo* MBL resistance. While treatment outcomes in patients appear suggestive of this discordance, these limited data are confounded by comorbidities and combination therapy. To that end, the goal of this review is to evaluate the extent of β-lactam activity against MBL-harboring *Enterobacterales* in published animal infection model studies and provide contemporary considerations to facilitate the optimization of current antimicrobials and development of novel therapeutics.

CAZ/AVI endikasyon FDA/EU

Complicated Intra-Abdominal Infections (cIAI)

AVYCAZ® (ceftazidime and avibactam), in combination with metronidazole, is indicated for the treatment of complicated intra-abdominal infections (cIAI), in adult and pediatric patients 3 months or older caused by the following susceptible Gram-negative microorganisms: *Escherichia coli, Klebsiella pneumoniae, Proteus mirabilis, Enterobacter cloacae, Klebsiella oxytoca, Citrobacter freundii* complex, and *Pseudomonas aeruginosa*.

Complicated Urinary Tract Infections (cUTI), including Pyelonephritis

AVYCAZ is indicated for the treatment of complicated urinary tract infections (cUTI) including pyelonephritis in adult and pediatric patients 3 months or older caused by the following susceptible Gram-negative microorganisms: *Escherichia coli, Klebsiella pneumoniae, Enterobacter cloacae, Citrobacter freundii* complex, *Proteus mirabilis,* and *Pseudomonas aeruginosa*.

Hospital-acquired Bacterial Pneumonia and Ventilator-associated Bacterial Pneumonia (HABP/VABP)

AVYCAZ is indicated for the treatment of hospital-acquired bacterial pneumonia and ventilator-associated bacterial pneumonia (HABP/VABP) in patients 18 years or older caused by the following susceptible Gram-negative microorganisms: *Klebsiella pneumoniae, Enterobacter cloacae, Escherichia coli, Serratia marcescens, Proteus mirabilis, Pseudomonas aeruginosa,* and *Haemophilus influenzae*.

Table 1: Recommended dose for adults with estimated CrCL > 50 mL/min[1]

Type of infection	Dose of ceftazidime/avibactam	Frequency	Infusion time	Duration of treatment
cIAI[2,3]	2 g/0.5 g	Every 8 hours	2 hours	5-14 days
cUTI, including pyelonephritis[3]	2 g/0.5 g	Every 8 hours	2 hours	5-10 days[4]
HAP/VAP[3]	2 g/0.5 g	Every 8 hours	2 hours	7-14 days
Bacteraemia associated with, or suspected to be associated with any of the above infections	2 g/0.5 g	Every 8 hours	2 hours	Duration of treatment should be in accordance with the site of infection.
Infections due to aerobic Gram-negative organisms in patients with limited treatment options[2,3]	2 g/0.5 g	Every 8 hours	2 hours	Guided by the severity of the infection, the pathogen(s) and the patient's clinical and bacteriological progress[5]

28 Nisan 2021 ÇARŞAMBA — Resmî Gazete — Sayı : 31468 **(Mükerrer)**

TEBLİĞ

Sosyal Güvenlik Kurumu Başkanlığından:

SOSYAL GÜVENLİK KURUMU SAĞLIK UYGULAMA TEBLİĞİNDE DEĞİŞİKLİK YAPILMASINA DAİR TEBLİĞ

6.1	Seftazidim pentahidrat ve Avibaktam sodyum	Komplike intraabdominal enfeksiyon, piyelonefrit dahil komplike idrar yolu enfeksiyonu veya ventilatör ile ilişkili pnömoni dahil hastanede kazanılmış pnömoni tedavisinde; karbapenem, aminoglikozid ve 3 üncü kuşak diğer sefalosporinlere dirençli ve seftazidim pentahidrat ve avibaktam sodyum tedavisine duyarlı olduğu in-vitro olarak ispatlanmış hastalarda enfeksiyon hastalıkları uzman hekimlerince düzenlenen sağlık raporuna istinaden ikinci ve/veya üçüncü basamak yoğun bakım tedavilerinde kullanılması halinde Kurumca bedelleri karşılanır.

CRE tedavi !

