İSTANBUL
MEDENİYET ÜNİVERSİTESİ

Sepsis Tedavisinde Yeni Antibiyotiklerin Rolü

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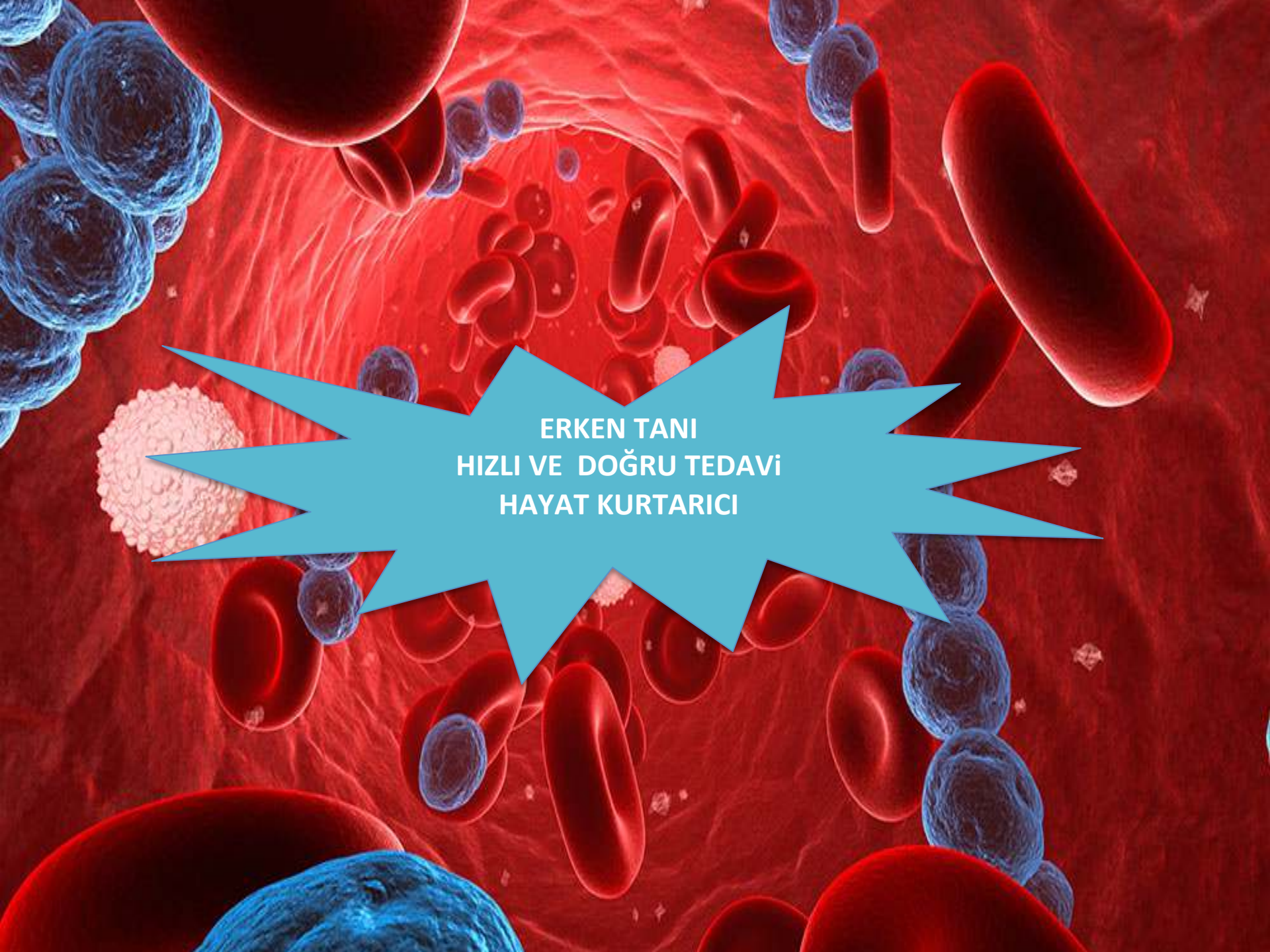
İstanbul Medeniyet Üniversitesi Tıp Fakültesi

Enfeksiyon Hast. ve Klinik Mikr. AD

EKMUD-2018

Sunum Planı

- Sepsiste uygun antimikrobiyal tedavi nasıl olmalıdır?
- MDR, XDR ve PDR suşlarla oluşan enfeksiyonlarda mevcut tedavi seçenekleri
- Yeni onay alan antibiyotikler ve bu antibiyotiklerin sepsis tedavisindeki yeri
  - Yeni betalaktam-betalaktamaz inhibitörleri kombinasyonları
  - Lipoglikopeptidler
  - Oksazolidinonlar
  - Florokinolonlar
  - Aminoglikozidler


ERKEN TANI
HIZLI VE DOĞRU TEDAVİ
HAYAT KURTARICI

CHEST Original Research
CRITICAL CARE MEDICINE

Initiation of Inappropriate Antimicrobial Therapy Results in a Fivefold Reduction of Survival in Human Septic Shock

Anand Kumar, MD; Paul Ellis, MD; Yaseen Arabi, MD, FCCP;
Dan Roberts, MD; Bruce Light, MD; Joseph E. Parrillo, MD, FCCP;

2009

Table 4—*Differences in Antimicrobial Appropriateness in Major Subgroups*

Characteristics	Cases, No. (% Total Cases)	Appropriate Initial Therapy, %	OR (95% CI)/p Value
Documented	4,698 (82.2)	78.3	
Suspected	1,017 (17.8)	88.6	0.4728 (0.3856–0.5799)/< 0.0001
Culture positive			
Culture negative			233 (0.3578–0.5007)/< 0.0001
Blood culture positive			
Blood culture negative			609 (0.8308–1.1114)/NS
Community-acquired infe			
Nosocomial infection			159 (1.5159–1.9423)/< 0.0001

NS = not significant.

- Vakaların %55'i toplum kökenli %45'i nozokomiyal septik şok
- Başlangıç antikrobiyal tedavinin uygunsuz olması septik şokta mortaliteyi 5 kat arttırmakta

