Yoğun Bakımda Dirençli Enterobacterales Enfeksiyonlarının Yönetimi

Dr. Halis Akalın

Bursa Uludağ Üniversitesi Tıp Fakültesi

Enfeksiyon Hastalıkları ve Klinik Mikrobiyoloji AD

ÇİD - Uzlaşı Toplantısı - 2011

- *Staphylococcus aureus*
- *Enterococcus* spp.
- *Enterobacteriaceae*
- *Pseudomonas aeruginosa*
- *Acinetobacter* spp.

Magiorakos AP et al. Clin Microbiol Infect 2011

Table 1e. *Acinetobacter* spp.; antimicrobial categories and agents used to define MDR, XDR and PDR

Antimicrobial category	Antimicrobial agent	Results of antimicrobial susceptibility testing (S or NS)
Aminoglycosides	Gentamicin	
	Tobramycin	
	Amikacin	
	Netilmicin	
Antipseudomonal carbapenems	Imipenem	
	Meropenem	
	Doripenem	
Antipseudomonal fluoroquinolones	Ciprofloxacin	
	Levofloxacin	
Antipseudomonal penicillins + β-lactamase inhibitors	Piperacillin-tazobactam	
	Ticarcillin-clavulanic acid	
Extended-spectrum cephalosporins	Cefotaxime	
	Ceftriaxone	
	Ceftazidime	
	Cefepime	
Folate pathway inhibitors	Trimethoprim-sulfamethoxazole	
Penicillins + β-lactamase inhibitors	Ampicillin-sulbactam	
Polymyxins	Colistin	
	Polymyxin B	
Tetracyclines	Tetracycline	
	Doxycycline	
	Minocycline	

Criteria for defining MDR, XDR and PDR in *Acinetobacter* spp.

MDR: non-susceptible to ≥ 1 agent in ≥ 3 antimicrobial categories

XDR: non-susceptible to ≥ 1 agent in all but ≤ 2 categories,

PDR: non-susceptible to all antimicrobial agents listed

Clinical Infectious Diseases
MAJOR ARTICLE

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

Sameer S. Kadri,[1,2,a] Jennifer Adjemian,[3,4,a] Yi Ling Lai,[3] Alicen B. Spaulding,[3] Emily Ricotta,[3] D. Rebecca Prevots,[3] Tara N. Palmore,[5] Chanu Rhee,[6,7] Michael Klompas,[6,7] John P. Dekker,[8] John H. Powers III,[9] Anthony F. Suffredini,[1] David C. Hooper,[2] Scott Fridkin,[10] and Robert L. Danner[1]; for the National Institutes of Health Antimicrobial Resistance Outcomes Research Initiative (NIH–ARORI)

Table 1. Phenotypic Definitions of Difficult-to-Treat Resistance and Centers for Disease Control and Prevention-defined Individual Resistance Phenotype Among 5 Taxa of Gram-negative Bloodstream Infections

Definitions	Agents Included	Defining Criteria
2015 CDC definitions		
Carbapenem resistant[a]	Imipenem, meropenem doripenem ertapenem[b]	Resistance to ≥1 carbapenem (*Escherichia coli*, *Klebsiella* spp, *Enterobacter* spp); intermediate or resistant to ≥1 carbapenem (*Pseudomonas aeruginosa*, *Acinetobacter baumannii*)
Extended-spectrum cephalosporin-resistant[c]	Ceftazidime, cefepime, ceftriaxone,[c] cefotaxime[c]	Resistance to ≥1 extended-spectrum cephalosporin
Fluoroquinolone resistant[a]	Ciprofloxacin, levofloxacin, moxifloxacin[c]	Resistance to ≥1 fluoroquinolone
Proposed definition		
Difficult-to-treat resistance	Intermediate or resistant to all reported agents in carbapenem, β-lactam, and fluoroquinolone categories (including additional agents[e] when results available)	

Abbreviation: CDC, Centers for Disease Control and Prevention.

[a]Based on 2015 CDC definitions.

[b]Applicable for Enterobacteriaceae only.

[c]Not applicable for *P. aeruginosa*.

[d]DTR assessment requires in vitro testing against ≥1 carbapenem, ≥1 extended-spectrum cephalosporin, and ≥1 fluoroquinolone.

[e]Intermediate or resistant to piperacillin-tazobactam and ampicillin-sulbactam (*A. baumannii* only) and intermediate or resistant to aztreonam (not applicable for *A. baumannii*). These drugs were only included in the assessment of DTR when results were reported.

Difficult-to-Treat Antibiotic-Resistant Gram-Negative Pathogens in the Intensive Care Unit: Epidemiology, Outcomes, and Treatment

Jeffrey R. Strich, MD, MS[1,2] Sameer S. Kadri, MD, MS[1]

[1] Critical Care Medicine Department, National Institutes of Health Clinical Center, Bethesda, Maryland
[2] United States Public Health Service, Commissioned Corps, Rockville, Maryland

Address for correspondence Sameer S. Kadri, MD, MS, Critical Care Medicine Department, NIH Clinical Center, 10 Center Drive B10, 2C145, Bethesda, MD 20892 (e-mail: sameer.kadri@nih.gov).

Semin Respir Crit Care Med 2019;40:419–434.