TABLE 3 Summary of recommended regimens for treatment of infections caused by carbapenem-resistant *Enterobacteriaceae*[a]

Risk level, therapy type, and isolate susceptibility	Drugs
High risk,[b] combination therapy	
Susceptible to a β-lactam (use according to susceptibility)	Backbone: ceftazidime-avibactam (preferred) or meropenem-vaborbactam; alternatively, meropenem (if MIC is ≤8 mg/liter) or ceftazidime or aztreonam Accompanying drug (no data available about the need for combination therapy if ceftazidime-avibactam or meropenem-vaborbactam is used as the backbone): colistin, tigecycline, aminoglycoside, or fosfomycin (if isolate is intermediate to the backbone drug, consider using 2 of these)
Resistant to all β-lactams (including isolates with meropenem MICs of >8 mg/liter), susceptible to at least 2 drugs, including colistin	Backbone: colistin Accompanying drug: tigecycline, aminoglycoside (high risk of nephrotoxicity), or fosfomycin
Resistant to all β-lactams and colistin, susceptible to at least 2 drugs	Backbone: tigecycline or aminoglycoside Accompanying drug: tigecycline or aminoglycoside, fosfomycin
Pandrug-resistant or susceptible to only one drug	Meropenem plus ertapenem or ceftazidime-avibactam plus aztreonam; add any active drug; consider active investigational drugs if available; consider *in vitro* testing of combinations for synergy
Low risk,[c] monotherapy	
According to susceptibility	Ceftazidime-avibactam, meropenem-vaborbactam, meropenem, ceftazidime, aztreonam, colistin, tigecycline, aminoglycoside (if intermediate susceptibility, choose another option or use combination)

CRE-tedavi (doz)

TABLE 2 Recommended dosing for the most frequently used drugs against carbapenem-resistant *Enterobacteriaceae* (CRE) for patients with normal renal function[a]

Drug	Usual/standard dose(s)	Dosing for CRE and comments
Meropenem	1 g/8 h	2 g/8 h by EI (isolates with MICs of 2–8 mg/liter; for isolates with higher MICs, it is probably not efficacious)
Ertapenem	1 g/24 h	Consider 2 g/day for double-carbapenem regimens
Colistin[b]	From the EMA, loading dose, 6–9 MU, and then 9 MU/day in 2–3 doses; from the FDA, 2.5–5 mg of colistin base activity/kg/day	EMA dose is recommended for severe CRE infections; the need for a loading dose and high continuation dose in patients without severe infection/shock is controversial
Polymyxin B[c]	From the FDA, 1.5–2.5 mg/kg/day in 2 doses	For mild infections and isolates with MICs of ≤1 mg/liter, the FDA dose is probably appropriate; for severe infections and isolates with MICs of up to 4 mg/liter, a loading dose of 2–2.5 mg/kg followed by 3 mg/kg/day in 2 doses is recommended (controversially)
Tigecycline	100-mg loading dose and then 50 mg/12 h	For HAP, cUTI, BSI, or shock, consider a 200-mg loading dose and then 100 mg/12 h
Gentamicin, tobramycin	5–7 mg/kg/day	For HAP or shock without other options, higher doses (10–15 mg/kg) might be considered, but the risk of toxicity is high; TDM is recommended
Amikacin	15–20 mg/kg/day	For HAP or shock without other options, higher doses (25–30 mg/kg) might be considered, but the risk of toxicity is high; TDM is recommended
Fosfomycin	4 g/6 h to 8 g/8 h	Use in combination; high sodium concn
Temocillin	2 g/8–12 h	KPC producers are occasionally susceptible; continuous infusion improves PK-PD target attainment
Aztreonam	1–2 g/8 h	MBL producers are susceptible if they are not ESBL or AmpC producers
Ceftazidime	1–2 g/8 h	OXA-48 producers are susceptible if they are not ESBL or AmpC producers
Ceftazidime-avibactam	2.5 g/8 h	KPC and OXA-48 producers are frequently susceptible
Meropenem-vaborbactam	2/2 g/8 h	KPC producers are frequently susceptible

[a]Please refer to the text for explanations and references. EI, extended infusion; EMA, European Medicines Agency; FDA, U.S. Food and Drug Administration; HAP, hospital-acquired pneumonia; cUTI, complicated urinary tract infection; BSI, bloodstream infection; MU, million units; TDM, therapeutic drug monitoring; MBL, metallo-β-lactamase.