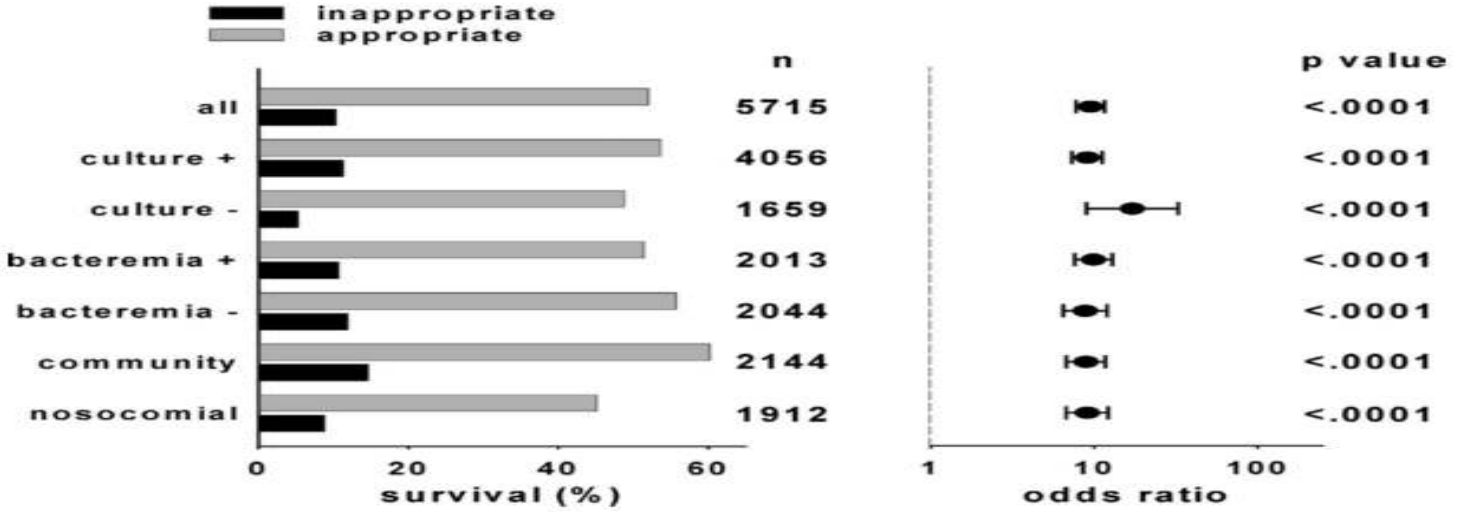


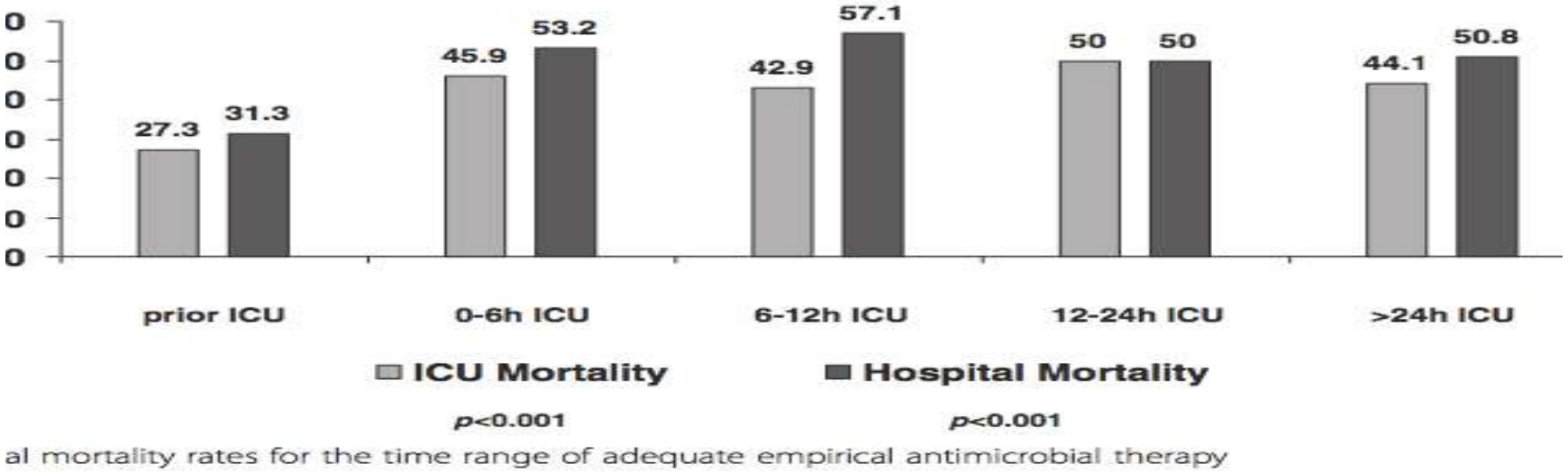
FIGURE 2. Impact of antimicrobial appropriateness on survival in major epidemiologic subgroups. See the legend of Figure 1 for abbreviations not used in the text.

Garnacho-Montero *et al. Critical Care* (2015) 19:302
DOI 10.1186/s13054-015-1000-z

CRITICAL CARE

RESEARCH Open Access

Adequate antibiotic therapy prior to ICU admission in patients with severe sepsis and septic shock reduces hospital mortality



al mortality rates for the time range of adequate empirical antimicrobial therapy

- Toplam 926 hasta, etken mikrorganizma üretilen 638 hasta
- Uygun antibiyotik tedavisi
  - 444 hasta YBÜ kabulü öncesi
  - 194 hasta YBÜ kabulü sonrası
- Acil servise başvuru ile YBÜ kabulü arasındaki süre ortalama 5 saat
- Antibiyotik tedavisindeki >24 saatlik gecikmede mortalite yaklaşık 2 kat artmış

Uygun Antimikrobiyal Seçimi

Dirençli bakteri enfeksiyonları açısından hastanın

- Son üç aydaki antibiyotik kullanım öyküsü,
- Bilinen bir mikroorganizma ile kolonizasyon öyküsü
- Hastaneye yatışı
- YBÜ yatışı
- Lokal epidemiyolojik veriler
- İmmun yetmezlik durumu dikkate alınmalı

Başlangıç ampirik tedavi

- olası mikroorganizmaları kapsayacak şekilde geniş spektrumlu
- bir veya daha fazla ajandan oluşmalıdır.

Baykara et al. Critical Care (2018) 22:93
https://doi.org/10.1186/s13054-018-2013-1

Critical Care

RESEARCH Open Access

Epidemiology of sepsis in intensive care units in Turkey: a multicenter, point-prevalence study

Nur Baykara[1*], Halis Akalın[2], Mustafa Kemal Arslantaş[3], Volkan Hancı[4], Çiğdem Çağlayan[5], Ferda Kahveci[6], Kubilay Demirağ[7], Canan Baydemir[8], Necmettin Ünal[9] and Sepsis Study Group

Abstract

Background: The prevalence and mortality of sepsis are largely unknown in Turkey, a country with high antibiotic resistance. A national, multicenter, point-prevalence study was conducted to determine the prevalence, causative microorganisms, and outcome of sepsis in intensive care units (ICUs) in Turkey.

Met

- ***Acinetobacter spp.* (%37) en sık izole edilen patojen.**
- **Karbapenem direnç oranları *Acinetobacter spp*. (%74.9), *Klebsiella spp.* (%39.1), *Pseudomonas spp.* (%26.5)**

Results: Of the 1499 patients included in the analysis, 237 (15.8%) had infection without SIRS, 163 (10.8%) had infection with SIRS, 260 (17.3%) had severe sepsis without shock, and 203 (13.5%) had septic shock. The mortality rates were higher in patients with severe sepsis (55.7%) and septic shock (70.4%) than those with infection alone (24.8%) and infection + SIRS (31.2%) ($p < 0.001$). According to SEPSIS-III, 104 (6.9%) patients had septic shock (mortality rate, 75.9%). The respiratory system (71.6%) was the most common site of infection, and *Acinetobacter* spp. (33.7%) were the most common isolated pathogen. Approximately, 74.9%, 39.1%, and 26.5% of *Acinetobacter*, *Klebsiella*, and *Pseudomonas* spp. isolates, respectively, were carbapenem-resistant, which was not associated with a higher mortality risk. Age, acute physiology and chronic health evaluation II score at ICU admission, sequential organ failure assessment score on study day, solid organ malignancy, presence of severe sepsis or shock, *Candida spp.* infection, renal replacement treatment, and a nurse-to-patient ratio of 1:4 (compared with a nurse-to-patient ratio of 1:2) were independent predictors of mortality in infected patients.

Conclusions: A high prevalence of sepsis and an unacceptably high mortality rate were observed in Turkish ICUs. Although the prevalence of carbapenem resistance was high in Turkish ICUs, it was not associated with a higher risk for mortality.