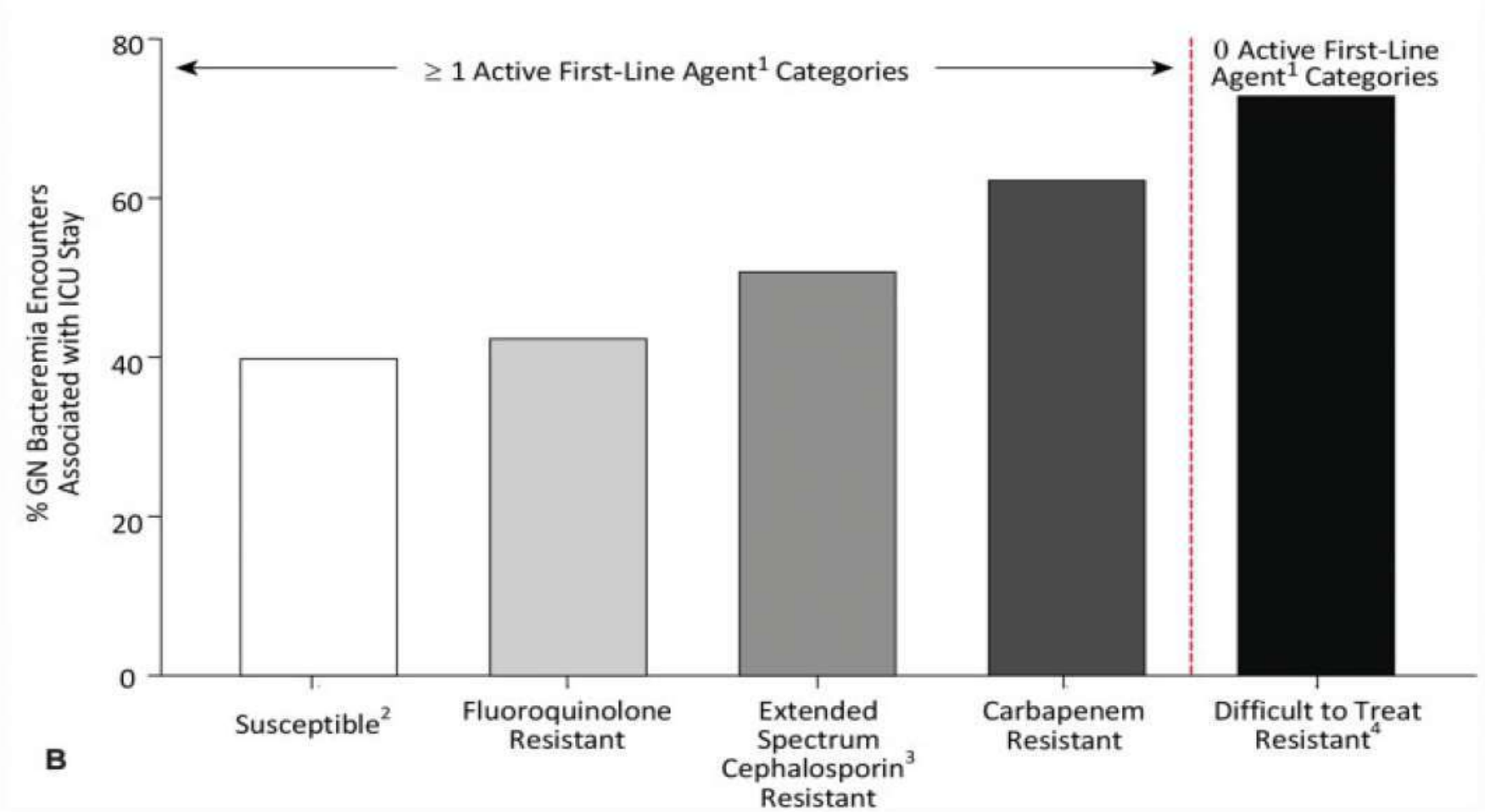
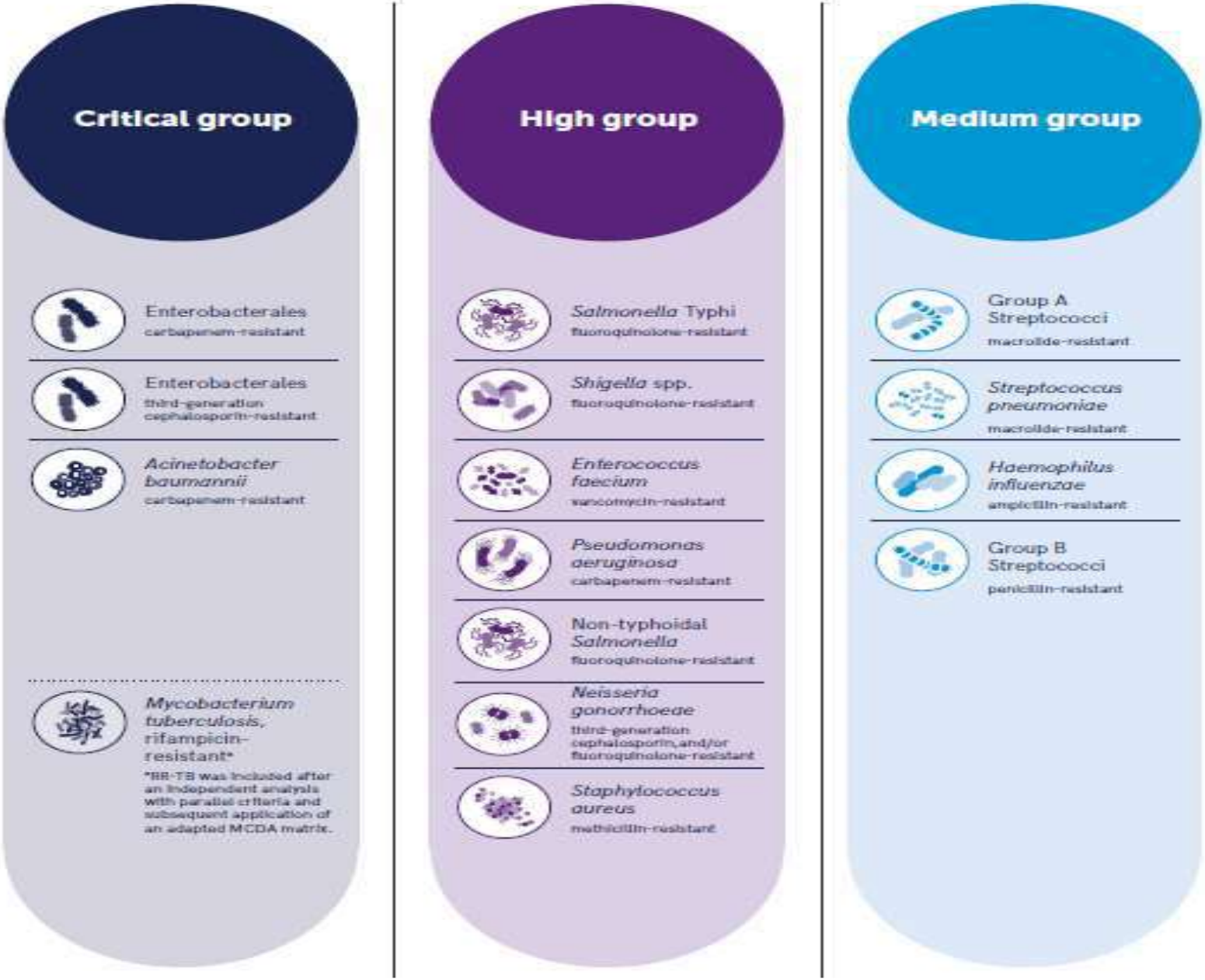


Fig 4. WHO Bacterial Priority Pathogens List, 2024



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).

IDSA - Enterobacterales

Clinical Infectious Diseases

IDSA GUIDELINES

Infectious Diseases Society of America 2024 Guidance on the Treatment of Antimicrobial-Resistant Gram-Negative Infections

Pranita D. Tamma,[1] Emily L. Heil,[2] Julie Ann Justo,[3] Amy J. Mathers,[4] Michael J. Satlin,[5] and Robert A. Bonomo[6]

[1]Department of Pediatrics, Johns Hopkins University School of Medicine, Baltimore, Maryland, USA; [2]Department of Practice, Sciences, and Health-Outcomes Research, University of Maryland School of Pharmacy, Baltimore, Maryland, USA; [3]Department of Pharmacy, Dartmouth Hitchcock Medical Center, Lebanon, New Hampshire, USA; [4]Departments of Medicine and Pathology, University of Virginia, Charlottesville, Virginia, USA; [5]Department of Medicine, Weill Cornell Medicine, New York, New York, USA; and [6]Medical Service and Center for Antimicrobial Resistance and Epidemiology, Louis Stokes Cleveland Veterans Affairs Medical Center, University Hospitals Cleveland Medical Center and Departments of Medicine, Pharmacology, Molecular Biology, and Microbiology, Case Western Reserve University, Cleveland, Ohio, USA

Table 2. 2024 Clinical and Laboratory Standards Institute Susceptible Breakpoints for Select Gram-Negative Organisms and Antibiotic Combinations as Suggested in the IDSA AMR Guidance Document[a]