[b]One million units of colistimethate sodium = 80 mg colistimethate sodium = 34 mg of colistin base activity.

[c]One million units of polymyxin B = 100 mg of colistin base activity.

IDSA Infectious Diseases Society of America hivma hiv medicine association OXFORD

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

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

Table 3. Recommended antibiotic treatment options for carbapenem-resistant Enterobacterales (CRE), assuming *in vitro* susceptibility to agents in table

Source of Infection	**Preferred Treatment**	**Alternative Treatment** (first-line options not available or tolerated)
Cystitis	Ciprofloxacin, levofloxacin, trimethoprim-sulfamethoxazole, nitrofurantoin, or a single-dose of an aminoglycoside Meropenem[1] (standard-infusion): only if ertapenem resistant, meropenem susceptible, AND carbapenemase testing results are either not available or negative.	Ceftazidime-avibactam, meropenem-vaborbactam, imipenem-cilastatin-relebactam, and cefiderocol Colistin (only when no alternative options are available)
Pyelonephritis or cUTI[2]	Ceftazidime-avibactam, meropenem-vaborbactam, imipenem-cilastatin-relebactam, and cefiderocol Meropenem[1] (extended-infusion): only if ertapenem resistant, meropenem susceptible, AND carbapenemase testing results are either not available or negative.	Once-daily aminoglycosides
Infections outside of the urinary tract Resistant to ertapenem, susceptible to meropenem, AND carbapenemase testing results are either not available or negative	Meropenem[1] (extended-infusion)	Ceftazidime-avibactam
Infections outside of the urinary tract Resistant to ertapenem, meropenem, AND carbapenemase testing results are either not available or negative	Ceftazidime-avibactam, meropenem-vaborbactam, and imipenem-cilastatin-relebactam	Cefiderocol Tigecycline, eravacycline (intra-abdominal infections)

Clinical Infectious Diseases

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KPC identified (Or carbapenemase positive but identity of carbapenemase unknown[3])	Ceftazidime-avibactam, meropenem-vaborbactam, imipenem-cilastatin-relebactam	Cefiderocol Tigecycline, eravacycline (intra-abdominal infections)
Metallo-β-lactamase (i.e., NDM, VIM, or IMP) carbapenemase identified	Ceftazidime-avibactam + aztreonam, cefiderocol	Tigecycline, eravacycline (intra-abdominal infections)
OXA-48-like carbapenemase identified	Ceftazidime-avibactam	Cefiderocol Tigecycline, eravacycline (intra-abdominal infections)

Clinical Infectious Diseases

IDSA FEATURES

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

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

Question 6: What is the role of polymyxins for the treatment of infections caused by CRE?

Recommendation: Polymyxin B and colistin should be avoided for the treatment of infections caused by CRE. Colistin can be considered as a last resort for uncomplicated CRE cystitis.

Rationale: Observational and randomized-controlled trial data indicate increased mortality and excess nephrotoxicity associated with polymyxin-based regimens relative to comparator agents [59-61, 63]. Concerns about the clinical effectiveness of polymyxins and accuracy of *in vitro* polymyxin susceptibility testing led the Clinical and Laboratory Standards Institute to eliminate a susceptible category for colistin and polymyxin B [18]. The panel recommends that these agents be avoided for the treatment of CRE infections, with the exception of colistin as a last resort agent against CRE cystitis. Polymyxin B should not be used as treatment for CRE cystitis, due to its predominantly nonrenal clearance.

59. Shields RK, Nguyen MH, Chen L, et al. Ceftazidime-Avibactam Is Superior to Other Treatment Regimens against Carbapenem-Resistant Klebsiella pneumoniae Bacteremia. Antimicrob Agents Chemother **2017**; 61(8): e00883-17.
60. van Duin D, Lok JJ, Earley M, et al. Colistin Versus Ceftazidime-Avibactam in the Treatment of Infections Due to Carbapenem-Resistant Enterobacteriaceae. Clin Infect Dis **2018**; 66(2): 163-71.
61. Wunderink RG, Giamarellos-Bourboulis EJ, Rahav G, et al. Effect and Safety of Meropenem-Vaborbactam versus Best-Available Therapy in Patients with Carbapenem-Resistant Enterobacteriaceae Infections: The TANGO II Randomized Clinical Trial. Infect Dis Ther **2018**; 7(4): 439-55.