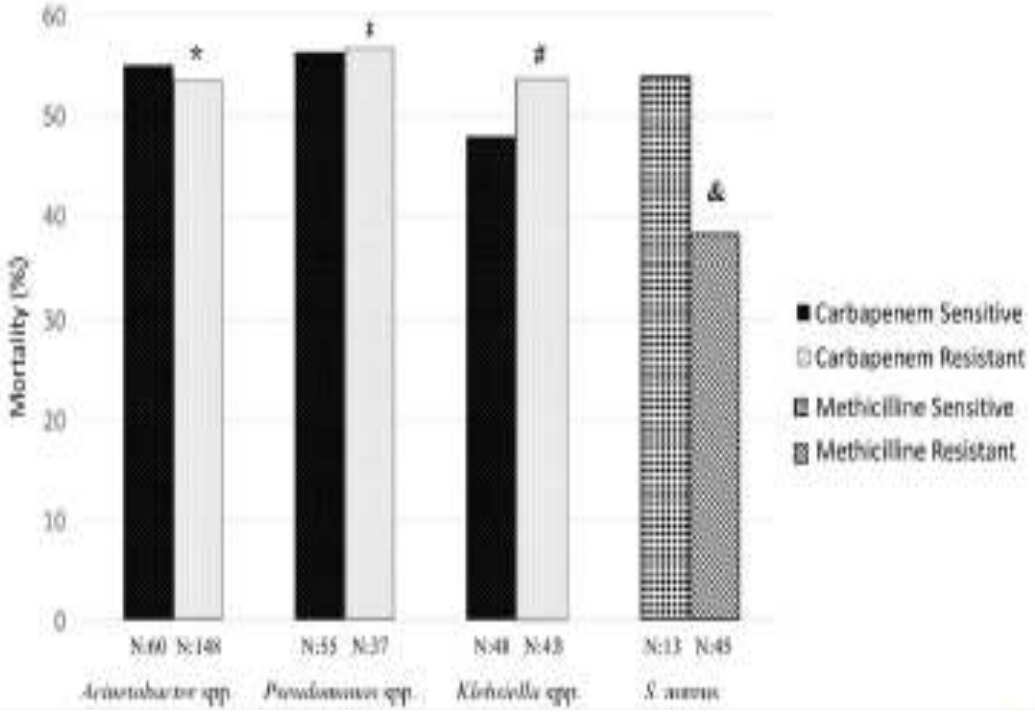


Fig. 2 Antibiotic su… …c-sensitive and -resistant strains … compared with carbapenem-s… … methicillin-sensitive *S. aureus*

Karbapenem direnci ve metisilin direncinin mortalite (30 günlük) artışı ile ilişkisi gösterilememiş.

WHO mikroorganizmaları yeni antibiyotik ihtiyacının aciliyetine göre kritik, yüksek ve orta öncelikli olarak üç kategoriye ayrırmış (February 27, 2017)

Priority 1: CRITICAL
1. ***Acinetobacter baumannii***, carbapenem-resistant
2. ***Pseudomonas aeruginosa***, carbapenem-resistant
3. ***Enterobacteriaceae***, carbapenem-resistant, ESBL-producing

Kolistin dirençli suşlar!!!

Priority 2: HIGH
1. ***Enterococcus faecium***, vancomycin-resistant
2. ***Staphylococcus aureus***, methicillin-resistant, vancomycin-intermediate and resistant
3. ***Helicobacter pylori***, clarithromycin-resistant
4. ***Campylobacter*** spp., fluoroquinolone-resistant
5. ***Salmonellae***, fluoroquinolone-resistant
6. ***Neisseria gonorrhoeae***, cephalosporin-resistant, fluoroquinolone-resistant

Priority 3: MEDIUM
1. ***Streptococcus pneumoniae***, penicillin-non-susceptible
2. ***Haemophilus influenzae***, ampicillin-resistant
3. ***Shigella*** spp., fluoroquinolone-resistant

Outcome of carbapenem resistant *Klebsiella pneumoniae* bloodstream infections

D. Ben-David, R. Kordevani, N. Keller, I. Tal, A. Marzel, O. Gal-Mor, Y. Maor and G. Rahav
Infectious Diseases Unit, Sheba Medical Center, Tel Hashomer, Israel

Clinical Microbiology and Infection 18.1 (2012).

Abstract

The aim of this study was to evaluate the impact of carbapenem-resistant *K. pneumoniae* bloodstream infections on mortality. During the study period 42, 68 and 120 patients were identified with carbapenem-resistant, extended-spectrum β-lactamase producers (ESBL) and susceptible *K. pneumoniae* bloodstream infections, respectively. Patients with carbapenem-resistant *K. pneumoniae* had higher rates of prior antimicrobial exposure, other nosocomial infections, and use of invasive devices. Infection-related mortality was 48% for carbapenem-resistant, 22% for ESBL producers and 17% for susceptible *K. pneumoniae*. Independent risk factors for infection-related mortality were Pitt bacteraemia score, Charlson score and carbapenem resistance.

K. pneumoniae **KDİ'da karbapenem direnci artmış mortaliteyle ilişkili bulunmuş.**

MDR Gram negatif bakterilerle oluşan enfeksiyonlarda tedavi seçenekleri

1- Karbapenemler ve pip/taz gibi antibiyotiklerin yüksek doz ve /veya uzamış infuzyonla uygulanması

- Artmış toksisite riski

2- Kolisitin gibi eski antibiyotiklerin kullanımı

- Artmış toksisite riski
- Monoterapide hızlı direnç gelişimi

3- Antibiyotiklerin çoklu kullanımı

- Artmış toksisite riski
- Yüksek maliyet

Cochrane Database Syst Rev. 2014 Jan 7;(1):CD003344. doi: 10.1002/14651858.CD003344.pub3.

Beta lactam antibiotic monotherapy versus beta lactam-aminoglycoside antibiotic combination therapy for sepsis.

Paul M[1], Lador A, Grozinsky-Glasberg S, Leibovici L.

Eur J Clin Microbiol Infe
DOI 10.1007/s10096-012-1568-z

ARTICLE

Impact of combination therapy with aminoglycosides on the outcome of ICU-acquired bacteraemias

P.-Y. Delannoy · N. Boussekey · P. Devos · S. Alfandari · C. Turbelin · A. Chiche · A. Meybeck · H. Georges ·

ANTIMICROBIAL AGENTS AND CHEMOTHERAPY, May 2010, p. 1742–1748 Vol. 54, No. 5

Literatürde GNB sepsis ve bakteremi tedavisinde kombinasyon tedavisinin etkinliği ile ilgili çok sayıda çalışma ve farklı sonuçlar mevcut

JAMA. 2012 Jun 13;307(22):2390-9. doi: 10.1001/jama.2012.5833.

Effect of empirical treatment with moxifloxacin and meropenem vs meropenem on sepsis-related organ dysfunction in patients with severe sepsis: a randomized trial.

Brunkhorst FM[1], Oppert M, Marx G, Bloos F, Ludewig K, Putensen C, Nierhaus A, Jaschinski U, Meier-Hellmann A, Weyland A, Gründling M, Moerer O, Riessen R, Seibel A, Ragaller M, Büchler MW, John S, Bach F, Spies C, Reill L, Fritz H, Kiehntopf M, Kuhnt E, Bogatsch H, Engel C, Loeffler M, Kollef MH, Reinhart K, Welte T; German Study Group Competence Network Sepsis (SepNet).

Collaborators (66)

- Mevcut antibiyotiklerle, özellikle dirençli mikroorganizmaların etken olduğu nozokomiyal sepsis tedavisinde güçlükler yaşanmaktadır.
- Tedavi seçenekleri oldukça sınırlıdır.
- Yeni geliştirilen antibiyotikler tedavide yeni alternatif oluşturmaktadır.

Yeni Onaylanan Antibiyotikler

- Yeni betalaktam-betalaktamaz inhibitörleri kombinasyonları
  - Seftazidim-avibaktam
  - Seftolozan-tazobaktam
  - Meropenem-vaborbaktam
- Lipoglikopeptidler
  - Dalbavansin
  - Oritovansin
- Oksazolidinonlar
  - Tedizolid
- Florokinolonlar
  - Delafloksasin
- Aminoglikozitler
  - Plazomisin

Beta-laktamaz İnhitörlerinin Etkinliği

Table 3 Activities of β-lactamase inhibitors against various β-lactamase enzymes

	β-lactamase inhibitor					
	Relebactam	Vaborbactam	Avibactam	Clavulanic acid	Sulbactam	Tazobactam
Class A						
TEM	+	+	+	+	+	+
SHV	+	+	+	+	+	+
CTX-M	+	+	+	+	+	+
KPC	+	+	+	−	−	−
Class B						
MBL	−	−	−	−	−	−
Class C						
AmpC	+	+	+	−	±[a]	−
Class D						
OXA	±	−[b]	±	−	−	−
Reference	[5]	[5]	[5, 24]	[25, 26]	[27]	[27]

− no inhibitory activity, + inhibitory activity, *MBL* metallo-β-lactamase

[a]Enterobacteriaceae resist inhibition by sulbactam, although *Klebsiella* spp., *Salmonella* spp., and *Proteus* spp. normally do not harbor chromosomal bla_{AmpC} genes