Antibiotic	Enterobacterales (μg/mL)	*Pseudomonas aeruginosa* (μg/mL)	Carbapenem-Resistant *Acinetobacter baumannii* (μg/mL)	*Stenotrophomonas maltophilia* (μg/mL)
Amikacin	≤4	≤16[b]	…	…
Ampicillin-sulbactam	…	…	≤8/4	…
Aztreonam	≤4	≤8	…	…
Cefepime	≤2[c]	≤8	…	…
Cefiderocol	≤4	≤4	≤4	≤1
Ceftazidime	≤4	≤8	…	…
Ceftazidime-avibactam	≤8/4	≤8/4	…	…
Ceftolozane-tazobactam	≤2/4	≤4/4	…	…
Ciprofloxacin	≤0.25	≤0.5	…	…
Colistin or Polymyxin B	…[d]	…[d]	…[d]	…
Doxycycline	≤4	…	…	…
Ertapenem	≤0.5	…	…	…
Fosfomycin	≤64[e]	…	…	…
Gentamicin	≤2	…	…	…
Imipenem	≤1	≤2	…	…
Imipenem-relebactam	≤1/4	≤2/4	…	…
Levofloxacin	≤0.5	≤1	…	≤2
Meropenem	≤1	≤2	…	…
Meropenem-vaborbactam	≤4/8	…	…	…
Minocycline	≤4	…	≤4	≤1
Nitrofurantoin	≤32	…	…	…
Piperacillin-tazobactam	≤8/4[f]	≤16/4	…	…
Plazomicin	≤2	…	…	…
Sulbactam-durlobactam	…	…	≤4/4	…
Tigecycline	…[g]	…	…[h]	…[h]
Trimethoprim-sulfamethoxazole	≤2/38	…	…	≤2/38
Tobramycin	≤2	≤1	…	…

[a]For full details of antibiotic susceptibility testing interpretations refer to: Clinical and Laboratory Standards Institute. 2024. M100: Performance Standards for Antimicrobial Susceptibility Testing. 34th ed. Wayne, PA. CLSI M100 document is updated annually; susceptibility criteria subject to changes in 2025.

[b]Breakpoints only available for infections originating from the urinary tract.

[c]Isolates with cefepime minimum inhibitory concentrations (MICs) of 4–8 μg/mL are susceptible dose-dependent.

[d]No susceptible category for colistin or polymyxin B; MICs ≤2 μg/mL considered intermediate.

[e]Applies to *Escherichia coli* urinary tract isolates only.

[f]Isolates with piperacillin-tazobactam MICs of 16 μg/mL are considered susceptible dose-dependent.

[g]No Clinical and Laboratory Standards Institute (CLSI) breakpoint. Food and Drug Administration (FDA) defines susceptibility as MICs ≤2 μg/mL.

[h]Neither CLSI nor FDA breakpoints are available.

Table 1. Suggested Dosing of Antibiotics for the Treatment of Antimicrobial-resistant Infections in Adults, Assuming Normal Renal and Hepatic function[a,b]

Amikacin	**Uncomplicated cystitis**: 15 mg/kg IV as a single dose **Pyelonephritis or complicated urinary tract infections**: 15 mg/kg IV once; subsequent doses and dosing interval based on pharmacokinetic evaluation Additional information in Supplementary Material.
Ampicillin-sulbactam	**Administer a total daily dose of 9 grams of sulbactam via 1 of the following regimens:** 9 grams of ampicillin-sulbactam (6 grams ampicillin, 3 grams sulbactam) IV every 8 h, infused over 4 h **OR** 27 grams of ampicillin-sulbactam (18 grams ampicillin, 9 grams sulbactam) IV as a continuous infusion over 24 h Additional information in Supplementary Material.
Cefepime	**Uncomplicated cystitis:** 1 gram IV every 8 h, infused over 30 min **All other infections:** 2 grams IV every 8 h, infused over 3 h
Cefiderocol	2 grams IV every 8 h, infused over 3 h CrCL ≥120 mL/min: 2 grams IV every 6 h, infused over 3 h
Ceftazidime-avibactam	2.5 grams IV every 8 h, infused over 3 h
Ceftazidime-avibactam PLUS aztreonam	**Ceftazidime-avibactam:** 2.5 grams IV every 8 h, infused over 3 h **PLUS** (administered simultaneously via Y-site administration) **Aztreonam:** 2 grams IV every 8 h, infused over 3 h Additional information in Supplementary Material.
Ceftolozane-tazobactam	**Uncomplicated Cystitis:** 1.5 grams IV every 8 h, infused over 1 h **All other infections:** 3 grams IV every 8 h, infused over 3 h
Ciprofloxacin	**Uncomplicated cystitis:** 400 milligrams IV every 12 h or 500 milligrams PO every 12 h **All other infections:** 400 milligrams IV every 8 h **OR** 750 milligrams PO every 12 h
Colistin	Refer to international consensus guidelines on polymyxins (Tsuji BT, et al Pharmacotherapy. 2019; 39:10–39).
Eravacycline	1 mg/kg per dose IV every 12 h
Ertapenem	1 gram IV every 24 h, infused over 30 min Additional information in Supplementary Material.
Fosfomycin	**Uncomplicated cystitis:** 3 grams PO as a single dose
Gentamicin	**Uncomplicated cystitis**: 5 mg/kg IV as a single dose **Pyelonephritis or complicated urinary tract infections**: 7 mg/kg IV once; subsequent doses and dosing interval based on pharmacokinetic evaluation Additional information in Supplementary Material.
Imipenem-cilastatin	**Uncomplicated cystitis**: 500 mg IV every 6 h, infused over 30 min **All other infections:** 500 mg IV every 6 h, infused over 3 h (if feasible) Additional information in Supplementary Material.
Imipenem-cilastatin-relebactam	1.25 grams IV every 6 h, infused over 30 min Additional information in Supplementary Material.
Levofloxacin	**All infections:** 750 milligrams IV/PO every 24 h
Meropenem	**Uncomplicated cystitis:** 1 grams IV every 8 h, infused over 30 min **All other infections:** 2 grams IV every 8 h, infused over 3 h (if feasible) Additional information in Supplementary Material.
Meropenem-vaborbactam	4 grams IV every 8 h, infused over 3 h
Minocycline	200 milligrams IV/PO every 12 h
Nitrofurantoin	**Macrocrystal/monohydrate (Macrobid®)**: 100 mg PO every 12 h **Oral suspension**: 50 milligrams PO every 6 h
Plazomicin	**Uncomplicated cystitis:** 15 mg/kg IV as a single dose **Pyelonephritis or complicated urinary tract infections**: 15 mg/kg IV once; subsequent doses and dosing interval based on pharmacokinetic evaluation Additional information in Supplementary Material.
Polymyxin B	Refer to international consensus guidelines on polymyxins (Tsuji BT, et al Pharmacotherapy. 2019;39:10–39).
Sulbactam-durlobactam	Sulbactam 1 gram/durlobactam 1 gram (2 grams total) IV every 6 h, infused over 3 h CrCL ≥130 mL/min: Sulbactam 1 gram/durlobactam 1 gram (2 grams total) IV every 4 h, infused over 3 h Additional information in Supplementary Material.
Tigecycline	200 mg IV as a single dose, then 100 mg IV every 12 h
Tobramycin	**Uncomplicated cystitis**: 5 mg/kg and the AST profile of the pathogen, IV as a single dose **Pyelonephritis or complicated urinary tract infections**: 7 mg/kg IV once; subsequent doses and dosing interval based on pharmacokinetic evaluation Additional information in Supplementary Material.
Trimethoprim-sulfamethoxazole	**Uncomplicated cystitis**: 160 mg (trimethoprim component) IV/PO every 12 h **Other infections**: 10–15 mg/kg/day (trimethoprim component) IV/PO divided every 8 to 12 h Additional information in Supplementary Material.

Abbreviations: CrCl, creatinine clearance; IV, intravenous; PO, enterally.

[a]Dosing suggestions limited to organisms and infectious syndromes discussed in the IDSA AMR Treatment Guidance document.

[b]Dosing suggested for several agents may differ from dosing recommended by the United States Food and Drug Administration.

