Çoklu Dirençli Mikroorganizmalarda Olgu Temelli Yönetim

Prof. Dr. Halis Akalın

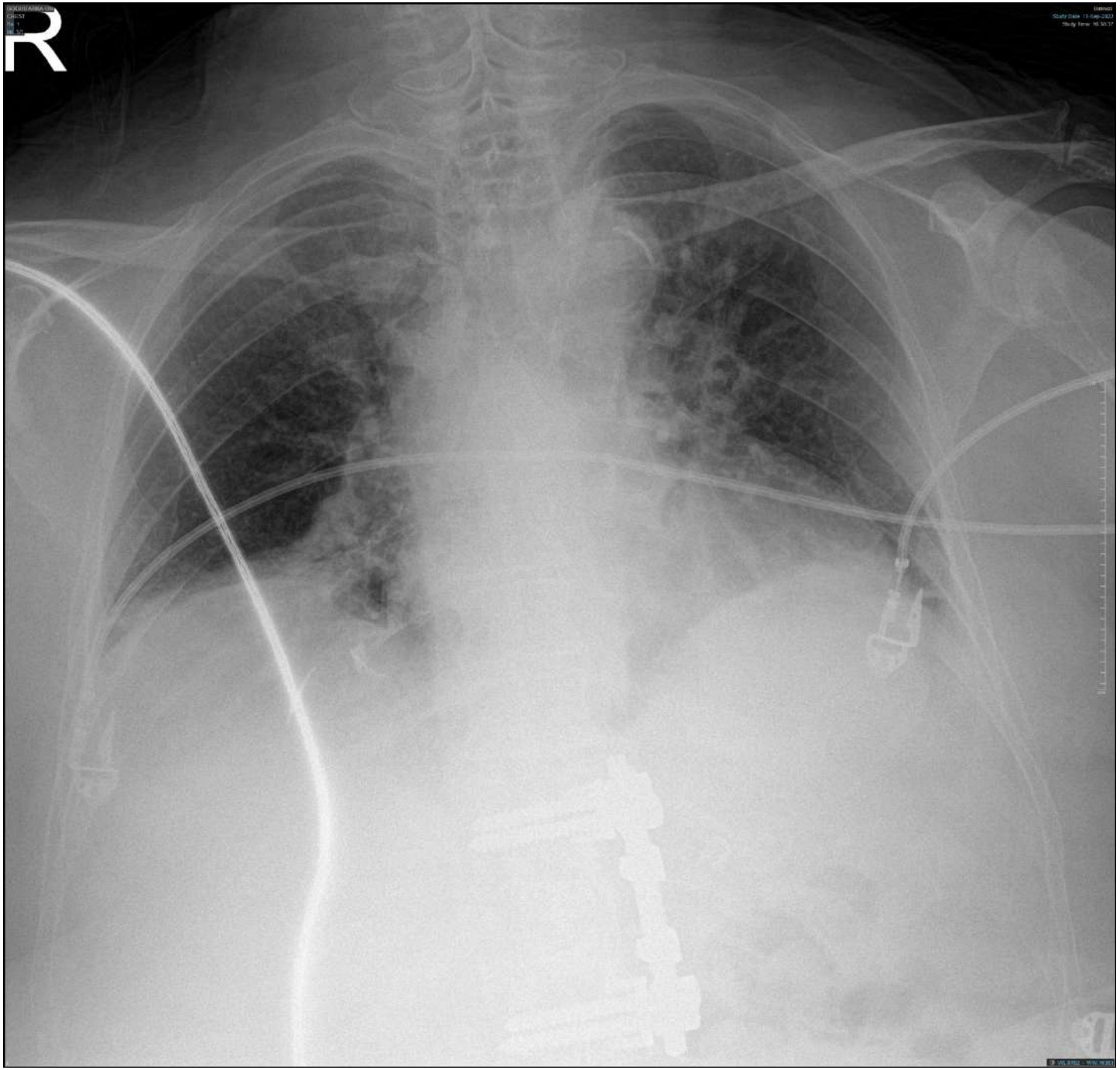
Bursa Uludağ Üniversitesi Tıp Fakültesi

Olgu Sunumu

- 74 yaşında kadın hasta
- Hipertansiyon
- Atrial Fibrilasyon
- Kor Pulmonale
- Hipotiroidi
- Astım
- Cordarone, levotiron, beta-bloker, ürikoliz, lasix
- Kardiyoloji YBÜ 11-16.8.2022
- Kardiyoloji Kliniği 16-23.8.2022
  -Deliryum ve ateş: Sepsis tanısı ile teikoplanin + sefepim(daha sonra meropenem) 12 günlük tedavi
- Göğüs Hastalıkları Kliniği 24.8.2022-11.09.2022
- Göğüs Hastalıkları Kliniğinden Reanimasyona alınmış(GKS'de gerileme olması nedeniyle)

- GKS 7
- 35.9 ^{0}C(aksiller) - 63/dk - 86/51 mmHg
- Maske ile oksijen alıyor 8 L/dk (SaO_2 %96)
- PaO_2 125 mmHg, Laktat 25 mg/dl
- Üst ve alt ekstremitede kızarıklık, ısı artışı ve ülserler mevcut
- Solunum sesleri derinden geliyor
- Yaygın kaba ral mevcut
- Sağ femoralde diyaliz kateteri mevcut
- Üriner kateter mevcut
- CVVHD
- Düşük doz noradrenalin

- Lökosit 10340/mm^3 (PNL %75)
- Hgb 8.6 g/dl
- Trombosit 152000/mm^3
- ALT 44 U/L, AST 24 U/L, TB 1.7 mg/dl, DB 0.73 mg/dl, Na 138 mmol/L, K 4.6 mmol/L
- Üre 176 mg/dl, kreatinin 2.88 mg/dl, GFR 15 ml/dk
- BNP 1340 ng/L(0-100)
- D-dimer 4055 µg/L(0-550)
- CRP 1.6 mg/dl
- PCT 0.18 ng/ml
- TİT: 2437 lökosit/HPF
- Kraniyal BT(11.9.2022): Kitle - ödem saptanmadı


R

Tanınız nedir?

- İhtimali Tanılar
  - -Sepsis
    - Pnömoni
    - Ürosepsis
    - Yumuşak doku enfeksiyonu

Sepsis

- quickSOFA(qSOFA) skoru
  -Solunum sayısı ≥ 22/dk
  -Mental durum değişikliği (GKS<15)
  -KB ≤ 100 mm Hg

- Septik Şok: Sepsis tanısı alan bir hastada OAB ≥ 65 mm Hg olarak sürdürmek için vazopressör gereksinimi olması ve serum laktat > 2mmol/L(18 mg/dl)

Singer M et al. JAMA 2016
Font MD et al. Med Clin N Am 2020

Table 1. Sequential [Sepsis-Related] Organ Failure Assessment Score[a]

	Score				
System	0	1	2	3	4
Respiration					
Pao_2/Fio_2, mm Hg (kPa)	≥400 (53.3)	<400 (53.3)	<300 (40)	<200 (26.7) with respiratory support	<100 (13.3) with respiratory support
Coagulation					
Platelets, $\times 10^3/\mu L$	≥150	<150	<100	<50	<20
Liver					
Bilirubin, mg/dL (μmol/L)	<1.2 (20)	1.2-1.9 (20-32)	2.0-5.9 (33-101)	6.0-11.9 (102-204)	>12.0 (204)
Cardiovascular	MAP ≥70 mm Hg	MAP <70 mm Hg	Dopamine <5 or dobutamine (any dose)[b]	Dopamine 5.1-15 or epinephrine ≤0.1 or norepinephrine ≤0.1[b]	Dopamine >15 or epinephrine >0.1 or norepinephrine >0.1[b]
Central nervous system					
Glasgow Coma Scale score[c]	15	13-14	10-12	6-9	<6
Renal					
Creatinine, mg/dL (μmol/L)	<1.2 (110)	1.2-1.9 (110-170)	2.0-3.4 (171-299)	3.5-4.9 (300-440)	>5.0 (440)
Urine output, mL/d				<500	<200

Abbreviations: Fio_2, fraction of inspired oxygen; MAP, mean arterial pressure; Pao_2, partial pressure of oxygen.

[a] Adapted from Vincent et al.[27]

[b] Catecholamine doses are given as μg/kg/min for at least 1 hour.

[c] Glasgow Coma Scale scores range from 3-15; higher score indicates better neurological function.

Hastanın yatış SOFA skoru 11

qSOFA skoru 3

Hemen antibiyotik başlayalım mı?