[b]Limited data available

Zhanel GG. Drugs. 2018 Jan;78(1)

Seftazidim-Avibaktam

- 3. kuşak sefalosporin olan seftazidimin, yeni bir geliştirilen bir non betalaktam beta laktamaz inhibitörü olan avibaktam ile kombinasyonu
- Avibaktam sınıf A, C ve kısmen de D beta laktamazlara karşı etkili, metallobetalaktamazlara karşı etkisiz
- ESBL üreten GNB ve karbapenem dirençli Enterobacteriaceae'ya etkili
- 2015 FDA onayı
  - Komplike intraabdominal enfeksiyonlar (metranidazol ile birlikte kullanım)
  - Piyelonefrit dahil komplike üriner sistem enfeksiyonları
- Pnömoni, nozokomiyal pnömoni, VİP

Falcone, M., & Paterson, D. 2016. *JAC*, *71*(10)

Seftazidim-Avibaktam

- Plazma proteinlerine bağlanma: Ceftazidime <%10; Avibactam %5.7% - %8.2
- Ceftazidime %80-90; Avibactam %97 değişmeden idrarla atılır
- 2.5 g (2 g/0.5 g) IV her 8 saatte, infüzyon süresi >2 saat
- Tedavi süresi 5-14 gün
- Orta ve ciddi renal yetmezlikte doz ayarı gerektirir
- Genellikle iyi tolere edilir. En sık bildirilen yan etkiler
  - Direk Coombs testi pozitifliği
  - Gastrointestinal rahasızlıklar, infüzyon bölgesinde reaksiyon

Falcone, M., & Paterson, D. 2016. *JAC*, *71*(10)

CMRO

Original article

Efficacy and safety of ceftazidime–avibactam versus imipenem–cilastatin in the treatment of complicated urinary tract infections, including acute pyelonephritis, in hospitalized adults: results of a prospective, investigator-blinded, randomized study

Journal of Antimicrobial Chemotherapy Advance Access published February 7, 2013

J Antimicrob Chemother
doi:10.1093/jac/dks523

Journal of Antimicrobial Chemotherapy

Comparative study of the efficacy and safety of ceftazidime/avibactam plus metronidazole versus meropenem in the treatment of complicated intra-abdominal infections in hospitalized adults: results of a randomized, double-blind, Phase II trial

Christopher Lucasti[1]*, Irinel Popescu[2], Mayakonda K. Ramesh[3], Joy Lipka[4]† and Carole Sable[4]‡

Ceftazidime-avibactam versus meropenem in nosocomial pneumonia, including ventilator-associated pneumonia (REPROVE): a randomised, double-blind, phase 3 non-inferiority trial

Antoni Torres, Nanshan Zhong, Jan Pachl, Jean-François Timsit, Marin Kollef, Zhangjing Chen, Jie Song, Dianna Taylor, Peter J Laud, Gregory G Stone, Joseph W Chow

-Komplike ÜSE'da C-A ve imipenem mikrobiyolojik etkinlik ve klinik kür oranları benzer. (Faz II)

-Komplike İAİ'da C-A ve metronidazolun birlikte kullanımı meropenem ile benzer sonuçlar. (Faz II)

-Nozokomiyal pnömonide C-A meropenem'e non-inferior. (Faz III)

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],

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.

Tüm nedenlere bağlı 30 günlük mortalite C-A grubunda %9, kolistin grubunda %32

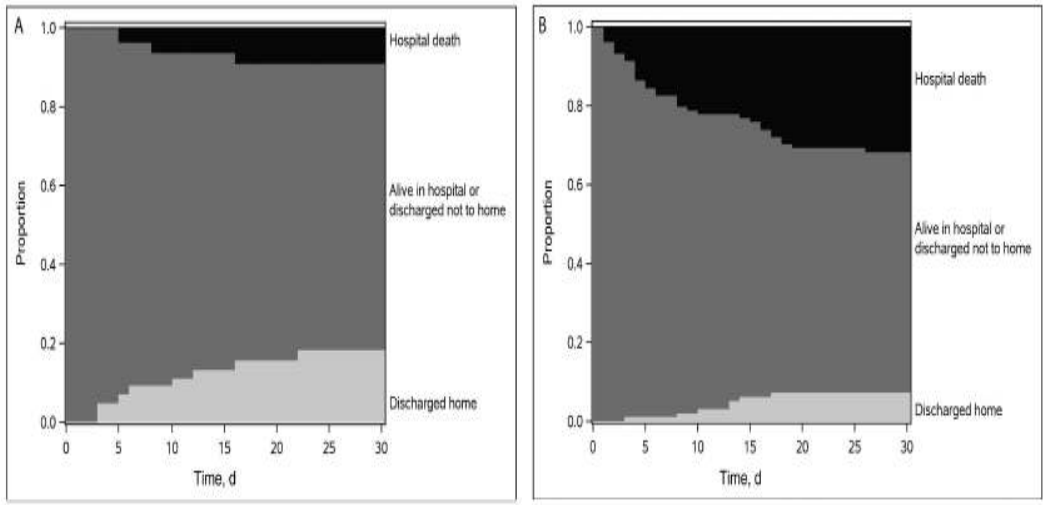


Figure 1. Inverse probability of treatment weighting (IPTW)–adjusted efficacy: disposition over time (n = 137; IPTW-adjusted probability estimates of hospital mortality and discharge status). *A*, Ceftazidime-avibactam group (n = 38). *B*, Colistin group (n = 99).

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]

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Ceftazidime-Avibactam Is Superior to Other Treatment Regimens against Carbapenem-Resistant *Klebsiella pneumoniae* Bacteremia

Ryan K. Shields,[a,c] M. Hong Nguyen,[a,c] Liang Chen,[d] Ellen G. Press,[a] Brian A. Potoski,[a,c,e] Rachel V. Marini,[c] Yohei Doi,[a,c] Barry N. Kreiswirth,[d] Cornelius J. Clancy[a,b,f]

online 30 May 2017

- C-A: 13 vaka
- Karbapenem -aminoglikozit: 25 vaka
- Karbapenem-kolistin: 30 vaka
- Diğer: 41 vaka
- 30 günlük klinik başarı C-A: %85, K-AG:%48, K-Kol:%40

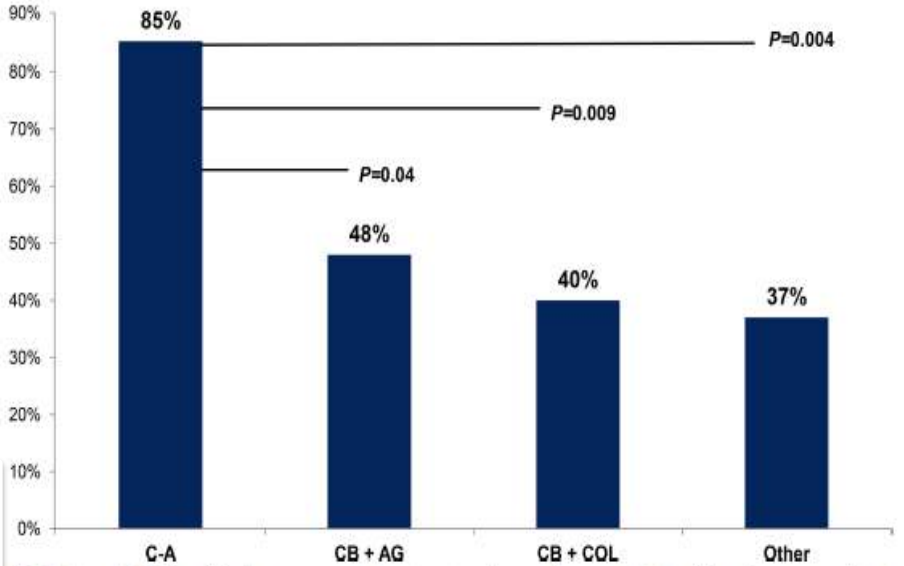


FIG 1 Rates of 30-day clinical success across treatment regimens. Among patients with carbapenem-resistant *Klebsiella pneumoniae* bacteremia, rates of clinical success were significantly higher among patients receiving ceftazidime-avibactam than among those who received a carbapenem plus aminoglycoside ($P = 0.04$) or colistin ($P = 0.009$) or other regimens ($P = 0.004$). Other regimens included aminoglycoside ($n = 11$), carbapenem ($n = 8$), colistin ($n = 4$), tigecycline ($n = 4$), and ciprofloxacin ($n = 2$) monotherapy, as well as combination regimens of colistin plus tigecycline ($n = 3$), aminoglycoside plus tigecycline ($n = 2$), and 1 each of aminoglycoside plus cefepime, aminoglycoside plus colistin plus tigecycline, colistin plus aztreonam, colistin plus cefepime, colistin plus ciprofloxacin, carbapenem plus doxycycline, and carbapenem plus tigecycline.