ESBL(+) Enterobacterales Komplike Olmayan Sistit

- Tercih edilen: Nitrofurantoin, TMP-SMX
- Alternatif: Siprofloksasin, levofloksasin, karbapenemler
- Alternatif: Fosfomisin(*E.coli* için), tek doz aminoglikozid

kÜSE ve Piyelonefrit

- Tercih edilen: TMP-SMX, Siprofloksasin, Levofloksasin
- Direnç ya da toksisite: Ertapenem, Meropenem, İmipenem-Silastatin
- Alternatif: Aminoglikozidler

Üriner Sistem Dışındaki Enfeksiyonlar

- Meropenem, İmipenem-Silastatin, Ertapenem
- Kritik hastalar ve/veya hipoalbuminemi: Meropenem, İmipenem-Silastatin
- Uygun klinik yanıt sonrası ardışık tedavi: TMP-SMX, Siprofloksasin, Levofloksasin

Piperasilin-Tazobaktam

- Sistit: Piperasilin-tazobaktam ampirik başlanmış ve ESBL(+) Enterobacterales üremiş ise, klinik iyileşme durumunda tedaviyi değiştirmeye ya da süreyi uzatmaya gerek yok
- kÜSE ve Piyelonefrit: TMP-SMX, Siprofloksasin, Levofloksasin, Karbapenemler
- Üriner sistem dışı enfeksiyonlar: Duyarlı bile olsa desteklenmiyor

Sefepim

- Sistit: Sefepim ampirik başlanmış ve ESBL(+) Enterobacterales üremiş ise, klinik iyileşme durumunda tedaviyi değiştirmeye ya da süreyi uzatmaya gerek yok
- kÜSE ve Piyelonefrit: Kullanmaktan kaçın
- Üriner sistem dışı enfeksiyonlar: Kullanmaktan kaçın

Yeni BL-BLI ve Sefiderokol

- Karbapenem dirençli Enterobacterales enfeksiyonlarında kullan

AmpC Üreten Enterobacterales

- Klinik olarak anlamlı İndüklenebilir AmpC(orta risk)
  -*E.cloacae complex, Klebsiella aerogenes, Citrobacter freundii*
- Önerilen: Sefepim
- Önerilmeyen: Piperasilin-tazobaktam
- Yeni BL-BLI ve sefiderokol: Karbapenem dirençli suşlar için kullan
- Seftolozan-tazobaktam tedavi seçeneği olarak desteklenmiyor
- Sistit: Duyarlı ise seftriakson verilebilir

Beta-Laktam Dışı Antibiyotikler

- Sistit: Nitrofurantoin, TMP-SMX
- Sistit(Alternatif): Siprofloksasin, Levofloksasin, Aminoglikozid(tek doz)
- kÜSE ve Piyelonefrit: TMP-SMX, Siprofloksasin, Levofloksasin, Aminoglikozid(alternatif)
- ÜSE dışı: Sefepim ve sonrasında ardışık tedavi(TMP-SMX, Levofloksasin, Siprofloksasin

Karbapenem Dirençli Enterobacterales

- En az 1 karbapenem antibiyotiğe dirençli ya da karbapenemaz üreten
- *Proteus* spp. , *Morganella* spp., *Providencia* spp. gibi bakteriler intrensek olarak imipeneme daha az duyarlı oldukları için, en az imipenem dışı bir karbapeneme dirençli
- Karbapenemaz üretenler ve üretmeyenler
- Karbapenemaz üretmeyenler: ESBL(+) + Dış membran protein bozulması

Sistit

- Tercih edilen: Nitrofurantoin, TMP-SMX, Siprofloksasin, Levofloksasin
- Alternatif: Aminoglikozid(tek doz), *Fosfomisin(E. coli* için), Kolistin, Seftazidim-Avibaktam, Meropenem-Vaborbaktam, İmipenem-Silastatin-Relebaktam ve Sefiderokol

kÜSE ve Piyelonefrit

- Tercih edilen: TMP-SMX, Siprofloksasin, Levofloksasin
- Alternatif: Seftazidim-Avibaktam, Meropenem-Vaborbaktam, İmipenem-Silastatin-Relebaktam ve Sefiderokol
- Alternatif: Aminoglikozidler

ÜSE Dışı ve Karbapenemaz Üretmeyen

- Meropenem MİK≤1µg/mL, İmipenem MİK ≤1µg/mL, Ertapenem MİK≥ 1µg/mL ise: Uzamış infüzyon Meropenem(veya İmipenem-Silastatin)
- Hiç duyarlılık yoksa: Seftazidim-Avibaktam, Meropenem-Vaborbaktam, İmipenem-Silastatin-Relebaktam

- KPC(+): Seftazidim-Avibaktam, Meropenem-Vaborbaktam, İmipenem-Silastatin-Relebaktam, Sefiderokol(alternatif)
- NDM(+) veya diğer MBL(+): Seftazidim-Avibaktam + Aztreonam, Sefiderokol
- OXA-48(+): Seftazidim-Avibaktam, Sefiderokol(alternatif)
- Kombinasyon(Aminoglikozid, Florokinolon, Tetrasiklin veya Polimiksin ile) önerilmiyor
- Polimiksin veya Kolistin(sadece sistit için öneriliyor) önerilmiyor

IDSA-2024 Önerileri

Table 1. Suggested Dosing of Antibiotics for the Treatment of Antimicrobial-resistant Infections in Adults, Assuming Normal Renal and Hepatic function[a,b]

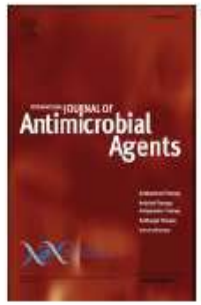
Amikacin	**Uncomplicated cystitis**: 15 mg/kg IV as a single dose **Pyelonephritis or complicated urinary tract infections**: 15 mg/kg IV once; subsequent doses and dosing interval based on pharmacokinetic evaluation Additional information in Supplementary Material.
Ampicillin-sulbactam	**Administer a total daily dose of 9 grams of sulbactam via 1 of the following regimens:** 9 grams of ampicillin-sulbactam (6 grams ampicillin, 3 grams sulbactam) IV every 8 h, infused over 4 h **OR** 27 grams of ampicillin-sulbactam (18 grams ampicillin, 9 grams sulbactam) IV as a continuous infusion over 24 h Additional information in Supplementary Material.
Cefepime	**Uncomplicated cystitis:** 1 gram IV every 8 h, infused over 30 min **All other infections:** 2 grams IV every 8 h, infused over 3 h
Cefiderocol	2 grams IV every 8 h, infused over 3 h CrCL ≥120 mL/min: 2 grams IV every 6 h, infused over 3 h
Ceftazidime-avibactam	2.5 grams IV every 8 h, infused over 3 h
Ceftazidime-avibactam PLUS aztreonam	**Ceftazidime-avibactam:** 2.5 grams IV every 8 h, infused over 3 h **PLUS** (administered simultaneously via Y-site administration) **Aztreonam:** 2 grams IV every 8 h, infused over 3 h Additional information in Supplementary Material.
Ceftolozane-tazobactam	**Uncomplicated Cystitis:** 1.5 grams IV every 8 h, infused over 1 h **All other infections:** 3 grams IV every 8 h, infused over 3 h
Ciprofloxacin	**Uncomplicated cystitis:** 400 milligrams IV every 12 h or 500 milligrams PO every 12 h **All other infections:** 400 milligrams IV every 8 h **OR** 750 milligrams PO every 12 h
Colistin	Refer to international consensus guidelines on polymyxins (Tsuji BT, et al Pharmacotherapy. 2019; 39:10–39).
Eravacycline	1 mg/kg per dose IV every 12 h
Ertapenem	1 gram IV every 24 h, infused over 30 min Additional information in Supplementary Material.
Fosfomycin	**Uncomplicated cystitis:** 3 grams PO as a single dose
Gentamicin	**Uncomplicated cystitis**: 5 mg/kg IV as a single dose **Pyelonephritis or complicated urinary tract infections**: 7 mg/kg IV once; subsequent doses and dosing interval based on pharmacokinetic evaluation Additional information in Supplementary Material.
Imipenem-cilastatin	**Uncomplicated cystitis**: 500 mg IV every 6 h, infused over 30 min **All other infections:** 500 mg IV every 6 h, infused over 3 h (if feasible) Additional information in Supplementary Material.
Imipenem-cilastatin-relebactam	1.25 grams IV every 6 h, infused over 30 min Additional information in Supplementary Material.
Levofloxacin	**All infections:** 750 milligrams IV/PO every 24 h
Meropenem	**Uncomplicated cystitis:** 1 grams IV every 8 h, infused over 30 min **All other infections:** 2 grams IV every 8 h, infused over 3 h (if feasible) Additional information in Supplementary Material.
Meropenem-vaborbactam	4 grams IV every 8 h, infused over 3 h