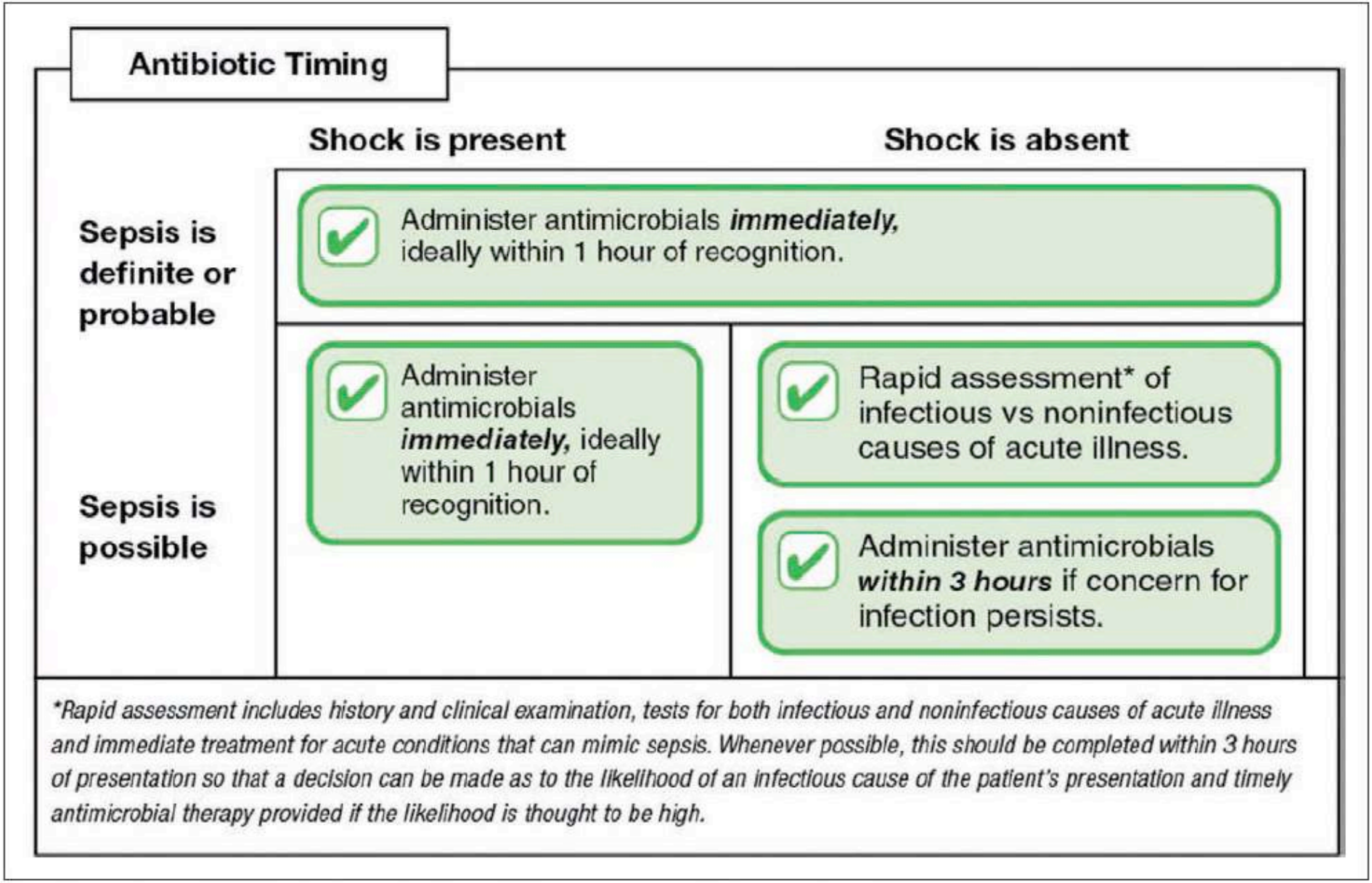


Figure 1. Recommendations on timing of antibiotic administration.

Evans L et al. Crit Care Med 2021

PCT 0.18 ng/ml. Yine de antibiyotik başlayalım mı?

Prokalsitonin ve Klavuzlar

- Sepsis: Antibiyotik başlama kararında kullanıma karşı görüş - Zayıf öneri ve çok düşük kalitede kanıt
- Antibiyotik tedavi sürelerinin ayarlanmasında klinik ile birlikte kullanımı öneriliyor – Zayıf öneri ve düşük kalitede kanıt

Evans L et al. Crit Care Med 2021

Enfeksiyon Hastalıkları Pratiği

1. Uygun ampirik tedavi

2. Direnç gelişiminin en aza indirilmesi
   "Kollateral Hasarın Önlenmesi"

Paterson DL. Clin Infect Dis 2003

Paterson DL. Clin Infect Dis 2004

Ampirik Antibiyotik Seçimi

- Anamnez
- Klinik durum
- Lokal epidemiyoloji

Ampirik Antibiyotik Seçimi

- Hastaya ait faktörler
  - -Enfeksiyonun yeri
  - -Altta yatan hastalık
  - -Kronik organ yetmezliği
  - -Kullandığı ilaçlar
  - -İnvazif işlem ve cihazlar
  - -Bağışıklığın kırılması
  - -İmmünsüpresyon
  - -Dirençli bakteri ile enfeksiyon ya da kolonizasyon
  - -Son 3 ay içinde antibiyotik kullanımı
  - -Enfeksiyon hangi ortamda gelişmiş

Önceki kültür sonuçları

- 24.8.2022 DTA *C.albicans ve C.glabrata*
- 28.8.2022 DTA 20000 kob/ml *K. pneumoniae* (Sadece seftazidim/avibaktam, gentamisin, amikasin ve TMP/SMX duyarlı)

PAS KRK ve VRE Sürveyans

- 12.9.2022 Negatif
- 19.9.2022 Negatif
- 26.9.2022 KRK Pozitif

En olası enfeksiyon etkeni hangisi olabilir?

A-*Candida* spp.

B-*Klebsiella pneumoniae*

C-*Acinetobacter baumannii*

D-*Staphylococcus* spp.

E-*Pseudomonas aeruginosa*

Sürveyans Kültürleri

- DTA (haftada bir kez alındığında) kültürlerinin rehberlik ettiği başlangıç antibiyotik tedavisi %85 yeterli

  Jung B et al. Intensive Care Med 2009

- DTA(haftada iki kez alındığında) kültürlerinin rehberlik ettiği başlangıç antibiyotik tedavisi %95 yeterli

  Michel F et al. Chest 2005

- Tanıdan 1-3 gün önce alınan kültürlerle(DTA veya BAL), tanı sırasında alınan kültürler arasında benzerlik zayıf(0.63)

  Sanders KM et al. J Crit Care 2008

CURRENT OPINION

Risk stratification for multidrug-resistant Gram-negative infections in ICU patients

Almudena Burillo[a,b,c], *Patricia Muñoz*[a,b,c,d], *and Emilio Bouza*[a,b,c,d]

Table 1. Risk factors for colonization or infection with multidrug-resistant Gram-negative microorganisms (MDR-GN)

Microorganism	Risk factor	C/I	Risk (95% CI)	In-patients or ICU patients	Reference
MDR-GN microorganism	Mechanical ventilation	C	OR 14.46 (8.45–24.70)	ICU	[48▪]
	Enteral feeding tube	C	OR 5.38 (1.56–18.56)	ICU	[6▪▪]
	Central venous catheter	C	OR 3.97 (2.04–7.70)	ICU	[48▪]
	Prior third-generation cephalosporins	C	OR 2.29 (1.07–4.90)	ICU	[6▪▪]
	Hemodialysis catheter	C	OR 2.20 (1.31–3.69)	ICU	[48▪]
	Prior carbapenems	C	OR 2.19 (1.02–4.74)	ICU	[6▪▪]
	Severe COPD	C	OR 1.90 (1.10–3.27)	ICU	[48▪]
	SAPS 3 (median 61 *vs.* 47)	C	OR 1.03 (1.01–1.04)	ICU	[48▪]
CR-E	Recent stay in a foreign healthcare facility	I	OR 18; $P<0.001$	In-patients	[3▪▪,20]
	Previous colonization	I	OR 3.06–17.69 $P<0.001$	In-patients	[21,22▪▪]
	Transfer from a postacute care facility	I	OR 2.88–3; $P<0.001$	In-patients	[20,22▪▪]
	Age >60 years	I	OR 2.16 $P<0.036$	In-patients	[21]
	Antibiotic treatment in the previous 3 months–2 years	I	OR 1.009–3.13 $P<0.02$	In-patients, ICU	[12▪,21,22▪▪]
	Longer pre-ICU hospital stay	I	9 (1–25) *vs.* 2 (0–11) days $P<0.001$	ICU	[2▪▪]

The Journal of Infectious Diseases
SUPPLEMENT ARTICLE

The Colonization of Carbapenem-Resistant *Klebsiella pneumoniae*: Epidemiology, Resistance Mechanisms, and Risk Factors in Patients Admitted to Intensive Care Units in China

Xiaohua Qin,[1,2,a] Shi Wu,[1,2,a] Min Hao,[1,2,a] Jing Zhu,[4] Baixing Ding,[1,2] Yang Yang,[1,2] Xiaogang Xu,[1,2] Minggui Wang,[1,2,©] Fan Yang,[1,2,3] and Fupin Hu[1,2]

Background. Carbapenem-resistant *Klebsiella pneumoniae* (CRKP) has become a threat to public health, most notably as a superbug causing nosocomial infections. Patients in the intensive care unit (ICU) are at increased risk of hospital-acquired *K pneumoniae* infection, especially CRKP. This study was conducted to investigate the frequency of gastrointestinal and nasopharyngeal *K pneumoniae* colonization and its contribution to infections in ICU patients.

Methods. A 3-month prospective cohort study was performed in which 243 ICU patients were screened for intestinal and nasopharyngeal carriage of *K pneumoniae* at admission and once per week thereafter. The colonization and clinical infection isolates were analyzed by antimicrobial susceptibility testing to identify CRKP and were characterized by multilocus sequence typing (MLST) and whole-genome sequencing combined with epidemiological data to investigate the resistance mechanisms and assess the possible transmitted infection.

Results. Twenty-eight percent (68 of 243) of patients tested positive for carriage of *K pneumoniae* immediately upon admission to ICU, 54% (37 of 68) of which were nonduplicate CRKP isolates. Patients with carbapenem-susceptible *K pneumoniae* (CSKP) colonization at admission were more likely to acquire CRKP colonization during the ICU stay compared with patients without *K pneumoniae* colonization at admission. The incidence of subsequent CRKP infection in the baseline CSKP (32.3%, 10 of 31) and CRKP (45.9%, 17 of 37) carrier group was significantly higher than that of the baseline non-KP carrier group (8.6%, 15 of 175). The risk factors associated with acquired CRKP colonization during the ICU stay among negative CRKP colonization at admission included previous exposure to carbapenem, tigecycline or β-lactam/β-lactamases inhibitor, and invasive processes or surgical operations. Sixty-four percent (27 of 42) of patients with *K pneumoniae* infection were colonized by clonally related *K pneumoniae* strains according to enterobacterial repetitive intergenic consensus sequence-polymerase chain reaction analysis. ST11 (72%, 53 of 74) was the most predominant MLST type of clonally related CRKP isolate colonizing these patients, followed by ST15 (26%, 19 of 74).

Conclusions. The colonization of *K pneumoniae* may increase the incidence of corresponding *K pneumoniae* infection in critically ill patients in the ICU. High prevalence of ST11 CRKP (due to bla_{KPC-2}) carriage and infection in ICU was observed.