28th ECCMID EUROPEAN CONGRESS OF CLINICAL MICROBIOLOGY AND INFECTIOUS DISEASES
Madrid, Spain
21 – 24 April 2018

O0932 Clinical experience with ceftazidime/avibactam (CAZ-AVI) in patients with infections caused by carbapenem and colistin-resistant *Klebsiella pneumoniae* (KPC Col R)

Thais Guimaraes*[1], Aleia Campos[1], Icaro Boszczowski[1], Maria Luisa Do Nascimento Moura[1], Matias Salomão[1], Alexandre Blikstad Mauro[1], Ana Paula Marchi[2], Lauro Perdigao Neto[2], Tatiana Orsi[2], Anna Sara Levin[1], Silvia Figueiredo Costa[2]

Results: We enrolled 17 patients, 10 (59%) were female. All patients had received antibiotics before CAZ-AVI (median, 3 drugs) and had failed treatment. The most commonly prescribed agents were colistin (*N=17*), meropenem (*N=15*), amikacin (*N=10*) and tigecycline (*N= 8*). The infection site were 6 (35,3%) bacteremias; 6 (35,3%) urinary tract infections; 3 (17,6%) intra-abdominal infections; 1 (5,9%) complicated soft and skin infection and 1 (5,9%) pneumonia. All infections were caused by KPC Col R an all isolates were susceptible to CAZ-AVI. The MIC 50 and MIC 90 for CAZ-AVI were 4/1 and 8/2 µg/mL, respectively. The length of treatment ranged from 7- 14 days

- 17 vakalık vaka serisi, etken karbapenem ve kolistin dirençli *K. pneumoniae.*
- Öncesinde median 3 gün (kolistin+ meropenem, amikasin veya tigesiklin) başarısız tedavi.
- Seftazidim-avibaktam kurtarma tedavisi.
- %82 klinik kür

28th ECCMID EUROPEAN CONGRESS OF CLINICAL MICROBIOLOGY AND INFECTIOUS DISEASES
Madrid, Spain
21 – 24 April 2018

O0936 Ceftazidime/avibactam to treat severe infections due to carbapenemases-producing *Klebsiella pneumoniae* in the critically ill

Alberto Corona*[1], Alberto Corona, Alice Veronese[1], Spinello Antinori[1], Mario Corbellino[1], Sara Rimoldi[1], Emanuele Catena[1]

[1] Ospedale Sacco, Milano, Italy

Results: Results From April to November 2017, 14 patients (10 M and 4 F), median age 57 (IQR = 42.5-70.5) were given ceftazidime/avibactam for major KP-cp (meropenem MIC > 16) infections: 9 bacteramia (B) (3 abdominal sepsis, 2 mediastinitis, 2 CVC, 2 primary); 3 secondary peritonitis and 2 UTI. 10/14 (71.5%) patients, developed a septic shock [median (IQR) SOFA score 10 (8-17)) and needed mechanical ventilation [median (IQR) 8 (4-17) days], norepinephrine infusion [median (IQR) 3 (2-5) days]; 4 patients underwent renal replacement therapy. The median treatment duration (IQR) was 14 (13-14) days. In 41.6% of cases, antibiotic-therapy therapy combination (phosphomycin and colistin) was chosen. All the patients experienced a clinical response by 72/96 hours from the ceftazidime/avibactam commencing. In 8/9 bacteraemic patients negativization of blood culture occurred by 96 hours as well as of the rectal swab in 5/14 patients. A (B) recurred and a second treatment was given. 11/14 (78.5%) patients survived, whereas death was caused by multi-organ failure. The susceptibility test of

- 14 vakalık bir vaka serisi. Vakaların 10'u septik şok,
- %41'i fosfomisin veya kolistinli bir kombinasyon kullanmış.
- 11/14 hastada sağkalım izlenmiş

Seftolozan-Tazobaktam

- Seftolozan yeni bir sefalosporin olup sefem çekirdeğinin 3. pozisyonundaki yan zincirin modifikasyonu ile seftazidimden farklı (oxyimino-sefalosporin)
  - Artmış antipsödomonal aktiviteye sahip
- Seftalozan'ın bilinen bir beta laktamaz inhibitörü olan tazobaktam ile kombinasyonundan oluşmakta
- 2014 FDA onayı
  - Komplike intraabdominal enfeksiyonların tedavisinde (metranidazol ile birlikte kullanım)
  - Piyelonefrit dahil komplike üriner sistem enfeksiyonlarının tedavisinde

Zhanel, George G. 2014. *Drugs* 74.1

Seftolozan-Tazobaktam

- Plazma proteinlerine bağlanma oranı %20
- >%92 değişmeden idrarla atılır

Cho, J C. *Pharmacotherapy: The Journal of Human Pharmacology and Drug Therapy* 35.7 (2015)

- 1.5g (1.5g = 1g seftolozon + 0.5g tazobactam)
- 1.5 g IV her 8 saatte, infüzyon süresi 1 saat
- Tedavi süresi 4-14 gün
- Orta ve ciddi renal yetmezlikte doz ayarı gerektirir
- Yan etkiler: Gastrointestinal rahasızlıklar, baş ağrısı, pireksi

Ceftolozane-tazobactam compared with levofloxacin in the treatment of complicated urinary-tract infections, including pyelonephritis: a randomised, double-blind, phase 3 trial (ASPECT-cUTI)

Florian M Wagenlehner, Obiamiwe Umeh, Judith Steenbergen, Guojun Yuan, Rabih O Darouiche

MAJOR ARTICLE

Ceftolozane/Tazobactam Plus Metronidazole for Complicated Intra-abdominal Infections in an Era of Multidrug Resistance: Results From a Randomized, Double-Blind, Phase 3 Trial (ASPECT-cIAI)

Joseph Solomkin,[1] Ellie Hershberger,[2] Benjamin Miller,[2] Myra Popejoy,[2] Ian Friedland,[2,a] Judith Steenbergen,[2] Minjung Yoon,[2] Sylva Collins,[2] Guojun Yuan,[2] Philip S. Barie,[3] and Christian Eckmann[4]

-Komplike ÜSE'da C-T levofloksasin ile benzer klinik kür oranları. (Faz III)

-Komplike İAİ'da C-T ve metronidazol ile birlikte kullanım meropenem ile benzer sonuçlar. (Faz III)

AMERICAN SOCIETY FOR MICROBIOLOGY | Antimicrobial Agents and Chemotherapy®

March 2017 Volume 61 Issue 3

Salvage Therapy with Ceftolozane-Tazobactam for Multidrug-Resistant *Pseudomonas aeruginosa* Infections

Juan José Castón,[a,b] Álvaro De la Torre,[c] Isabel Ruiz-Camps,[d] María Luisa Sorlí,[e] Vicente Torres,[f] Julián Torre-Cisneros[a,b,g]

ABSTRACT Infections caused by multidrug-resistant *Pseudomonas aeruginosa* (MDRPA) present a major problem for therapeutic management. We report here our experience with 12 patients with a severe MDRPA infection (6 of which were pneumonia) who received salvage therapy with ceftolozane-tazobactam after inappropriate empirical treatment and/or suboptimal targeted treatment. Although 10 of the 12 patients (83.3%) experienced septic shock, only 3 patients (25%) died during the follow-up period. Microbiological cure in 7 patients (58.3%) was observed.