International Journal of Antimicrobial Agents 64 (2024) 107186

Contents lists available at ScienceDirect

International Journal of Antimicrobial Agents

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



Treatment of infections caused by multidrug-resistant Gram-negative bacilli: A practical approach by the Italian (SIMIT) and French (SPILF) Societies of Infectious Diseases

Marianna Meschiari[a], Antoine Asquier-Khati[b], Giusy Tiseo[c], David Luque-Paz[d], Rita Murri[e], David Boutoille[b], Marco Falcone[c], Cristina Mussini[a], Pierre Tattevin[d,*], on behalf of the Italian Society of Infectious and Tropical Diseases (SIMIT), and the French Society of Infectious Diseases (SPILF)

[a] *Infectious Diseases Unit, Azienda Ospedaliera-Universitaria of Modena, University of Modena and Reggio Emilia, Modena, Italy*
[b] *Infectious Diseases Department, Nantes University Hospital, INSERM CIC 1413, Nantes, France*
[c] *Infectious Diseases Unit, Department of Clinical and Experimental Medicine, Azienda Ospedaliero Universitaria Pisana, University of Pisa, Pisa, Italy*
[d] *Infectious Diseases and Intensive Care Units, Pontchaillou University Hospital, Rennes, France*
[e] *Infectious Diseases, Fondazione Policlinico Gemelli IRCCS Rome, Italy*

Ventilatörle İlişkili Pnömoni - AmpC Beta-Laktamaz Üreten Enterobacterales

- ESCMID klavuzunda 3.kuşak sefalosporinlere dirençli Enterobacterales'in neden olduğu VİP için sefepim önerilmiyor(bu endikasyondaki etkisi için düşük kanıt düzeyi nedeniyle)
- IDSA klavuzunda MİK ≤ 2 mg/L suşlar için sefepim öneriliyor
- Sefepim epitel döşeyici sıvıda PK/PD hedeflerine ulaşıyor
- Öneri: Sefepim 3x2 g IV

Üriner Sistem Enfeksiyonları
ESBL(+) Enterobacterales-Ağır kÜSE

- MERINO çalışmasına dayanarak karbapenemler ilk tercih olarak öneriliyor(IDSA ve ESCMID)
- Pip-Tazo MİK ≤ 8 mg/L ise 9 g(30 dk infüzyon) yükleme dozunu takiben her 6-8 saatte bir 4.5 g sürekli infüzyon karbapenem tedavisinden daha aşağı kalmıyor
- ÜSE'de düşük inokulum ve antibiyotiklerin yüksek difüzyonu
- Pip-Tazo MİK > 8 mg/L ise Aminoglikozidler veya İV Fosfomisin

Üriner Sistem Enfeksiyonları
ESBL(+) Enterobacterales - Ağır kÜSE

- Aminoglikozid monoterapisi *E.coli* dışındaki Enterobacterales'in neden olduğu üriner kaynaklı bakteriyemilerde daha aşağı kalmama kriterlerini karşılayamamış
- ZEUS ve FOREST çalışmalarında ESBL(+) suş oranı düşük – İV Fosfomisin monoterapisi kÜSE'de önerilmiyor
- Öneriler: Meropenem, Seftolozan-Tazobaktam, Sefoksitin, Temosilin

Üriner Sistem Enfeksiyonları
AmpC(+) Enterobacterales - Ağır kÜSE

- Sefepim MİK ≤ 2 mg/L, 2 g yükleme sonrası 8 saatte bir 2 g
- Sefepim MİK > 2 mg/L, Meropenem veya yeni BL-BLİ

İntraabdominal Enfeksiyonlar - 3.Kuşak Sefalosporin Dirençli Enterobacterales

- ESCMID: Ağır enfeksiyonlarda karbapenemler
- ESCMID: Yeni BL-BLİ önerilmiyor(Antibiyotik Yönetimi Çerçevesinde)
- Karbapenem önerisi eski BL-BLİ ile olan kan dolaşımı enfeksiyonu karşılaştırma çalışmalarından kaynaklanıyor
- MERINO çalışmasında intraabdominal enfeksiyon oranı düşük(<%20)
- Yeni BL-BLİ, yapılan çalışmalarda(ASPECT, REPRISE, RECLAIM 1 ve 2) Meropenem kadar etkili
- Öneri: Seftolozan-Tazobaktam + Metronidazol, Seftazidim-Avibaktam + Metronidazol
- Hemodinamisi stabil olmayan, septik şoklu hastalarda Karbapenem(stabil olunca daraltma)

Ağır İntraabdominal Enfeksiyonlar - Karbapenem Dirençli Enterobacterales

- ESCMID: KPC için Seftazidim-Avibaktam veya Meropenem-Vaborbaktam
- ESCMID Klavuzu hazırlandığı sırada İmipenem-Silastatin-Relebaktam için sınırlı kanıt nedeniyle öneri yapılmamış
- İmipenem-Silastatin-Relebaktam öneriliyor

  -Karşılaştırmalı olmayan bir çalışmada klinik yanıt %85.7

  -DTR *P.aeruginosa*'ya etkili

  -Meropenem-Vaborbaktam ve İmipenem-Silastatin-Relebaktam, Seftazidim-Avibaktam'a dirençli KPC-3 izolatlarına etkili

  -Enterokoklara etkili tek yeni BL-BLİ

- MBL(+) ise: Seftazidim-Avibaktam + Aztreonam

  -Kolistin önerilmiyor: Periton sıvısı konsantrasyonu? Peritonit modellerinde yüksek inokulum varlığında azalmış in vitro aktivite, dirençli mutantların hızlı ortaya çıkışı

SIMIT - SPILF Önerileri

Table 5
Antibiotic doses suggested for treatment of multidrug-resistant Gram-negative bacilli.

Antibiotic	Loading dose	Daily dose in patients with normal renal clearance
Piperacillin-tazobactam	9 g over 30 min	4.5 g every 6–8 h (continuous infusion)
Ampicillin-sulbactam	No	24 g/12 g
Temocillin	2 g over 30 min	2 g every 8 h (continuous infusion)
Cefoxitin	2 g over 30 min	2 g every 8 h (continuous infusion)
Cefepime	2 g over 30 min	2 g every 8 h (continuous infusion)
Ceftazidime-avibactam	2.5 g over 30 min	2.5 g every 8 h (continuous infusion)
Ceftolozane-tazobactam	1 g/0.5 g over 30 min 3 g over 30 min for HAP/VAP	1 g/0.5 g every 6 h (continuous infusion) 9 g (continuous infusion) for HAP/VAP
Imipenem-relebactam	No	500 mg/250 mg every 6 h (bolus 30 min, prolonged infusion over 3 h preferred)
Meropenem-vaborbactam	2 g/2 g over 30 min	2 g/2 g every 8 h (infusion over 3 h)
Cefiderocol	2 g over 30 min	2 g every 6–8 h (infusion over 3 h)
Colistin	4.5 M IU	9 M IU/day (infusion over 30 min, extended infusion over 6 h preferred)
Fosfomycin	4 g	4-8 g every 6–8 h (infusion over 30 min, 16–24 g continuous infusion, preferred)

HAP, hospital-acquired pneumonia; VAP, ventilator-associated pneumonia.