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Incidence of a subsequent carbapenem-resistant Enterobacteriaceae infection after previous colonisation or infection: a prospective cohort study

Sarah S.L. Tang[a], Enqing Chee[a], Jocelyn Q. Teo[a,b], Maciej P. Chlebicki[c,d], Andrea L.H. Kwa[a,d,e,*]

ABSTRACT

Objectives: In patients with a history of carbapenemase-producing, carbapenem-resistant Enterobacteriaceae (CP-CRE), the need for CP-CRE targeted treatment in subsequent sepsis episodes is unclear. This study aimed to characterise the incidence of subsequent CP-CRE infective episodes in individuals with prior CP-CRE colonisation and/or infection, and identify predictors for these subsequent CP-CRE infections.

Methods: All adult inpatients with CP-CRE detected from any site between June 2012 and May 2014 at a tertiary-care hospital were prospectively followed for two years to assess for any subsequent CP-CRE infections. Potential factors to which patients were exposed during the follow-up period were collected from medical records and analysed.

Results: A total of 171 patients were enrolled. Of 151 patients who entered the follow-up period, 16 (10.6%) developed a subsequent CP-CRE infection. The median time to a subsequent infective episode was 24.5 days (12–105 days). The type of carbapenemase was highly conserved within index and subsequent paired episodes (16 of 17 pairs). Patients with first CP-CRE isolated from intra-abdominal or respiratory sources were ≥7 times more likely to develop a subsequent infection, while most rectal carriers remain colonised. For carriers (n = 133), *Klebsiella* spp. (OR 4.7) and OXA carbapenemase (OR 9.4) were significant predictors of subsequent infection. In patients with initial infection (n = 18), end-stage renal failure requiring dialysis (OR 22.0) was the only predisposing factor.

Conclusion: The incidence of subsequent infections in patients with prior colonisation was low. Consideration for CP-CRE targeted therapy is recommended in patients on dialysis and previous CP-CRE infections involving the bloodstream and/or respiratory tract.

- İhtimali Tanı: Sepsis? Ürosepsis? Pnömoni? Yumuşak doku enfeksiyonu?

- Kateter ve periferden kan kültürü, DTA, idrar kültürü ve yara kültürü alındı

- 24.8.2022 DTA *C.albicans ve C.glabrata*
- 28.8.2022 DTA 20000 kob/ml *K. pneumoniae*(Sadece seftazidim/avibaktam, gentamisin, amikasin ve TMP/SMX duyarlı)

- Seftazidim/Avibaktam + Teikoplanin + Flukonazol(11.9.2022) başlandı

Örnek No :	22336764	**İstem Tarihi :**	11.09.2022 15:50	**Çalışma Tarihi :**	
Örnek Tipi :	İDRAR	**Numune Alım Tarihi :**	11.09.2022 15:51	**Sonuç Tarihi :**	14.09.2022 11:14
Örn-A.Yeri:	SONDA DAN	**Kabul Tarihi :**	11.09.2022 20:30	**Onay Tarihi :**	14.09.2022 12:33

İŞLEM ADI : İDRAR KÜLTÜRÜ

SONUÇ: Üreme Var

ORGANİZMA

(1) PROTEUS MİRABİLİS RMK[Potential Carbapenemase Producer]
100.000 CFU/ml
(2) ESCHERİCHİA COLİ 100.000 CFU/ml

ANTİBİYOGRAM	SONUÇ 1	SONUÇ 2	SONUÇ 3	SONUÇ 4	SONUÇ 5	SONUÇ 6
AMIKASIN	Duyarlı (<=8)	Duyarlı (<=8)				
AMOKSİSİSLİN/KLAVULANİK ASİT	Duyarlı (4/2)	Duyarlı (4/2)				
AMPİSİLİN	Dirençli (>16)	Duyarlı (<=4)				
ERTAPENEM	Duyarlı (<=0.25)	Duyarlı (<=0.25)				
FOSFOMİSİN W/G6P	Duyarlı (<=16)					
GENTAMISIN	Dirençli (>8)	Duyarlı (<=2)				
IMIPENEM		Duyarlı (0.5)				
LEVOFLOKSASİN	Dirençli (>4)	Duyarlı (<=0.5)				
MEROPENEM	Duyarlı (2)	Duyarlı (<=0.125)				
NİTROFURANTOİN		Duyarlı (<=32)				
PİPERASİLİN/TAZOBAKTAM	Duyarlı (<=4/4)	Duyarlı (<=4/4)				
SEFAZOLIN		Orta Duyarlı (<=4)				
SEFIKSIM	Duyarlı (1)	Duyarlı (1)				
SEFTRIAKSON	Duyarlı (<=1)	Duyarlı (<=1)				
SİPROFLOKSASİN	Dirençli (>1)	Duyarlı (<=0.25)				
TOBRAMISIN	Dirençli (>8)	Duyarlı (<=2)				
TRİMETOPRİM SÜLFAMETOKSAZOL	Dirençli (>8/152)	Duyarlı (<=2/38)				

Örnek No :	22337255	**İstem Tarihi :**	11.09.2022 19:37	**Çalışma Tarihi :**	
Örnek Tipi :	DERİN TRAKEAL ASPİRAT (DTA)	**Numune Alım Tarihi :**	11.09.2022 19:37	**Sonuç Tarihi :**	15.09.2022 10:18
Örn-A.Yeri:		**Kabul Tarihi :**	11.09.2022 20:31	**Onay Tarihi :**	15.09.2022 11:42

İŞLEM ADI : KANTİTATİF (DTA) KÜLTÜRÜ

SONUÇ: Üreme Var

ORGANİZMA

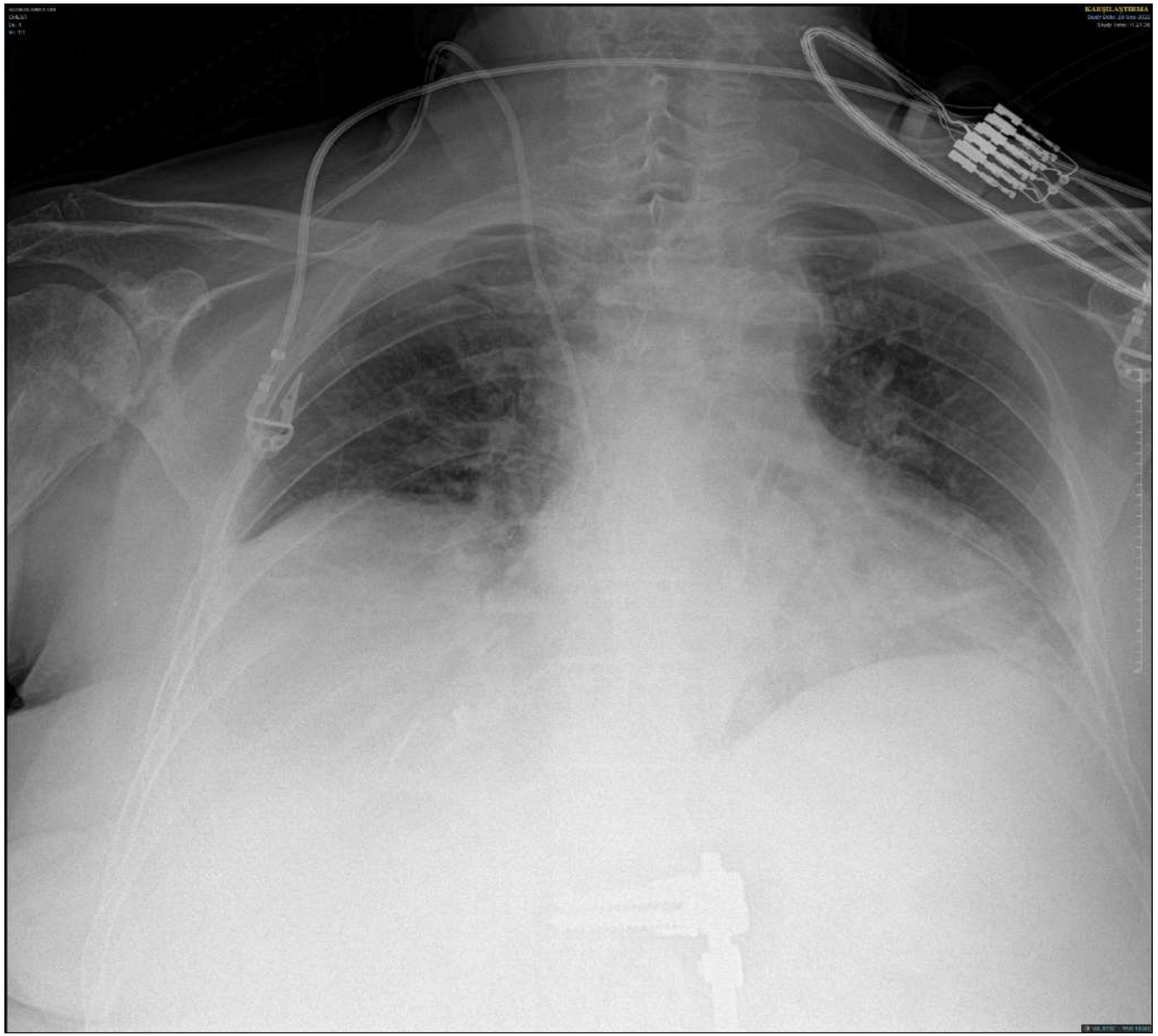
(1) PSEUDOMONAS AERUGİNOSA 10.000 CFU/ml
(2) ENTEROBACTER SPECİES ENTEROBACTER CLOACAE 3.000 CFU/ml
(3) STAPHYLOCOCCUS AUREUS 5.000 CFU/ml