- Retrospektif, çok merkezli vaka serisi
- Başlangıç tanıları 10/12 septik şok, 1 sepsis, 1 ciddi sepsis
- Odak: 6 hasta pnömoni, 3 abdominal, 3 diğer
- Tüm hastalar meropenem, siprofloksasin ve pip-taz dirençli, 8 hasta kolistin hassas
- Başlangıç empirik tedaviden median 7. günde hedefe yönelik tedaviye (Çogunlukla kolistin) geçilmiş.
- Tedavi yanıtsızlığı gelişmesi üzerine median 12. günde seftolozan-tazobaktam'a geçilmiş.
- 8/12 Klinik kür, 3/12 ölüm, 1 relaps

Meropenem-Vaborbaktam

- Vaborbactam siklik boranik asit bazlı bir betalaktamaz inhibitörü
- Serin beta laktamazlara karşı geniş inhibitör aktivite göstermektedir. KPC, Ambler class A ve C'ye etkili
- 2017 FDA onayı
  - Piyelonefrit dahil komplike üriner sistem enfeksiyonlarının tedavisi
- 4 g (meropenem 2g/vaborbactam 2g) IV her 8 saatte, infuzyon süresi >3 saat

JAMA | Original Investigation

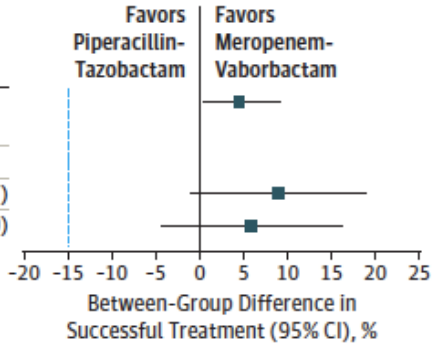
Effect of Meropenem-Vaborbactam vs Piperacillin-Tazobactam on Clinical Cure or Improvement and Microbial Eradication in Complicated Urinary Tract Infection

The TANGO I Randomized Clinical Trial

Keith S. Kaye, MD, MPH; Tanaya Bhowmick, MD; Symeon Metallidis, MD; Susan C. Bleasdale, MD; Olexiy S. Sagan, MD; Viktor Stus, MD, PhD; Jose Vazquez, MD; Valerii Zaitsev, PhD; Mohamed Bidair, MD; Erik Chorvat, MD; Petru Octavian Dragoescu, MD; Elena Fedosiuk, MD;

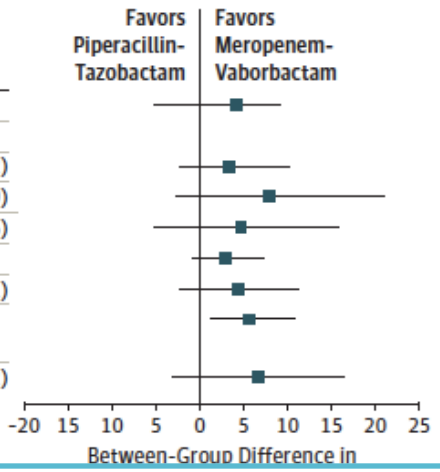
A Primary end points

	No. of Patients Successfully Treated/Total No. (%)		Between-Group Difference (95% CI), %
	Meropenem-Vaborbactam	Piperacillin-Tazobactam	
FDA primary: overall success at end of intravenous treatment (microbiologic MITT analysis)[a,b]	189/192 (98.4)	171/182 (94.0)	4.5 (0.7 to 9.1)
EMA primary: microbial eradication at test of cure			
Microbiologic MITT analysis[b]	128/192 (66.7)	105/182 (57.7)	9.0 (-0.9 to 18.7)
Microbiologic evaluable analysis	118/178 (66.3)	102/169 (60.4)	5.9 (-4.2 to 16.0)



B Secondary end points

	No. of Patients Successfully Treated/Total No. (%)		Between-Group Difference (95% CI), %
	Meropenem-Vaborbactam	Piperacillin-Tazobactam	
Overall success at test of cure[a]	143/192 (74.5)	128/182 (70.3)	4.1 (-4.9 to 9.1)
Overall success at end of intravenous treatment[a]			
Acute pyelonephritis	117/120 (97.5)	95/101 (94.1)	3.4 (-2.0 to 10.2)
Complicated UTI, removable infection source[c]	35/35 (100)	35/38 (92.1)	7.9 (-2.5 to 20.9)
Complicated UTI, nonremovable infection source	37/37 (100)	41/43 (95.3)	4.7 (-5.1 to 15.6)
Clinical cure at end of intravenous treatment[d]	189/192 (98.4)	174/182 (95.6)	2.8 (-0.7 to 7.1)
Clinical cure at test of cure	174/192 (90.6)	157/182 (86.3)	4.4 (-2.2 to 11.1)
Microbial eradication at end of intravenous treatment (FDA criteria)	188/192 (97.9)	168/182 (92.3)	5.6 (1.4 to 10.7)
Microbial eradication at test of cure (FDA criteria)	132/192 (68.8)	113/182 (62.1)	6.7 (-3.0 to 16.2)



28th ECCMID EUROPEAN CONGRESS OF CLINICAL MICROBIOLOGY AND INFECTIOUS DISEASES
Madrid, Spain
21 – 24 April 2018

O0608 Meropenem-vaborbactam versus best available therapy for infections due to carbapenem-resistant Enterobacteriaceae in TANGO II: impact of prior antibiotic failure on clinical outcomes

Matteo Bassetti*[1], Marin Kollef[2], David Nicolau[3], Galia Rahav[4], Warren Rose[5], Elizabeth Alexander[6], Nkechi Azie[6], Jeffery S. Loutit, Edward Spindler[6], Richard G Wunderink[7]

Materials/methods: Eligible patients were randomised 2:1 to M-V or BAT for 7 to 14 days. BAT included any of the following, alone or in combination: carbapenems, aminoglycosides, polymyxin B, colistin, tigecycline, or ceftazidime-avibactam (monotherapy only). Clinical cure was defined as complete resolution of symptoms such th
p

- Randomize kontrollü çalışma, M-V ile mevcut en iyi tedavi karşılaştırılmış
- 20 hasta bakteremi, 15 komplike ÜSE, 5 VİP, 3 komplike İAİ
- Klinik kür, mikrobiyolojik kür ve 28 günlük mortalite M-V grubunda üstün

R
1
and 3 had cIAI. 9 patients had baseline investigator-ascertained failure of prior antimicrobials, all of which were randomised to M-V. Baseline demographics and clinical characteristics were similar in patients with and without prior antibiotic failures. Clinical cure, microbiologic cure, and Day 28 mortality among patients with and without prior antibiotic failure in the mCRE-MITT are shown.

Efficacy Endpoints	M-V[1] (N = 28) n (%)	M-V[2] (N = 19) n (%)	BAT[2] (N = 15) n (%)	Absolute Difference[3] (95% CI, *P*)	*P* value
Clinical cure at EOT	18 (64.3)	16 (84.2)	5 (33.3)	+50.9 (21.9 to 79.8)	<0.001
Clinical cure at TOC	16 (57.1)	13 (68.4)	4 (26.7)	+41.8 (11.1 to 72.4)	<0.01
Microbiologic cure at EOT	18 (64.3)	16 (84.2)	6 (40)	+44.2 (14.5 to 73.9)	<0.01
Microbiologic cure at TOC	14 (50)	13 (68.4)	5 (33.3)	+35.1 (3.4 to 66.8)	0.03
Day 28 mortality	5 (17.9)	1 (5.3)	5 (33.3)	-28.1 (-54.0 to -2.2)	0.03

Abbreviations: EOT, end of treatment; TOC, test of cure.
1 mCRE-MITT population (with baseline CRE pathogen), prior antibiotic failure at randomisation (M-V, 9; BAT, 0) included.
2 Prior antibiotic failure at randomisation (M-V, 9; BAT, 0) excluded.
* mCRE-MITT population (with baseline CRE pathogen); there were no prior antibiotic failures in the BAT group and therefore none were excluded.
3 Data represent the difference in percentages for M-V* and BAT* (95%-CI for that difference).