Seftazidim-Avibaktam Enterobacterales

scientific reports

OPEN

Multicenter evaluation of ceftazidime-avibactam use in carbapenem-resistant *Klebsiella pneumoniae* bloodstream infections in OXA-48 endemic regions

Ali Mert[1], Okan Derin[2,3], Halis Akalın[4], Rıdvan Dumlu[5], Sibel Gündeş[6], Rehile Zengin[7], Sesin Kocagöz[7,8], Yasemin Gündoğdu[9,10], İftihar Köksal[8,11], Demet Yalçın[12], Cemal Üstün[13], Mahir Kapmaz[14], Levent Görenek[15], Kadriye Karahangil[16], Füsun Can[17], Consortium* & Önder Ergönül[14]

Data in the literature on the use of ceftazidime-avibactam (CAZ-AVI) in carbapenem-resistant *Klebsiella pneumoniae* bloodstream infections (CRKP-BSIs) are limited especially in OXA-48 (Oxacillinase-48) predominant regions. Our study aimed to evaluate the effect of CAZ-AVI use on outcomes in CRKP-BSIs in Turkey, where OXA-48 is endemic. A multicenter retrospective observational study was conducted between January 2017 and September 2021. The effects of clinical and treatment characteristics on 30-day mortality and relapse in CRKP-BSIs were analyzed. Predictors of outcomes were detected using a Cox regression model. The study enrolled 106 adults with CAZ-AVI-sensitive CRKP-BSIs who received CAZ-AVI for at least 72 h. Patients who received CAZ-AVI as initial therapy had lower mortality rates when compared to those who switched from last resort regimens [14.3% ($n = 3/21$) vs. 37.7% ($n = 32/85$), $p = 0.04$]. In multivariate analysis, older age and severe neutropenia were detected to be associated with higher mortality, significantly. Initiation of CAZ-AVI on the day of blood culture was obtained, was found to be significantly associated with lower mortality (HR: 0.25, CI: 0.07–0.84, $p = 0.025$). CAZ-AVI monotherapy is an important treatment option for CRKP-BSIs in OXA-48 endemic areas. Early initiation of CAZ-AVI should be preferred rather than switching from a last-resort regimen as it profoundly improves the survival rates.

Multicenter evaluation of ceftazidime-avibactam use in carbapenem-resistant *Klebsiella pneumoniae* bloodstream infections in OXA-48 endemic regions

- Çok merkezli(23), retrospektif, 2017-2021
- Karbapenem dirençli *Klebsiella pneumoniae*
- Kan dolaşımı enfeksiyonları(monomikrobiyal)
- İlk 7 gün içinde CAZ-AVİ başlanan ve en az 72 saat alan hastalar, 106 hasta
- 30. gün mortalitesi

	Survived $n = 71$ (67%)	Fatal $n = 35$ (33%)	p
Male gender	44 (62)	21 (60)	0.845
Mean Age	51 (sd: 17)	59 (sd: 18)	0.033
Mean Pitt bacteremia score	4.1 (sd: 3.2)	7 (sd: 2.6)	<0.001
Charlson Comorbidity index	5.2 (sd: 11.6)	4.3 (sd: 2.7)	0.648
Severe neutropenia	12 (17)	9 (26)	0.284
Malignancy	27 (38)	14 (40)	0.845
Mean initiation time of CAZ-AVI after blood culture collection (days)	2.1 (sd: 1.9)	2.9 (sd: 1.85)	0.035
Patients initiated with CAZ-AVI on the day of blood culture was obtained	23 (32.3)	3 (8.5)	0.007

Table 1. Univariate analysis of 106 patients with Carbapenem-Resistant-*Klebsiella pneumonia* bacteremia who received the ceftazidime-avibactam (CAZ-AVI) within 7 days of positive blood culture.

- Mortalite %33
- İlk tercih CAZ-AVİ başlananlar ile daha sonra CAZ-AVİ'ye geçilen grup mortalitesi

%14.3(3/21) ve %37.7(32/85), p=0.04

- Direnç gelişimi ve rekürrens saptanmamış

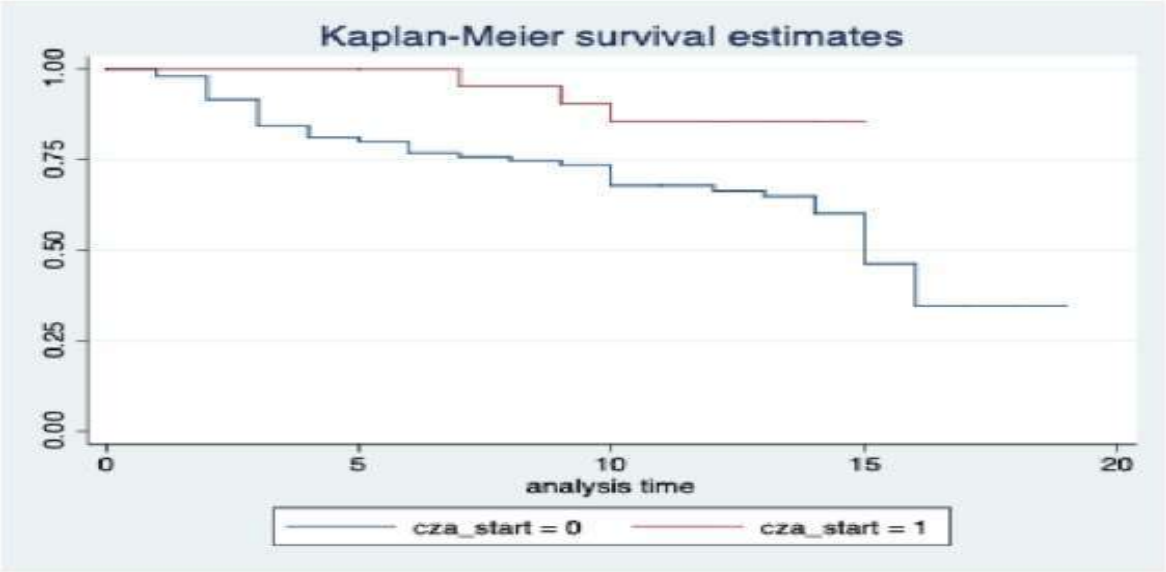


Fig. 1. The role of ceftazidim-avibactam (CAZ-AVI) initiated on the day of blood culture was obtained compared to CAZ-AVI started later days in predicting 30-day fatality.

	Univariate			Multivariate		
	HR	CI	P	HR	CI	p
Male gender	0.89	0.45–1.75	0.743	0.91	0.45–1.81	0.796
Age	1.02	1.01–1.04	0.033	1.04	1.01–1.07	0.004
Charlson comorbidity index	0.99	0.94–1.03	0.771	0.96	0.83–1.11	0.599
Severe Neutropenia (neutrophil count < 500)	1.54	0.72–3.29	0.264	4.4	1.60–12.56	0.004
Patients initiated with CAZ-AVI on the day of blood culture was obtained	0.22	0.07–0.74	0.015	0.24	0.07–0.79	0.019

Table 2. Univariate and multivariate analysis (cox regression) for the predictors of fatality among the patients with Carbapenem-resistant Klebsiella pneumonia blood stream infection (BSI) who received ceftazidime-avibactam (CAZ-AVI) within 7 days after bacterial identification ($n = 106$ patients with CRKP-BSI, who received CAZ-AVI).