ANTİBİYOGRAM	SONUÇ 1	SONUÇ 2	SONUÇ 3	SONUÇ 4	SONUÇ 5	SONUÇ 6
AMIKASIN	Duyarlı (<=4)	Duyarlı (<=8)	Duyarlı (<=4)			
AMOKSİSİSLİN/KLAVULANİK ASİT		Dirençli (>16/2)				
AMPİSİLİN		Dirençli (8)	Dirençli			
DAPTOMİSİN			Duyarlı (<=1)			
ERİTROMİSİN			Duyarlı (<=0.25)			
ERTAPENEM		Duyarlı (<=0.25)				
FOSFOMİSİN W/G6P			Duyarlı (<=8)			
FUSİDİK ASİT			Duyarlı (<=1)			
GENTAMISIN		Duyarlı (<=2)	Duyarlı (<=1)			
IMIPENEM	Orta Duyarlı (4)	Duyarlı (<=0.25)				
KLİNDAMİSİN			Duyarlı (<=0.25)			
KOLİSTİN	Duyarlı (<=1)	Duyarlı (<=1)				
LEVOFLOKSASİN	Orta Duyarlı (1)	Duyarlı (<=0.5)	Orta Duyarlı (<=1)			
LİNEZOLİD			Duyarlı (<=2)			
MEROPENEM	Duyarlı (1)	Duyarlı (<=0.125)				
MOKSİFLOKSASİN			Duyarlı (<=0.25)			
PENISILIN			Dirençli (0.25)			
PİPERASİLİN/TAZOBAKTAM	Orta Duyarlı (16/4)	Duyarlı (<=4/4)				
SEFEPIM	Orta Duyarlı (<=1)	Duyarlı (<=1)				
SEFTAZIDIM	Orta Duyarlı (4)	Duyarlı (<=1)				
SEFTAZİDİM/AVİBAKTAM	Duyarlı (2/4)					
SEFTRIAKSON		Duyarlı (<=1)				
SİPROFLOKSASİN	Orta Duyarlı (0.25)	Duyarlı (<=0.125)	Orta Duyarlı (<=1)			
TEİKOPLANİN			Duyarlı (<=1)			
TETRASIKLIN			Duyarlı (<=0.5)			
TOBRAMISIN	Duyarlı (<=2)					
TRİMETOPRİM SÜLFAMETOKSAZOL		Dirençli (>8/152)	Duyarlı (<=2/38)			
VANKOMİSİN			Duyarlı (<=1)			

16.9.2022

- GKS 14
- HFNO (aralıklı NIMV13.9.2022'de başlandı)
- Kan kültürleri ve yara kültüründe üreme yok
- Noradrenalin kesildi ve hemodinamisi stabil(15.9.2022)
- Mevcut antibiyotikleri kesilerek meropenem 2x1 g IV(GFR'ye göre) başlandı
- Meropenem kesildi(23.9.2022)
- Göğüs Hastalıkları Kliniğine yatırıldı(27.9.2022)

20.9.2022



Göğüs Hastalıkları Kliniği

- 28.9.2022
  -Somnolans mevcut
  -Nazal oksijen alıyor
  -Ajite ve oksijen maskesini çıkarıyor
  -2 kez damar yolunu çekmiş
  -Psikiyatri konsültasyonu istenmiş
- Kardiyak arrest ve KPR sonrası tekrar Reanimasyona alındı
- Exitus

Current options for the treatment of infections due to extended-spectrum beta-lactamase-producing Enterobacteriaceae in different groups of patients

B. Gutiérrez-Gutiérrez*, J. Rodríguez-Baño

Table 1
Definitions used for the classification of patients in this review

Dimension	Classification	Conditions
Severity at presentation	Severe	Any of the following: Pitt score ≥4, APACHE II score >10, ICU admission, and presentation with severe sepsis or septic shock
	Non-severe	All others
Source of infection	High risk	High-inoculum Infections, drainage not possible or inadequate (e.g. pneumonia, endocarditis, inadequately drained deep-seated infections)
	Intermediate risk	Not included in high or low risk (e.g. vascular catheter Infection with catheter removal, drained biliary tract or intra-abdominal)
	Low risk	Urinary tract Infection without obstruction or released obstruction
Immune status	Severely immunocompromised	Any of the following: neutropenia (<500/μL), leukaemia, lymphoma, HIV infection with <200 CD4/μL, solid organ or hematopoietic stem cell transplantation, cytotoxic chemotherapy, steroids (>15 mg of prednisone daily for >2 weeks).
	Non-severe	All others

[5] Sterne J, Hernán M, Reeves B, Savovic J, Berkman N, Viswanathan M, et al. ROBINS-I: a tool for assessing risk of bias in non-randomized studies of interventions. BMJ 2016;355.
[6] Higgins J, Sterne J, Savovic J, Page M, Hróbjartsson A, Boutron I, et al. A revised tool for assessing risk of bias in randomized trials. In: Chandler J, McKenzie J, Boutron I, Welch V, editors. Cochrane methods. Cochrane database syst. Rev; 2016. p. 29–31. 10 (Suppl 1).

Eski Antibiyotikler

(MDR-Gram Negatifler İçin İntravenöz Kullanılabilen)

- Kolistin
- Polimiksin-B
- Aminoglikozidler
- TMP-SMX
- Kloramfenikol
- Minosiklin
- Temosilin
- Meropenem
- Sulbaktam
- Fosfomisin
- Tigesiklin

Karbapenem Dirençli Enterobacterales

KPC(+) *K. pneumoniae* - Tedavi

- 2010-2013, ÇM(5), İtalya, KPC-Kp
- 447 Bakteriyemi
- 214 Bakteriyemi ile seyretmeyen enfeksiyon
- İn vitro etkili 2 ilaç kombinasyonu ile daha düşük mortalite(OR, 0.52)
- Meropenem MİK ≤ 8 mg/L ise, meropenem içeren kombinasyonlarda daha yüksek sağkalım

Tumbarello M et al. J Antimicrob Chemother 2015

OXA-48(+) Enterobacteriaceae

- 36 Kan Dolaşımı Enfeksiyonu, KDE
- 26 *K.pneumoniae*
- 28.gün mortalitesi %50
- Kolistin içeren kombinasyonlarda mortalite daha az($p<0.001$)

Balkan İİ et al. Int J Infect Dis 2014

In vitro synergistic activity of fosfomycin in combination with meropenem, amikacin and colistin against OXA-48 and/or NDM-producing *Klebsiella pneumoniae*

Buket Erturk Sengel[1], Gulsen Altinkanat Gelmez[2], Guner Soyletir[2] and Volkan Korten[1]

Journal of Chemotherapy 2020

Table 1. Chequerboard results obtained with fosfomycin in combination with meropenem, amikacin and colistin against 17 CPKp blood isolates.

		MIC values (mg/L)				MRP/FOS		AMK/FOS		COL/FOS	
Isolate no	Carbapenemase	FOS	MRP	AMK	COL	Activity	FICI	Activity	FICI	Activity	FICI
1	OXA-48	>256	16	16	8	I	0.51	I	1.24	A	4.16
2	OXA-48 + NDM	16	128	2560	0.5	S	0.36	S	0.05	S	0.32
3	NDM	16	64	>5120	1	S	0.20	Undetermined[a]		S	0.32
4	OXA-48	16	16	64	32	I	0.81	I	0.86	I	2.33
5	NDM	64	64	4096	>32	S	0.39	I	0.75	S	0.21
6	NDM	8	64	>5120	8	S	0.35	Undetermined[a]		A	4.86
7	NDM	256	256	2560	1	S	0.48	I	0.75	S	0.27
8	OXA-48 + NDM	64	256	2560	32	S	0.44	I	0.80	I	2.0
9	OXA-48	32	64	512	16	S	0.26	S	0.29	I	3.0
10	OXA-48 + NDM	64	64	4608	32	S	0.33	I	0.77	I	2.51
11	OXA-48	16	32	256	8	S	0.07	S	0.15	I	0.54
12	OXA-48	32	16	8	8	S	0.29	I	1.80	I	0.88
13	OXA-48 + NDM	256	512	>5120	32	S	0.42	Undetermined[a]		I	1.20
14	NDM	32	64	4608	16	S	0.12	S	0.24	S	0.06
15	OXA-48 + NDM	64	64	2560	1	S	0.18	S	0.38	S	0.31
16	OXA-48	16	16	2	1	S	0.23	I	1.35	I	0.67
17	OXA-48	32	16	4	1	S	0.32	I	1.70	S	0.45

[a]Three results were not interpretable due to off-scale MICs and labeled indeterminate for the AMK/FOS combination.
S: Synergy (FICI ≤0.5), I: Indifference (FICI >0.5 but ≤4), A: Antagonism (FICI >4), Undetermined: FICI not interpretable.

CURRENT OPINION

The management of multidrug-resistant *Enterobacteriaceae*

Matteo Bassetti, Maddalena Peghin, and Davide Pecori

Curr Opin Infect Dis 2016, 29:583–594

Table 5. Expert opinion treatment options for *Klebsiella pneumoniae* carbapenemase-producing *K. pneumoniae*. Dose adjustment is recommended depending on renal function and antimicrobial susceptibility tests[a]

KPC-Kp meropenem MIC ≤ 8–16 mg/l			
Primary BSIs	**Pneumonia**	**Abdominal infection**	**Urinary tract infection**
Meropenem 2 g q 8 h i.v. (f) + tigecycline 100 mg every 12 h i.v. (g) + colistin 4.5 MU every 12 h i.v. (h) or gentamicin 3–5 mg/kg/day every 24 h i.v. (i) or fosfomycin 4 g every 4 h i.v.	Inhaled antibiotics[b] + meropenem 2 g q 8 h i.v. (f) + tigecycline 100 mg every 12 h i.v. (g) + colistin 4.5 MU every 12 h i.v. (h) or gentamicin 3–5 mg/kg/day every 24 h i.v. (i) or fosfomycine 4 g every 4 h i.v.	Meropenem 2 g q 8 h i.v. (f) + tigecycline 100 mg every 12 h i.v. (g) + colistin 4.5 MU every 12 h i.v. (h) or gentamicin 3–5 mg/kg/day every 24 h i.v. (i) or fosfomycin 4 g every 4 h i.v.	Meropenem 2 g q 8 h i.v. (f) + fosfomycin 4 g every 4 h i.v. + gentamicin 3–5 mg/kg/day every 24 h i.v. (i) or colistin 4.5 MU every 12 h i.v. (h)
Ceftazidime–avibactam 2.5 g every 8 h i.v.	Ceftazidime–avibactam 2.5 g every 8 h i.v.	Ceftazidime–avibactam 2.5 g every 8 h i.v. + metronidazole i.v.	Ceftazidime–avibactam 2.5 g every 8 h i.v.