Seftarolin

Ceftaroline fosamil 5. kuşak parenteral sefalosporin

- Geniş gram negatif etkinlik yanında MRSA and PRSP dahil gram pozitif etkinlik (PBP-2a'ya yüksek affinite)
- *Pseudomonas spp.* ve anaerobik m.org etkisiz
- 2010 FDA onayı
  - Komplike deri ve yumuşak doku enfeksiyonları ve Toplum kökenli bakteriyel pnömoni tedavisi
- 600 mg her 12 saatte, >1 saat infüzyon süresi
- Tedavi süresi 5-12 gün
- Orta ve ciddi renal yetmezlik ve hemodiyaliz hastalarında doz ayarı gerekli
- En önemli yan etkiler: diyare ve başağrısı

Frampton J E. *Drugs*, 2013, 73.10

AAC
Journals.ASM.org

Large Retrospective Evaluation of the Effectiveness and Safety of Ceftaroline Fosamil Therapy

Anthony M. Casapao,[a] Susan L. Davis,[a,b] Viktorija O. Barr,[c] Kenneth P. Klinker,[d] Debra A. Goff,[e,f] Katie E. Barber,[a] Keith S. Kaye,[g,h] Ryan P. Mynatt,[i] Leah M. Molloy,[i] Jason M. Pogue,[g,i] Michael J. Rybak[a,g,i]

Ceftaroline has been approved for acute bacterial skin infections and community-acquired bacterial pneumonia. Limited clinical experience exists for use outside these indications. The objective of this study was to describe the outcomes of patients treated with ceftaroline for various infections. Retrospective analyses of patients receiving ceftaroline ≥72 h from 2011 to 2013 were included. Clinical and microbiological outcomes were analyzed. Clinical success was defined as resolution of all signs and symptoms of infection with no further need for escalation while on ceftaroline treatment during hospitalization. A total of 527 patients received ceftaroline, and 67% were treated for off-label indications. Twenty-eight percent (148/527) of patients had bacteremia. Most patients (80%) were initiated on ceftaroline after receipt of another antimicrobial, with 48% citing disease progression as a reason for switching. The median duration of ceftaroline treatment was 6 days, with an interquartile range of 4 to 9 days. A total of 327 (62%) patients were culture positive, and the most prevalent pathogen was *Staphylococcus aureus*, with a frequency of 83% (271/327). Of these patients, 88.9% (241/271) were infected with methicillin-resistant *S. aureus* (MRSA). Clinically, 88% (426/484) achieved clinical success and hospital mortality was seen in 8% (40/527). While on ceftaroline, adverse events were experienced in 8% (41/527) of the patients and 9% (28/307) were readmitted within 30 days after discharge for the same infection. Patients treated with ceftaroline for both FDA-approved and off-label infections had favorable outcomes. Further research is necessary to further describe the role of ceftaroline in a variety of infections and its impact on patient outcomes.

- 2yıllık sürede seftarolin alan 527 hasta retrospektif olarak değerlendirilmiş
- %28 bakteremik
- %62 kültür pozitif, bunların %89'u MRSA
- Klinik başarı %88

Clin Ther. 2014 Oct 1;36(10):1317-33. doi: 10.1016/j.clinthera.2014.05.061. Epub 2014 Jul 10.

Antimicrobial salvage therapy for persistent staphylococcal bacteremia using daptomycin plus ceftaroline.

Sakoulas G[1], Moise PA[2], Casapao AM[3], Nonejuie P[4], Olson J[4], Okumura CY[4], Rybak MJ[3], Kullar R[5], Dhand A[6], Rose WE[7], Goff DA[8], Bressler AM[9], Lee Y[10], Pogliano J[4], Johns S[11], Kaatz GW[12], Ebright JR[12], Nizet V[4].

⊕ Author information

Abstract

PURPOSE: Guidelines recommend daptomycin combination therapy as an option for methicillin-resistant Staphylococcus aureus (MRSA) bacteremia after vancomycin failure. Recent data suggest that combining daptomycin with a β-lactam may have unique benefits; however, there are very limited clinical data regarding the use of ceftaroline with daptomycin.

METHODS: All 26 cases from the 10 medical centers in which ceftaroline plus daptomycin was used for treatment of documented refractory staphylococcal bacteremia from March 2011 to November 2012 were included. In vitro (synergy studies, binding assays, cathelicidin LL-37 killing assays), and in vivo (virulence assays using a murine subcutaneous infection model) studies examining the effects of ceftaroline with daptomycin were also performed.

FINDINGS: Daptomycin plus ceftaroline was used in 26 cases of staphylococcal bacteremia (20 MRSA, 2 vancomycin-intermediate S aureus, 2 methicillin-susceptible S aureus [MSSA], 2 methicillin-resistant S epidermidis). Bacteremia persisted for a median of 10 days (range, 3-23 days) on previous antimicrobial therapy. After daptomycin plus ceftaroline was started, the median time to bacteremia clearance was 2 days (range, 1-6 days). In vitro studies showed ceftaroline synergy against MRSA and enhanced MRSA killing by cathelicidin LL-37 and neutrophils. Ceftaroline also induced daptomycin binding in MSSA and MRSA to a comparable degree as nafcillin. MRSA grown in subinhibitory concentrations of ceftaroline showed attenuated virulence in a murine subcutaneous infection model.

IMPLICATIONS: Ceftaroline plus daptomycin may be an option to hasten clearance of refractory staphylococcal bacteremia. Ceftaroline offers dual benefit via synergy with both daptomycin and sensitization to innate host defense peptide cathelicidin LL37, which could attenuate virulence of the pathogen.

- 26 tedavi altında persistan stafilokok bakteremisi
- 23 vankomisin, 3 daptomisin tedavisi (median 10 gün)
- Daptomisin + seftarolin kurtarma tedavisi ile median 2 günde klirens sağlanmış

Tedizolid

- Yeni kuşak bir oksazolidinon grubu antibiyotik
- *S. aureus* (MRSA, MSSA), *S. pyogenes, S. agalactiae, S. anginosus grup, E. faecalis*
- FDA onayı 2014
  - Deri ve yumuşak doku infeksiyonlarının tedavisi
- 200 mg PO/IV 1x1/gün, 6 gün
- Hepatik ve renal yetmezlikte doz ayarı gerektirmez

Dalbavansin

- Yeni uzun etki süreli lipoglikopeptid
- *S. aureus* (MRSA, MSSA), *S. pyogenes, S. agalactiae, S. anginosus grup*
- 1500 mg IV tek doz veya 1000 mg IV takiben 1 hafta sonra 500 mg IV

  Infüzyon süresi > 30 dk
- FDA onayı 2014
  - Deri ve yumuşak doku enfeksiyonlarının tedavisi
- CrCl <30 mL/dk doz ayarı gerekli
- Hafif KC yetmezliğinde doz ayarı gereksiz, orta ve ileri yetmezlikte veri yok

Oritovansin

- Yeni uzun etki süreli lipoglikopeptid
- *S. aureus* (MRSA, MSSA), *S. pyogenes, S. agalactiae, S. dysagalactiae, S. anginosus grup, E. faecalis* (vankomisin duyarlı izolatlar)
- 1200-mg tek doz IV, infüzyon süresi > 3 saat
- FDA onayı 2014
  - Deri ve yumuşak doku enfeksiyonlarının tedavisi
- Hafif ve orta renal ve hepatik yetmezlikte doz ayarı gerekmez. İleri yetmezliklerde veri yok

Delafloksasin

- Yeni kuşak bir fluorokinolon
- Aerobik Gram pozitif mikroorganizmalar (MRSA), *Pseudomonas spp.* dahil Gram negatif basillere etkili
- FDA onayı 2017
  - Deri ve yumuşak doku enfeksiyonlarının tedavisi
- 300 mg IV her 12 saatte, 5-14 gün,
- 450-mg tb PO her 12 saatte, 5-14 gün
- IV formu orta renal yetmezlikte doz ayarı gerekli, ileri renal yetmezlikte önerilmiyor, tablet formunda doz ayarı gerekmez.