24. TÜRK KLİNİK MİKROBİYOLOJİ VE İNFEKSİYON HASTALIKLARI KONGRESİ
6–9 MART 2024 PINE BEACH BELEK / ANTALYA

SS-018

Karbapenem Dirençli Gram Negatif Bakteri İnfeksiyonlarının Tedavisinde Seftazidim – Avibaktam: Çok Merkezli Gerçek Yaşam Verilerinin Analizi ve Mortaliteye Etki Eden Faktörlerin Belirlenmesi

Nazlım Aktuğ Demir[1], Fatih Temoçin[2], Onur Ural[1], Ezgi Gülten[3], Ayşe Seza İnal[4], Çiğdem Kader[5], Yasemin Ersoy[6], Ali Asan[7], Pınar Aysert Yıldız[8], Şua Sümer[1], Eyüp Arslan[9], Yakup Gezer[10], Güle Çınar[3], Elife Mukime Sarıcaoğlu[3], Tuba Tatlı Kış[11], Serap Özçimen[12], Barçın Öztürk[13], Burak Sarıkaya[14], Merve Türkmen[14], Tuba Kuruoğlu[2], Ceren Atasoy Tahtasakal[15], Emel Yılmaz[16]

- Çok Merkezli(16), retrospektif, 2021-2023
- Karbapenem dirençli, CAZ-AVİ duyarlı gram negatif bakteri enfeksiyonları
- 1245 hasta
- %81.3 *Klebsiella pneumoniae*
- %12.4 *Pseudomonas aeruginosa*

- %47.8 Hastane kökenli pnömoni
- %19.3 Kan dolaşımı enfeksiyonu
- %31.6 Sekonder bakteriyemi
- %80 Monoterapi
- 28. gün mortalitesi %45.2
- 14.gün klinik başarı %71.1
- Mikrobiyolojik kür %82.3
- Mortalite için bağımsız risk faktörleri

  SOFA yüksekliği
  APACHE II yüksekliği
  SRRT
  MV
  CRP yüksekliği

J Antimicrob Chemother 2022; 77: 1452–1460
https://doi.org/10.1093/jac/dkac049 Advance Access publication 21 February 2022

Journal of Antimicrobial Chemotherapy

Impact of ceftazidime/avibactam versus best available therapy on mortality from infections caused by carbapenemase-producing Enterobacterales (CAVICOR study)

Juan José Castón[1,2,3,4]*, Angela Cano[1,2,3,4], Inés Pérez-Camacho[5], Jose M. Aguado[4,6,7], Jordi Carratalá[4,8,9], Fernando Ramasco[10], Alex Soriano[4,11], Vicente Pintado[12], Laura Castelo-Corral[13], Adrian Sousa[14], María Carmen Fariñas[4,15,16], Patricia Muñoz[4,17,18,19,20], Vicente Abril López De Medrano[21], Óscar Sanz-Peláez[22], Ibai Los-Arcos[4,23,24], Irene Gracia-Ahufinger[3,25], Elena Pérez-Nadales[1,2,3], Elisa Vidal[1,2,3,4], Antonio Doblas[1], Clara Natera[1,2], Luis Martínez-Martínez[3,4,25,26] and Julian Torre-Cisneros[1,2,3,4]

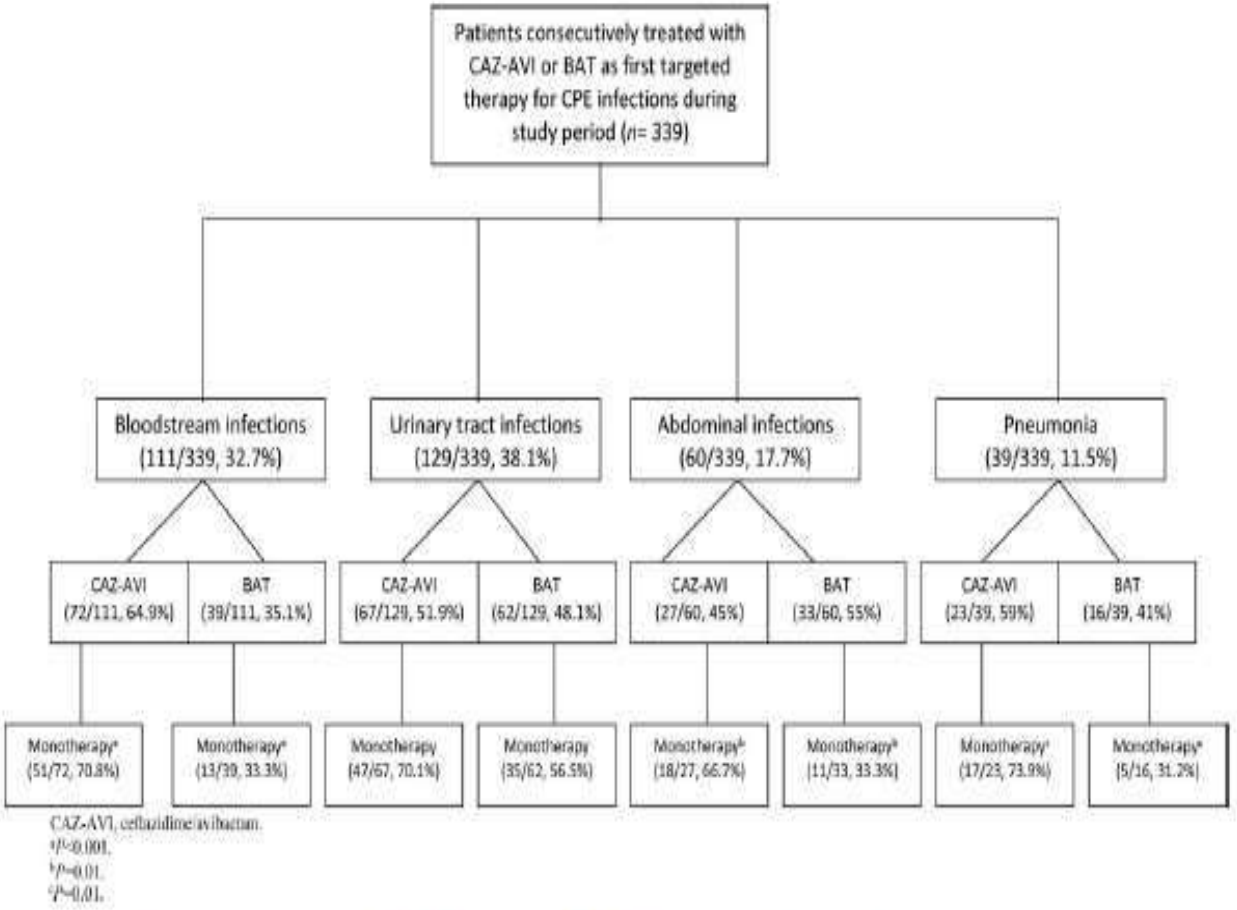


Figure 1. Flow chart showing patient enrolment. CAZ-AVI, ceftazidime/avibactam. [a]P<0.001. [b]P=0.01. [c]P=0.01.