KPC-Kp meropenem MIC > 8–16 mg/l			
Primary BSIs	**Pneumonia**	**Abdominal infection**	**Urinary tract infection**
Tigecycline 100 mg every 12 h .i.v (g) + colistin 4.5 MU every 12 h i.v. (h) + fosfomycin 4 g every 4 h i.v. or gentamicin 3–5 mg/kg/ every 24 h i.v. (i)	Inhaled antibiotics[b] + colistin 4.5 MU every 12 h i.v. (h) + tigecycline 100 mg every 12 h i.v. (g) or gentamicin 3 mg/kg/day every 24 h i.v. (i) +/− rifampin 600–900 mg every 24 h i.v.	Tigecycline 100 mg every 12 h i.v. (g) + colistin 4.5 MU every 12 h i.v. (h) + gentamicin 3–5 mg/kg/day every 24 (i)	Colistin 4.5 MU every 12 h i.v. (i) + fosfomycin 4 g every 6 h i.v. +/− trimethoprim–sulfamethoxazole 20 mg/kg/day (m)
Ceftazidime–avibactam 2.5 g every 8 h i.v.	Ceftazidime–avibactam 2.5 g every 8 h i.v.	Ceftazidime–avibactam 2.5 g every 8 h i.v. + metronidazole i.v.	Ceftazidime–avibactam 2.5 g every 8 h i.v.
KPC-Kp meropenem MIC > 8–16 mg/l Colistin-R			
Primary BSIs	**Pneumonia**	**Abdominal infection**	**Urinary tract infection**
Tigecycline 100 mg every 12 h i.v. (g) + colistin 4.5 MU every 12 h i.v. (h) + rifampin 600–900 mg every 24 h i.v.	As for BSIs + inhaled antibiotics[b]	As for BSIs	As for BSIs
Ertapenem 500 mg every 6 h i.v. (c) + meropenem 2 g q 8 h i.v. (f)			
Ertapenem 500 mg every 6 h i.v. (c) + doripenem 500 mg every 8 h (l)			
Ceftazidime-avibactam 2.5 g every 8 h i.v.			

(c) Ertapenem: maintenance dose with continuous infusion (500 mg every 6 h in 4 h).
(f) Meropenem: loading dose (2 g in 1 h) followed by maintenance doses with continuous infusion (2 g every 8 h in 6 h).
(g) Tigecycline: loading dose (200 mg) followed by maintenance doses with 100 mg every 12 h.
(h) Colistin: loading dose (9 MU) followed by maintenance doses with 4.5 MU every 12 h.
(i) Gentamicin once a day or amikacin 15–20 mg/kg/day every 24 h i.v.
(l) Doripenem: maintenance doses with doripenem 500 mg every 8 h (infusion in 1 h).
(m) Trimethoprim–sulfamethoxazole divided every 6 h.
BSI, bloodstream infection; i.v., intravenous; KPC-Kp, *Klebsiella pneumoniae* carbapenemase *Klebsiella pneumoniae*; MIC, minimum inhibitory concentration; MU, million units.
[a]Antimicrobial susceptibility test. Colistin: MIC 2 mg/l or less, continue colistin; MIC more than 2 mg/l, consider alternative in-vitro active antimicrobial. Tigecycline: MIC 1 mg/l or less, consider tigecycline; MIC more than 1 mg/l, consider alternative in-vitro active antimicrobial. Fosfomycin: MIC 32 mg/l or less, consider fosfomycin; MIC more than 32 mg/l, consider alternative in-vitro active antimicrobial. Aminoglycoside: MIC 2 mg/l or less for gentamicin/tobramycin or 4 mg/l or less for amikacin, consider aminoglycoside; MIC more than 2 for gentamicin/tobramycin or more than 4 mg/l for amikacin, consider alternative in-vitro active antimicrobial.
[b]Inhaled antibiotic: colistin 2 MU every 8 h or tobramycin 300 mg every 12 h or amkacin 250 mg every 24 h.

Clinical Infectious Diseases

MAJOR ARTICLE

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

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

[1]Division of Infectious Diseases, University of North Carolina, Chapel Hill; [2]Department of Biostatistics and the Center for Biostatistics in AIDS Research, Harvard T. H. Chan School of Public Health, Boston, Massachusetts; Departments of [3]Infectious Diseases and [4]Laboratory Medicine, Cleveland Clinic, [5]Research Service, Louis Stokes Cleveland Department of Veterans Affairs Medical Center, [6]Division of Infectious Diseases and HIV Medicine, Department of Medicine, Case Western Reserve University School of Medicine, and [7]Department of Medicine, MetroHealth Medical Center, Cleveland, [8]Department of Internal Medicine, Northeast Ohio Medical University, Rootstown, and [9]Division of Infectious Diseases, Cleveland Clinic Akron General, Ohio; [10]Division of Infectious Diseases, University of Pittsburgh School of Medicine, Pennsylvania; [11]Division of Infectious Diseases, University of Michigan, Ann Arbor; [12]Duke Clinical Research Institute and [13]Division of Infectious Diseases, Duke University, Durham, North Carolina; [14]University of Queensland Centre for Clinical Research, Royal Brisbane and Women's Hospital Campus, Australia; and Departments of [15]Molecular Biology and Microbiology and [16]Pharmacology, Case Western Reserve University School of Medicine, Cleveland, Ohio

Background. The efficacy of ceftazidime-avibactam—a cephalosporin–β-lactamase inhibitor combination with in vitro activity against *Klebsiella pneumoniae* carbapenemase–producing carbapenem-resistant Enterobacteriaceae (CRE)—compared with colistin remains unknown.

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

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

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

Keywords. carbapenem-resistant Enterobacteriaceae; *Klebsiella pneumoniae*; colistin; ceftazidime-avibactam; benefit-risk.

Seftazidim/Avibaktam ve Kolistin Karşılaştırması

- Prospektif, gözlemsel çalışma
- 2011-2016, ÇM, ABD
- 137 hasta(133 CR-Kp)
- 38(%28) hasta seftazidim/avibaktam
- 99(%72) hasta kolistin
- 63(%46) bakteriyemi, 30(%22) pnömoni ve 19(%14) ÜSE

van Duin D et al. Clin Infect Dis 2018

Table 4. Treatment Characteristics

Characteristic	Patients, No. (%)[a]			
	Ceftazidime-Avibactam (n = 38)	Colistin (n = 99)	All (N = 137)	*P* Value
Time to treatment, median (IQR), d[b]	3 (2–4)	2 (1–4)	3 (1–4)	.22[c]
Duration of treatment, median (IQR), d	10 (5–26)	10 (4–18)	10 (5–19)	.52[d]
Additional antibiotics				
None	14 (37)	6 (6)	20 (15)	<.001[e]
Tigecycline	12 (32)	60 (61)	72 (53)	.002[e]
Amikacin	6 (16)	23 (23)	29 (21)	.34[e]
Gentamicin	12 (32)	14 (14)	26 (19)	.02[e]
TMP/SMX	4 (11)	12 (12)	16 (12)	.80[e]
Carbapenem	11 (29)	59 (60)	70 (51)	.001[e]
Fosfomycin	1 (3)	3 (3)	4 (3)	>.99[c]

Abbreviations: IQR, interquartile range; TMP/SMX, trimethoprim/sulfamethoxazole.

[a]Data represent No. (%) of patients, unless otherwise specified.

[b]Days from index culture until first dose of colistin or ceftazidime-avibactam.

[c]Determined with Fisher exact test.

[d]Determined with Wilcoxon rank-sum test.

[e]Determined with χ^2 test.

Seftazidim/Avibaktam ve Kolistin Karşılaştırması

- Seftazidim/avibaktam duyarlılığı 23/24(%96)
- KPC-2 ve KPC-3
- 30. gün mortalitesi

  -Seftazidim/Avibaktam 3/38(%8)
  -Kolistin 33/99(%33), p=0.001

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Clinical Infectious Diseases

MAJOR ARTICLE

Efficacy of Ceftazidime-Avibactam Salvage Therapy in Patients With Infections Caused by *Klebsiella pneumoniae* Carbapenemase–producing *K. pneumoniae*

Mario Tumbarello,[1,a] Enrico Maria Trecarichi,[1,a] Alberto Corona,[2] Francesco Giuseppe De Rosa,[3] Matteo Bassetti,[4] Cristina Mussini,[5] Francesco Menichetti,[6] Claudio Viscoli,[7] Caterina Campoli,[8] Mario Venditti,[9] Andrea De Gasperi,[10] Alessandra Mularoni,[11] Carlo Tascini,[12] Giustino Parruti,[13] Carlo Pallotto,[14] Simona Sica,[15] Ercole Concia,[16] Rosario Cultrera,[17] Gennaro De Pascale,[18] Alessandro Capone,[19] Spinello Antinori,[20] Silvia Corcione,[3] Elda Righi,[4] Angela Raffaella Losito,[1] Margherita Digaetano,[5] Francesco Amadori,[6] Daniele Roberto Giacobbe,[7] Giancarlo Ceccarelli,[9] Ernestina Mazza,[10] Francesca Raffaelli,[1] Teresa Spanu,[21] Roberto Cauda,[1] and Pierluigi Viale[8]

Table 4. Multivariate Analysis of Factors Associated With 30-Day Mortality in the 208 Patients With *Klebsiella pneumoniae* Carbapenemase–producing *K. pneumoniae* Bacteremia

	Without Propensity Score Adjustment		Adjusted for the Propensity Score for Therapy With CAZ-AVI	
Variable	*P* Value	OR (95% CI)	*P* Value	OR (95% CI)
Mechanical ventilation	<.001	4.25 (1.99–9.09)	<.001	4.31 (1.99–9.33)
Charlson comorbidity index ≥3	.001	3.31 (1.61–6.77)	.001	3.30 (1.61–6.77)
Neutropenia	.01	3.22 (1.25–8.29)	.03	3.36 (1.25–8.75)
Septic shock	.002	2.95 (1.46–5.94)	.003	2.94 (1.46–5.92)
Any regimen that included CAZ-AVI	<.001	0.25 (.13–.51)	.001	0.27 (.13–.57)

Abbreviations: CAZ-AVI, ceftazidime-avibactam; CI, confidence interval; OR, odds ratio.