Plazomisin

- Yeni kuşak bir aminoglikozit
- MDR Enterobacteriaceae (mevcut aminoglikozitlere dirençli ve ESBL üreten karbapenem dirençli) etkili
- FDA tavsiyesi komplike üriner sistem infeksiyonlarında ve tedavi alternatifi olmayan veya çok kısıtlı olan durumlarda
- Bakteremi tedavisinde tavsiye edilmiyor Medscape, 3 may 2018
- 15 mg/kg/ her 24 saat IV, infüzyon süresi 30 dk

28th ECCMID EUROPEAN CONGRESS OF CLINICAL MICROBIOLOGY AND INFECTIOUS DISEASES

Madrid, Spain
21 – 24 April 2018

P0095 *In vitro* activity of plazomicin against *Klebsiella* spp. blood isolates

Ümran Liste[1], Seyma Nigiz[1], Asli Cakar[1], Belgin Altun[1], Banu Sancak[1], Deniz Gür*[1]

[1] Microbiology, Hacettepe University Faculty of Medicine, Ankara, Turkey

Ülkemizde *Klebsiella spp*. izolatlarında plazomisin düşük Mİk değerleri tespit edilmiş.

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Mutations in bla_{KPC-3} That Confer Ceftazidime-Avibactam Resistance Encode Novel KPC-3 Variants That Function as Extended-Spectrum β-Lactamases

Ghady Haidar,[a] Cornelius J. Clancy,[b,c,d] Ryan K. Shields,[b,c] Binghua Hao,[c] Shaoji Cheng,[b] M. Hong Nguyen[a,b,c]

Case Reports in Infectious Diseases
Volume 2016, Article ID 1520404, 5 pages
http://dx.doi.org/10.1155/2016/1520404

Case Report

Persistent Bacteremia from *Pseudomonas aeruginosa* with *In Vitro* Resistance to the Novel Antibiotics Ceftolozane-Tazobactam and Ceftazidime-Avibactam

Louie Mar Gangcuangco,[1] Patricia Clark,[2] Cynthia Stewart,[2] Goran Miljkovic,[1,3] and Zane K. Saul[1,3]

28th ECCMID EUROPEAN CONGRESS OF CLINICAL MICROBIOLOGY AND INFECTIOUS DISEASES
Madrid, Spain
21 – 24 April 2018

P1179 Genomic analysis of *E. coli* bearing 16S rRNA methyltransferases conferring resistance to plazomicin in waste water and rivers

José Francisco Delgado Blas*[1], Cristina Martinez Ovejero[1], William Calero-Caceres[2], Sara Monzon[3], Fernando De

Conclusions: High level plazomicin resistant *E. coli* are present in rivers and waste water. The human influence favours the selection and maintenance of specific resistance genes associated to certain plasmids and sequence types. The resistome and plasmidome structure is more similar among different sequence types in *E. coli* isolates

Literatürde seftazidim-avibaktam'a, sefttolozan- tazbaktam'a, plazomisin'e dirençli suşlar ve vakalar bildirilmekte

Clinical Infectious Diseases
EDITORIAL COMMENTARY

Ceftazidime-Avibactam and Carbapenem-Resistant Enterobacteriaceae: "We're Gonna Need a Bigger Boat"

Brad Spellberg[1,2] and Robert A. Bonomo[3]

- They (microbes) will never stop adapting to what we conceive of to combat them, and, in turn, we must never stop conceiving of new ways to stay one step ahead.

Ufuktaki Antibiyotikler-1

Table 1: Summary of new β-lactam/β-lactam inhibitors for multidrug-resistant Gram-negative infections

Anti-infective	Company	CRE Activity	MDR *P. aeruginosa* Activity	MDR *A. baumannii* Activity	Key Microbiologic Features and/or Dosage Regimens Studied	Citation(s)
Cefepime/zidebactam	Wockhardt	✓	✓	✓	(+) activity: AmpC, ESBL, KPC, OXA, MBL	[12-17]
WCK-5153	Wockhardt	NA	✓	✓	(+) activity: OXA-23, MBL	[16,17]
Meropenem/nacubactam	Roche	✓	✓[1]		(+) activity: AmpC, ESBL, KPC, OXA	[19-22]
Cefepime/AAI101	Allecra	✓			(+) activity: AmpC, ESBL, KPC, OXA 2000/500 mg (30-min infusion) q8h	[23-26]
VNRX5133	VenatoRx	NA	NA	NA	(+) activity: AmpC, ESBL, KPC, OXA, MBL	[27]
Aztreonam/avibactam	Pfizer	✓			(+) activity: AmpC, ESBL, KPC, OXA, MBL	[28-30]
Ceftaroline/avibactam	Pfizer	✓			(+) activity: AmpC, ESBL, KPC	[31-33]
Cefiderocol	Shionogi	✓	✓	✓	(+) activity: AmpC, ESBL, KPC, OXA, MBL; 2 grams IV (3-hr infusion) q8h	[44-47]
Imipenem/relebactam	Merck	✓	✓		(+) activity: AmpC, ESBL, KPC 500/250 mg IV q6h; 200/100 mg in renal impairment	[56-61]
Recently Approved						
Meropenem/vaborbactam	Melinta	✓			(+) activity: AmpC, ESBL, KPC; 4 grams IV (3-hr infusion) q8h (reduce if eGFR <50)	[81-85]

[1] Hyper-AmpC-producing *P. aeruginosa* only. Abbreviations: CRE, carbapenem-resistant Enterobacteriaceae; eGFR, estimated glomerular filtration rate; ESBL, extended-spectrum β-lactamase; KPC, *K. pneumoniae* carbapenemase; IV, intravenous; MBL, metallo-β-lactamase; MDR, multidrug-resistant; NA, not available; q6h, every 6 hours; q8h, every 8 hours; q12h, every 12 hours

AVERY LM, Lindsay M *Expert opinion on investigational drugs*, 2018

Ufuktaki Antibiyotikler-2

Table 2: Summary of novel non-β-lactams for multidrug-resistant Gram-negative infections

Anti-infective	Company	CRE Activity	MDR *P. aeruginosa* Activity	MDR *A. baumannii* Activity	Dosage Regimens Studied	Citation(s)
Murepavadin	Polyphor		✓		2.5 mg/kg IV (2-hr infusion) q8h	[36-38]
Finafloxacin	MerLion	✓		✓[1]	800 mg IV or orally once daily	[35,40-43]
Eravacycline	Tetraphase	✓		✓	1 mg/kg IV q12h; 1.5 mg/kg IV once daily	[48,50-55]
Omadacycline	Paratek	✓[2]		✓	100 mg IV daily, or 200-300 mg orally once daily	[62-67]
Plazomicin	Achaogen	✓	✓	✓[3]	15 mg/kg IV (30-min infusion) daily	[68-75]
Recently Approved						
Delafloxacin	Melinta	✓		✓[1]	300 mg IV (1-hr infusion) or 450 mg orally q12h Dose reduction recommended if eGFR <30	[76-80]

[1] Enhanced activity demonstrated against ciprofloxacin-resistant strains [2] Company pursuing indication for *E. coli* only [3] Moderate activity against carbapenem-non-susceptible isolates. Abbreviations: CRE, carbapenem-resistant Enterobacteriaceae; eGFR, estimated glomerular filtration rate; ESBL, extended-spectrum β-lactamase; KPC, *K. pneumoniae* carbapenemase; IV, intravenous; MBL, metallo-β-lactamase; MDR, multidrug-resistant; q6h, every 6 hours; q8h, every 8 hours; q12h, every 12 hours

AVERY, Lindsay M *Expert opinion on investigational drugs*, 2018

SONUÇ

- ÇID Gram pozitif ve Gram negatif bakterilerlerin etken olduğu nozokomiyal sepsis tedavisinde yeni antibiyotikler umut vadetmektedir.
- Ancak özellikle sepsis tedavisinde kanıt düzeyi yüksek çalışmalara ihtiyaç vardır.
- Yeni antibiyotikler de akılcı kullanılmadığı sürece direnç gelişimi ve mevcut direnç oranlarında artış kaçınılmaz olacaktır.


Teşekkürler
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