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MAJOR ARTICLE

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

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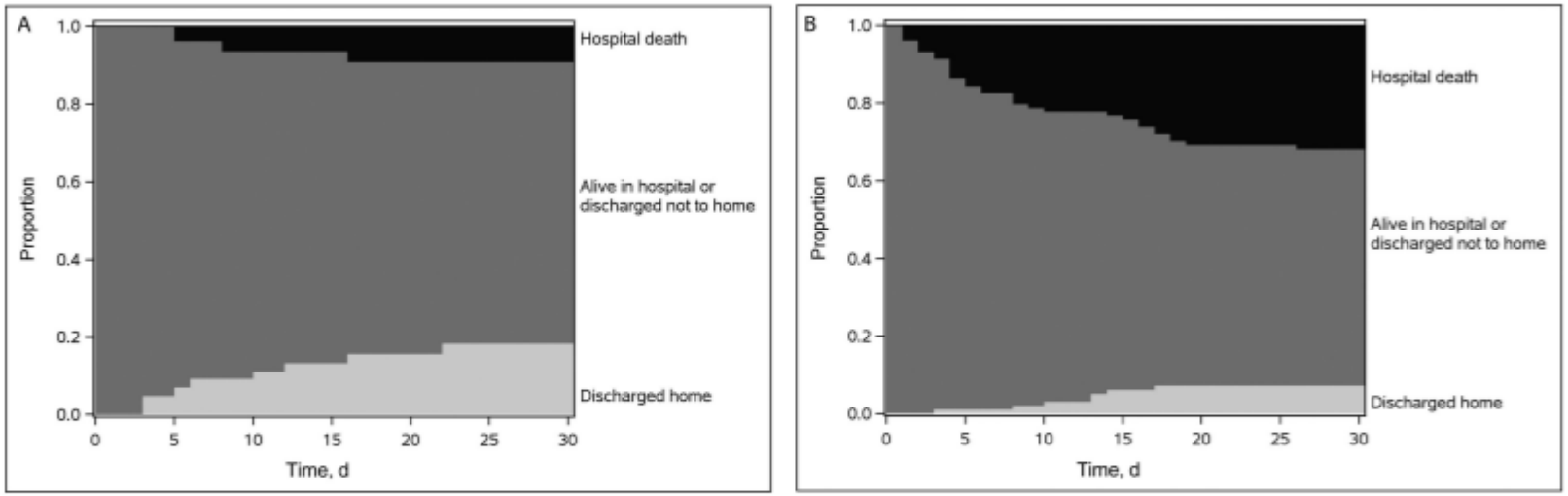

Figure 1. Inverse probability of treatment weighting (IPTW)–adjusted efficacy: disposition over time (n = 137; IPTW-adjusted probability estimates of hospital mortality and discharge status). *A*, Ceftazidime-avibactam group (n = 38). *B*, Colistin group (n = 99).

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IDSA FEATURES

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Table 4: Recommended antibiotic treatment options for difficult-to-treat (DTR) *Pseudomonas aeruginosa*, assuming *in vitro* susceptibility to agents in table

Source of Infection	**Preferred Treatment**	**Alternative Treatment** (when first-line options not available/tolerated)
Cystitis	Ceftolozane-tazobactam, ceftazidime-avibactam, imipenem-relebactam, cefiderocol, or a single-dose of an aminoglycoside	Colistin
Pyelonephritis or cUTI[1]	Ceftolozane-tazobactam, ceftazidime-avibactam, imipenem-cilastatin-relebactam, and cefiderocol	Once-daily aminoglycosides
Infections outside of the urinary tract	Ceftolozane-tazobactam, ceftazidime-avibactam, or imipenem-cilastatin-relebactam	Cefiderocol Aminoglycoside monotherapy: limited to uncomplicated bloodstream infections with complete source control[2]

SONUÇ

- Karbapenem direnci ve direnç genleri izlenmeli !
- Karbapenem direncinde CAZ/AVI önemli bir seçenek
- Hızlı etken ve antibiyotik direnç tayini !
- Hızlı karbapenemaz saptanması !
- CAZ/AVI direnci ?
- Enfeksiyon Kontrolü önceliğimiz olmalı

ENFEKSİYON KONTROLÜ ELLERİNİZDEDİR