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]

Table 3. Recommended Antibiotic Treatment Options for Carbapenem-Resistant Enterobacterales, Assuming In Vitro Susceptibility to Agents in Table

Source of Infection	Preferred Treatment	Alternative Treatment if First-line Options not Available or Tolerated
Cystitis	Ciprofloxacin, levofloxacin, trimethoprim-sulfamethoxazole, nitrofurantoin, or a single dose of an aminoglycoside Meropenem[a] (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 (when no alternative options are available)
Pyelonephritis or complicated urinary tract infection[b]	Ceftazidime-avibactam, meropenem-vaborbactam, imipenem-cilastatin-relebactam, and cefiderocol Meropenem[a] (extended-infusion): only if ertapenem-resistant, meropenem-susceptible, AND carbapenemase testing results are either not available or negative	Once-daily aminoglycosides

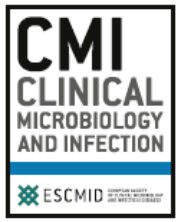
Table 3. Recommended Antibiotic Treatment Options for Carbapenem-Resistant Enterobacterales, Assuming In Vitro Susceptibility to Agents in Table

Source of Infection	Preferred Treatment	Alternative Treatment (first-line options not available or tolerated)
Infections outside of the urinary tract Resistant to ertapenem, susceptible to meropenem, AND carbapenemase testing results are either not available or negative	Meropenem[a] (extended-infusion)	Ceftazidime-avibactam
Infections outside of the urinary tract	Ceftazidime-avibactam, meropenem-vaborbactam, and imipenem-cilastatin-relebactam	Cefiderocol
Resistant to ertapenem, resistant to meropenem, AND carbapenemase testing results are either not available or negative		Tigecycline, eravacycline (generally limited to intra-abdominal infections)
Klebsiella pneumoniae carbapenemases identified (or carbapenemase positive but identify of carbapenemase unknown[c])	Ceftazidime-avibactam, meropenem-vaborbactam, imipenem-cilastatin-relebactam	Cefiderocol Tigecycline, eravacycline (generally limited to intra-abdominal infections)
Metallo-β-lactamase (ie, NDM, VIM, IMP) carbapenemase identified	Ceftazidime-avibactam + aztreonam, cefiderocol	Tigecycline, eravacycline (generally limited to intra-abdominal infections)
OXA-48-like carbapenemase identified	Ceftazidime-avibactam	Cefiderocol Tigecycline, eravacycline (generally limited to intra-abdominal infections)

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,§]



ESCMID - CRE

- Ağır enfeksiyon(CRE duyarlı ise)
  -CAZ/AVI veya MER/VAB
- Ağır enfeksiyon(MBL pozitif veya diğer AB'lere dirençli ise)
  -Cefiderocol
- Ağır enfeksiyon(MBL pozitif ve/veya yeni AB'lere dirençli ise)
  -CAZ/AVI + Aztreonam

ESCMID - CRE

- Ağır enfeksiyon(Polimiksin, Tigesiklin, AG, FOS)
  -Yeni antibiyotikler temin edilemiyorsa in vitro etkili 2 ilaç kombinasyonu
  -Meropenem MİK ≤ 8 olmadıkça kombinasyonda yer almasın
- Ağır olmayan enfeksiyon(CRE duyarlı ise)
  -Polimiksin, Tigesiklin, AG, FOS
  -k-ÜSE'de AG

Table 2. Possible antimicrobial combination therapy for C-C-RKp infections, according to the meropenem MIC value and the site of infection. The choice of antimicrobials depends on in vitro susceptibility assays.

Site of Infection	Serine Carbapenemases Producer Strain (i.e., KPC, OXA-48 Like)		Metallo-β-Lactamase Producer Strain (i.e., VIM, IMP, NDM)
	Meropenem MIC ≤ 16 mg/L	Meropenem MIC > 16 mg/L	
Bloodstream infections	• ceftazidime/avibactam • meropenem double dosage (prolonged infusion) + fosfomycin • meropenem double dosage (prolonged infusion) + gentamicin • meropenem double dosage (prolonged infusion) + fosfomycin + gentamicin	• ceftazidime/avibactam • ceftazidime/avibactam ± fosfomycin or gentamicin • Consider fosfomycin plus gentamicin in case of resistance to ceftazidime/avibactam Future options: • cefiderocol • plazomicin • meropenem/vaborbactam (not active against OXA-48-like carbapenemases)	• ceftazidime/avibactam + aztreonam Future option: • cefiderocol
Hospital acquired pneumonia, including VAP	• meropenem double dosage (prolonged infusion) + fosfomycin • ceftazidime/avibactam ± fosfomycin ± gentamicin	• ceftazidime/avibactam + fosfomycin ± gentamicin Consider fosfomycin plus gentamicin in case of resistance to ceftazidime/avibactam Future options: • meropenem/vaborbactam (not active against OXA-48-like carbapenemases)	• ceftazidime/avibactam + aztreonam Future option: • cefiderocol • eravacycline
Abdominal infections	• ceftazidime/avibactam + tigecycline ± gentamicin • meropenem double dosage (prolonged infusion) + tigecycline ± gentamicin	• ceftazidime/avibactam + tigecycline ± gentamicin • ceftazidime/avibactam + tigecycline ± fosfomycin Future options: • plazomicin • meropenem/vaborbactam (not active against OXA-48-like carbapenemases)	• ceftazidime/avibactam + aztreonam Future option: • cefiderocol

Table 2. *Cont.*

Site of Infection	Serine Carbapenemases Producer Strain (i.e., KPC, OXA-48 Like)		Metallo-β-Lactamase Producer Strain (i.e., VIM, IMP, NDM)
	Meropenem MIC ≤ 16 mg/L	Meropenem MIC > 16 mg/L	
Urinary tract infections	• ceftazidime/avibactam ± fosfomycin ± gentamicin • meropenem double dosage (prolonged infusion) ± fosfomycin ± gentamicin • consider fosfomycin trometamol for uncomplicated urinary tract infections	• ceftazidime/avibactam ± fosfomycin ± gentamicin • consider fosfomycin + gentamicin in case of resistance to ceftazidime/avibactam Future options: • meropenem/vaborbactam (not active against OXA 48-like carbapenemases)	• ceftazidime/avibactam + aztreonam Future option: • cefiderocol • plazomicin
Complicated skin and skin structure infections	• meropenem double dosage (prolonged infusion) ± tigecycline • ceftazidime/avibactam ± tigecycline	• ceftazidime/avibactam ± tigecycline • ceftazidime/avibactam ± fosfomycin • ceftazidime/avibactam + tigecycline ± fosfomycin	• ceftazidime/avibactam + aztreonam Future option: • cefiderocol

Source control is recommended within 24 h of the diagnosis of intra-abdominal infection to remove infected fluid and tissue and to prevent ongoing contamination. C-C-RKp = Colistin-, Carbapenem-resistant *K. pneumoniae*; KPC: *K. pneumoniae* carbapenemase; VIM: Verona integrin encoded metallo-β-lactamase; IMP: Imipenemase; NDM: New Delhi metallo-β-lactamase; VAP: Ventilator associated pneumonia.

Karbapenem Dirençli *Acinetobacter baumannii*

Sulbaktam - *A.baumannii*

- Sulbaktam MİK'leri(direnci) giderek artıyor

  Dağı HT ve ark. Mikrobiyoloji Bul 2014
  Dafopoulou K et al. J Med Microbiol 2018
  Betrosian AP et al. J Infection 2008

- Sulbaktamın etkisi MİK'ten(dirençten) bağımsız

  Oliveira MS et al. Clinics 2013

- Çalışmalarda Sulbaktam dozu: 4-12 g/gün

  Jimenez-Mejias ME et al. Clin Infect Dis 1997
  Levin AS et al. Int J Antimicrob Agents 2003
  Betrosian AP et al. J Infection 2008

  Betrosian AP et al. Scand J Infect Dis 2007

Sulbaktam - *A.baumannii*

- Kritik hastalarda ve dirençli *A.baumannii* infeksiyonlarında 2-4 g/gün ile klinik başarı düşük
- Yüksek dozlarda kolistin ile aynı düzeyde
- Kritik hastalarda ve MDR: 6 g/gün veya daha yüksek olmalı
- Sulbaktam/Ampisilin ile imipenem, meropenem, fosfomisin, rifampisin ve kolistin kombinasyonu sinerjik
- Meropenem + Sulbaktam + Kolistin: Çok yüksek düzeyde sinerji

Adnan S et al. Int J Antimicrob Agents 2013

Sulbaktam - *A.baumannii*

- Ventilatörle ilişkili pnömonide ampisilin/sulbaktam = kolistin

  Zalts R et al. Am J Ther 2016

- Ventilatörle ilişkili pnömonide meropenem + kolistin = meropenem + ampisilin/sulbaktam

  Khalili H et al. J Comp Eff Res 2018

- Ventilatörle ilişkili pnömonide, sulbaktam MİK'leri yüksek olsa bile kolistin + karbapenem = kolistin + sulbaktam(6 g/gün)

  Ungthammakhun C et al. Infect Drug Resist 2019

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

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

Summary

Background Colistin–carbapenem combinations are synergistic in vitro against carbapenem-resistant Gram-negative bacteria. We aimed to test whether combination therapy improves clinical outcomes for adults with infections caused by carbapenem-resistant or carbapenemase-producing Gram-negative bacteria.

Lancet Infect Dis 2018

Published Online
February 15, 2018
http://dx.doi.org/10.1016/

Kolistin
Monoterapi - Kombinasyon

- Açık etiketli, randomize, kontrollü
- Karbapenem dirençli GNB
- Erişkin hastalar
- Bakteriyemi, VİP, HGP, Ürosepsis
- 406 hasta
- %87(355/406) pnömoni veya bakteriyemi
- %77(312/406) *A baumannii*

Paul M et al. Lancet Infect Dis 2018

Kolistin
Monoterapi - Kombinasyon

- Tedavi başarısı
  -Yaşamda kalma
  -Hemodinamik stabilite
  -SOFA skorunun stabil kalması ya da iyileşmesi
  -PaO2/FiO2 oranının stabil kalması ya da iyileşmesi(pnömonide)
  -Mikrobiyolojik kür(bakteriyemide)
- Klinik başarısızlık: Tüm başarı kriterlerinde buluşulamaması(14. günde)

Kolistin
Monoterapi - Kombinasyon

- *A baumannii* için tedavi kollarında fark yok
- Kombinasyon kolunda daha fazla diyare
- Kombinasyon kolunda daha az hafif böbrek yetmezliği

Journal of Infection 79 (2019) 130–138

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Journal of Infection

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

Bloodstream infections caused by carbapenem-resistant *Acinetobacter baumannii*: Clinical features, therapy and outcome from a multicenter study

Alessandro Russo[a], Matteo Bassetti[a], Giancarlo Ceccarelli[b], Novella Carannante[c], Angela Raffaella Losito[d], Michele Bartoletti[e], Silvia Corcione[f], Guido Granata[g], Antonella Santoro[h], Daniele Roberto Giacobbe[i,j], Maddalena Peghin[a], Antonio Vena[a], Francesco Amadori[k], Francesco Vladimiro Segala[f], Maddalena Giannella[e], Giovanni Di Caprio[c], Francesco Menichetti[k], Valerio Del Bono[l], Cristina Mussini[h], Nicola Petrosillo[g], Francesco Giuseppe De Rosa[f], Pierluigi Viale[e], Mario Tumbarello[d], Carlo Tascini[c], Claudio Viscoli[i,j], Mario Venditti[b,*], ISGRI-SITA (Italian Study Group on Resistant Infections of the Società Italiana Terapia Antinfettiva)

Table 2
Cox regression analysis about risk factors associated with 14-day and 30-day mortality.

14-day mortality				30-day mortality			
Variables	HR	CI 95%	p	Variables	HR	CI 95%	p
Septic shock	10.79	1.12–141	0.04	Septic shock	1.54	1.04–2.27	0.03
Adequate source control of infection	0.22	0.01–0.42	0.01	Colistin-containing regimen	0.41	0.27–0.63	<0.001
Charlson comorbidity index > 3	1.44	1.04–2	0.02	Aminoglycoside-containing regimen	2.57	1.33–4.94	0.005
Combination therapy	0.36	0.01–0.89	0.03	Previous surgery (30 days)	1.63	1.16–2.29	0.005

HR: hazard ratio; CI: confidence interval.

Infection and Drug Resistance

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ORIGINAL RESEARCH

Colistin Plus Carbapenem versus Colistin Monotherapy in the Treatment of Carbapenem-Resistant *Acinetobacter baumannii* Pneumonia

This article was published in the following Dove Press journal:
Infection and Drug Resistance

HyeJin Shi[1]
Jin Seo Lee[2]
So Yeon Park[2]
Yousang Ko[2]
Joong Sik Eom[1]

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Purpose: Colistin alone may not be sufficient for treating carbapenem-resistant *Acinetobacter baumannii* (CRAB); thus, efforts are needed to increase treatment success rates. We compared the effects of colistin plus carbapenem therapy versus colistin monotherapy in treating pneumonia caused by CRAB and attempted to identify specific populations or factors that could benefit from combination therapy.

Methods: We retrospectively collected data on cases of CRAB pneumonia. The patients were divided into colistin plus carbapenem therapy and colistin monotherapy groups. The primary outcome was 14-day mortality. The secondary outcomes were in-hospital mortality, clinical improvement at days 2 and 14, and microbiological improvement at day 14.

Results: Of 160 cases meeting criteria for CRAB pneumonia, 83 (52%) and 77 (48.0%) were treated with carbapenem combination therapy or colistin monotherapy, respectively. Among these patients, 50 (63.3%) in the combination group and 27 (39.7%) in the monotherapy group had Acute Physiologic Assessment and Chronic Health Evaluation (APACHE) II scores >24 points (p=0.010). Overall, there was no significant difference in 14-day mortality between the combination and monotherapy groups (24.1% vs 20.8%, p=0.616). Clinical improvement and sputum-negative conversion also showed no significant difference. After adjusting for disease severity according to APACHE II score, the 14-day mortality was significantly lower in the combination group than in the monotherapy group among patients with APACHE II scores of 25–29 points (9.1% vs 53.8%, P=0.020).

Conclusion: Despite more severe conditions, compared with colistin monotherapy, colistin plus carbapenem combination therapy showed equivalent primary mortality outcome in treating CRAB pneumonia. Combination therapy was more effective in patients with APACHE II score ranging from 25 to 29 points.

Keywords: carbapenem-resistant *Acinetobacter baumannii*, CRAB, pneumonia, colistin, combination therapy, risk factor

PHARMACOTHERAPY

SPECIAL ARTICLE

International Consensus Guidelines for the Optimal Use of the Polymyxins: Endorsed by the American College of Clinical Pharmacy (ACCP), European Society of Clinical Microbiology and Infectious Diseases (ESCMID), Infectious Diseases Society of America (IDSA), International Society for Anti-infective Pharmacology (ISAP), Society of Critical Care Medicine (SCCM), and Society of Infectious Diseases Pharmacists (SIDP)†

Brian T. Tsuji,[1,*,‡] Jason M. Pogue,[2,‡] Alexandre P. Zavascki,[3,4] Mical Paul,[5,6] George L. Daikos,[7] Alan Forrest,[8] Daniele R. Giacobbe,[9,10] Claudio Viscoli,[9,10] Helen Giamarellou,[11] Ilias Karaiskos,[11] Donald Kaye,[12] Johan W. Mouton,[13] Vincent H. Tam,[14] Visanu Thamlikitkul,[15] Richard G. Wunderink,[16] Jian Li,[17,§] Roger L. Nation,[18,§] and Keith S. Kaye[19,*,§]

(Pharmacotherapy 2019;39(1):10–39) doi: 10.1002/phar.2209

XVII. Should Monotherapy or Combination Therapy for Polymyxin B or Colistin Be Used to Treat Patients with CRAB?

Recommendations. **R29**: We recommend that for invasive infections due to CRAB, polymyxin B or colistin should be used in combination with one or more additional agents to which the pathogen displays a susceptible MIC (*Best practice recommendation*; panel voted 10–5 in favor of combination).

R30: If a second active agent to which the infecting CRAB displays a susceptible MIC is unavailable, we recommend that polymyxin B or colistin should be used alone as monotherapy (*Weak recommendation, moderate quality evidence*; panel voted 8–7 in favor of monotherapy).

Contents lists available at ScienceDirect

Clinical Microbiology and Infection

journal homepage: www.clinicalmicrobiologyandinfection.com

Narrative review

Carbapenem-resistant *Acinetobacter baumannii*: in pursuit of an effective treatment

E.-T. Piperaki [1], L.S. Tzouvelekis [1], V. Miriagou [2], G.L. Daikos [3,*]

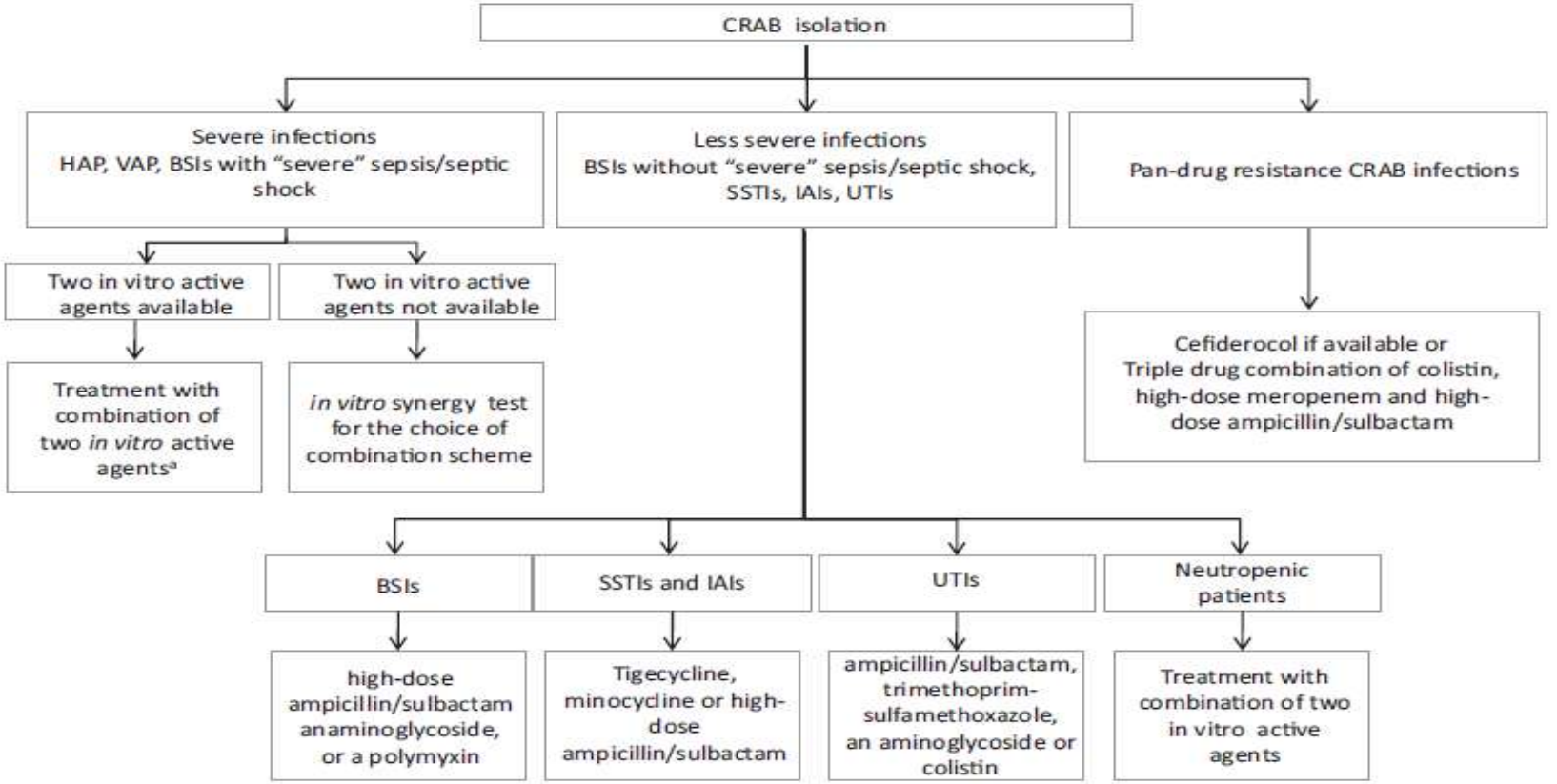


Fig. 1. Proposed therapeutic approach for carbapenem resistant *Acinetobacter baumannii* infections (CRAB).HAP, hospital-acquired pneumonia; VAP, ventilator-associated pneumonia; BSI, bloodstream infections; SSTI, skin and soft tissue infection; IAI, intra-abdominal infection; UTI, urinary tract infection. [a] Preferable combinations: an aminoglycoside or a polymyxin with high-dose ampicillin–sulbactam or high-dose tigecycline or high-dose minocycline.

TMP/SMX - *A.baumannii*

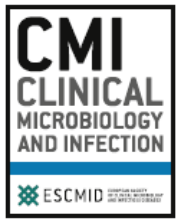
- Eğer *A.baumannii* duyarlı ise kombinasyonun bir parçası olabilir
- Monoterapi açısından deneyim oldukça az
- Sepsis ile seyretmeyen üriner sistem infeksiyonlarında seçenek olabilir

Falagas ME et al. Int J Antimicrob Agents 2015
Raz-Pasteur A et al. J Glob Antimicrob Resist 2019

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,§]



ESCMID-2021 Klavuzu

- Polimiksin + Meropenem veya polimiksin + rifampisin önerilmiyor
- Sulbaktam duyarlı ise HAP/VAP için ampisilin-sulbaktam
- Sulbaktam dirençli ise polimiksin veya yüksek doz tigesiklin(in vitro duyarlı ise)-öneri yok
- Ağır ve yüksek riskli enfeksiyonda in vitro etkili 2 AB(polimiksin, AG, tigesiklin, sulbaktam), meropenem MİK < 8 ise kombinasyonda yer alabilir

IDSA-2021 Klavuzu

- Hafif enfeksiyon(ÜSE, CYDE, trakeit, hemodinamik olarak stabil)
  -Ampisilin-Sulbaktam(duyarlı ise)
  -Yüksek doz ampisilin-sulbaktam + in vitro etkili AB(ampisilin-sulbaktam R ise)
  -Alternatif(minosiklin, tigesiklin, polimiksinler, sefiderokol)

IDSA-2021 Klavuzu

- Orta-Ağır enfeksiyonlar
  -İdeal olarak in vitro etkili en az 2 AB kombinasyonu(klinik iyileşme sonrası monoterapi yapılabilir)
  Yüksek doz ampisilin-sulbaktam (direnç olsa bile) kombinasyonda yer alabilir
  Fosfomisin kombinasyonda önerilmiyor
  Rifampisin kombinasyonda önerilmiyor
  Pnömonide nebulize AB önerilmiyor

Karbapenem Dirençli *Pseudomonas aeruginosa*

Çoklu Dirençli *P.aeruginosa* Tedavisi

- Karbapenem dirençli olgularda Seftolozan/Tazobaktam tedavisi

Munita JM et. Clin Infect Dis 2017

- Kolistin dirençli olgularda Seftolozan/Tazobaktam tedavisi

Alvarez Lerma A et al. Revista Espanola de Quimioterapia 2017

- Karbapenem dirençli VİP tedavisinde Kolistin + Meropenem(yüksek doz, uzamış infüzyon)

Sarda C et al. Expert Rev Respir Med 2019

PHARMACOTHERAPY accp

SPECIAL ARTICLE

International Consensus Guidelines for the Optimal Use of the Polymyxins: Endorsed by the American College of Clinical Pharmacy (ACCP), European Society of Clinical Microbiology and Infectious Diseases (ESCMID), Infectious Diseases Society of America (IDSA), International Society for Anti-infective Pharmacology (ISAP), Society of Critical Care Medicine (SCCM), and Society of Infectious Diseases Pharmacists (SIDP)†

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- Karbapenem-R *P.aeruginosa*
  -Kolistin + in vitro etkili 1 veya daha fazla AB
- Sadece kolistin duyarlı ise
  -Kolistin + en düşük MİK'e sahip 1 ve/veya 2 AB

(Pharmacotherapy 2019;39(1):10–39) doi: 10.1002/phar.2209

Clinical Infectious Diseases

MAJOR ARTICLE

Ceftolozane/Tazobactam vs Polymyxin or Aminoglycoside-based Regimens for the Treatment of Drug-resistant *Pseudomonas aeruginosa*

Jason M. Pogue,[1] Keith S. Kaye,[2] Michael P. Veve,[3] Twisha S. Patel,[4] Anthony T. Gerlach,[5] Susan L. Davis,[6] Laura A Puzniak,[7] Tom M. File,[8] Shannon Olson,[9] Sorabh Dhar,[10] Robert A. Bonomo,[11] and Federico Perez[11]

Table 3. Comparative clinical outcomes between Ceftolozane/Tazobactam and Polymyxin or Aminoglycoside treated patients

Outcome	Ceftolozane/ Tazobactam (N = 100)	Polymyxin/Aminoglycoside (N = 100)	*P* Value	Odds Ratio (95% CI)	Adjusted Odds Ratio[a] (95% CI)
Clinical cure	81	61	.002	2.72 (1.43–5.17)	2.63 (1.31–5.30)
In-hospital mortality	20	25	.40	0.75 (0.38–1.46)	0.62 (.30–1.28)
Acute kidney injury	6	34	<.001	0.12 (0.05–0.31)	0.08 (.03–.22)
Risk	2	8	…	…	…
Injury	3	12	…	…	…
Failure	1	14	…	…	…
Renal replacement therapy	0	7	…	…	…
Hypersensitivity reaction	0	1	.32	…	…
Neuropathies	0	2	.16	…	…
Seizures	0	0	N/A	…	…
Clostridium difficile on therapy	4	5	.73	…	…
C. difficile after therapy before discharge	2	3	.65	…	…
C. difficile on readmission	1	2	.46	…	…
Discharge status					
Home	26	14	.15	…	…
Skilled nursing facility/long-term acute care facility/Other hospital	54	61		…	…
30-day readmission[b]	21 (26)	18 (24)	.59	…	…
30-day readmission due to infection[b]	12 (15)	11 (15)	.82	…	…
30-day recurrence[b]	11 (14)	12 (16)	1.0	…	…
90-day recurrence[b]	13 (16)	12 (16)	1.0	…	…
Length of stay from onset of bacteremia (days)[c]	14.5 (9–26)	14 (9–24.5)	.65	…	…
Intensive care unit length of stay (days)[c]	16 (9–25)	13 (7–23)	.22	…	…
Mechanical ventilation duration (days)[c]	11 (4–18)	11 (4–22)	.96	…	…

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]

Table 4. Recommended Antibiotic Treatment Options for Difficult-to-Treat *Pseudomonas aeruginosa*, Assuming In Vitro Susceptibility to Agents in Table

Source of Infection	Preferred Treatment	Alternative Treatment if First-line Options not Available or Tolerated
Cystitis	Ceftolozane-tazobactam, ceftazidime-avibactam, imipenem-relebactam, cefiderocol, or a single dose of an aminoglycoside	Colistin
Pyelonephritis or complicated urinary tract infection[a]	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[b]

[a]A complicated urinary tract infection (UTI) is defined as a UTI that occurs in association with a structural or functional abnormality of the genitourinary tract, or any UTI in a male patient.

[b]Uncomplicated bloodstream infections include a bloodstream infection that is due to a urinary source or a catheter-related bloodstream infection with removal of the infected vascular catheter.

Guidelines

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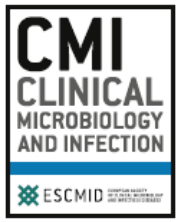
Mical Paul [1,2,§], Elena Carrara [3,§], Pilar Retamar [4,5], Thomas Tängdén [6], Roni Bitterman [1,2], Robert A. Bonomo [7,8,9], Jan de Waele [10], George L. Daikos [11], Murat Akova [12], Stephan Harbarth [13], Celine Pulcini [14,15], José Garnacho-Montero [16], Katja Seme [17], Mario Tumbarello [18], 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,§]



ESCMID-2021 Klavuzu

- Ağır enfeksiyonlarda, in vitro etkili ise seftolozan-tazobaktam
- Ağır enfeksiyonlarda 2 etkili AB kombinasyonu(polimiksin, AG, fosfomisin)
- Ağır olmayan ya da düşük riskli enfeksiyonda in vitro etkili AB-monoterapi(polimiksin, AG, fosfomisin)

Özet

- Kolistin + Aminoglikozid kombinasyonundan mümkünse kaçınalım(nefrotoksisite)
- Meropenem yüksek doz ve uzamış infüzyon
- Klavuzlardaki ya da Uzman Görüşlerindeki tigesiklin dozu ruhsatlı dozun 2 katı - Yan etkiler?
- Fosfomisin tek başına kullanılmamalı
- Kolistin inhalasyon?
- Seçenekler çok sınırlı ise Çift karbapenem?

Özet

- Enzim tipi
- Sinerji testleri
- İlaç düzeylerinin izlenmesi
- PK/PD
- Tedavi süreleri