J Antimicrob Chemother 2022; **77**: 1452–1460
https://doi.org/10.1093/jac/dkac049 Advance Access publication 21 February 2022

Journal of Antimicrobial Chemotherapy

Impact of ceftazidime/avibactam versus best available therapy on mortality from infections caused by carbapenemase-producing Enterobacterales (CAVICOR study)

Juan José Castón[1,2,3,4]*, Angela Cano[1,2,3,4], Inés Pérez-Camacho[5], Jose M. Aguado[4,6,7], Jordi Carratalá[4,8,9], Fernando Ramasco[10], Alex Soriano[4,11], Vicente Pintado[12], Laura Castelo-Corral[13], Adrian Sousa[14], María Carmen Fariñas[4,15,16], Patricia Muñoz[4,17,18,19,20], Vicente Abril López De Medrano[21], Óscar Sanz-Peláez[22], Ibai Los-Arcos[4,23,24], Irene Gracia-Ahufinger[3,25], Elena Pérez-Nadales[1,2,3], Elisa Vidal[1,2,3,4], Antonio Doblas[1], Clara Natera[1,2], Luis Martínez-Martínez[3,4,25,26] and Julian Torre-Cisneros[1,2,3,4]

Variable	Ceftazidime/avibactam (*n*=189)	BAT (*n*=150)	*P* value
21 day clinical cure, *n* (%)	169 (89.4)	119 (79.3)	0.01
Microbiological response, *n* (%)	100 (52.9)	50 (33.3)	<0.001
Infection relapse, *n* (%)	24 (12.7)	13 (8.6)	0.24
Crude mortality (30 days), *n* (%)	26 (13.7)	33 (22)	0.04

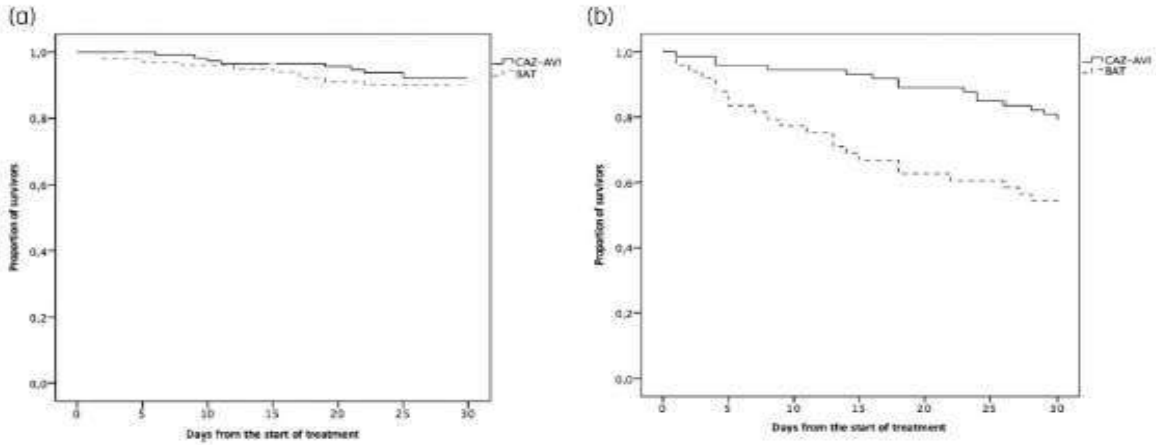


Figure 2. Kaplan–Meier survival curves in patients treated with ceftazidime/avibactam (CAZ-AVI; continuous line) or BAT (discontinuous line) for infections caused by CPE. (a) Survival in patients with INCREMENT-CPE score of ≤7 points (log rank 0.73). (b) Survival in patients with INCREMENT-CPE score of >7 points (log rank 0.004).

Table 2. INCREMENT-CPE risk score.

Variable	Score
Severe sepsis or septic shock	5
Pitt bacteremia score ≥6	4
Charlson Comorbidity Index >2	3
Origin of bacteremia other than urinary tract or biliary tract	3
Inappropriate early antibiotic therapy	2

Note: The cut-off point for defining high mortality risk and need for combination therapy is established when the score is ≥8.
Source: Elaboration based on Gutiérrez-Gutiérrez *et al.*[51]

Table 3. Pitt Score

Criterium		Score
Temperature	<35ºC o >40ºC 35.1-36ºC o 39-39.9ºC 36.1-38.9ºC	2 1 0
Hypotension	Acute event with drop in systolic blood pressure >30mmHg and diastolic blood pressure >20mmHg or requirement for vasopressor agents or systolic blood pressure <90mmHg	2
Mechanical ventilation		2
Cardiac arrest		4
Mental status	Alert Disoriented Stuporous Coma	0 1 2 4

Note: This table presents the Pitt bacteremia score used in the INCREMENT-CPE score.
Source: Elaboration based on Gutiérrez-Gutiérrez *et al.*[51] and Hilf *et al.*[52]

Ceftazidime-avibactam with or without Aztreonam vs Polymyxin-based Combination Therapy for Carbapenem-resistant Enterobacteriaceae: A Retrospective Analysis

Parikshit S Prayag[1], Sampada A Patwardhan[2], Shweta Panchakshari[3], Ramya Sambasivam[4], Surabhi Dhupad[5], Rajeev N Soman[6], Amrita P Prayag[7]

Received on: 08 May 2023; *Accepted on:* 18 May 2023; *Published on:* 31 May 2023

Abstract

Introduction: Gram-negative sepsis remains one of the most difficult to treat infections in intensive care units (ICUs). Carbapenems are often considered to be robust and reliable options for treating infections due to Gram-negative bacteria. The dominance of carbapenem-resistant enterobacteriaceae (CRE) has emerged as one of the greatest challenges faced by the medical community today. Carbapenem-resistant enterobacteriaceae may be resistant to all beta lactam antimicrobials including carbapenems and often, are even resistant to other classes of drugs. There are limited studies comparing polymyxin-based therapies with ceftazidime-avibactam (CAZ-AVI)-based therapies for treating infections caused by CRE.

Methods: A retrospective study comparing outcomes between patients with bacteremia caused by CRE treated with polymyxin-based combination therapy and CAZ-AVI-based therapy (with or without aztreonam).

Results: Of total 104 patients, 78 (75%) were in the CAZ-AVI group. There was no significant difference in the underlying comorbidities between the two groups. The incidence of nephrotoxicity was significantly higher in the polymyxin group ($p = 0.017$). Ceftazidime-avibactam-based therapy was 66% less likely to be associated with day 14 mortality ($p = 0.048$) and 67% less likely to be associated with day 28 mortality ($p = 0.039$) as compared with polymyxin-based therapy.

Conclusion: Ceftazidime-avibactam-based therapy may be a superior option to polymyxin-based therapy for infections caused by CRE. This can have significant practical applications, in terms of optimizing therapy for the individual patient as well as sparing polymyxins and reducing the use of polymyxins in our hospitals.

Keywords: Carbapenems, Carbapenem-resistant enterobacteriaceae, Ceftazidime-avibactam, Gram-negative sepsis, Polymyxin.

Indian Journal of Critical Care Medicine (2023): 10.5005/jp-journals-10071-24481

Ceftazidime-Avibactam versus Polymyxin-Based Therapies: A Study on 30-Day Mortality in Carbapenem-Resistant Enterobacterales Bloodstream Infections in an OXA-48 Endemic Region

Rıdvan Dumlu[1], Meyha Şahin[1], Okan Derin[2], Özlem Gül[3], Sedef Başgönül[4], Rehile Zengin[5], Çiğdem Arabacı[6], Funda Şimşek[7], Serap Gencer[8], Sesin Kocagöz[8], Ali Mert[9]

[1] *Department of Infectious Diseases and Clinical Microbiology,Faculty of Medicine, Istanbul Medipol University, Istanbul, Türkiye;* [2] *Epidemiology Doctorate Program, Graduate School of Health Sciences, Istanbul Medipol University, Istanbul, Türkiye;* [3] *Department of Infectious Diseases and Clinical Microbiology, Istanbul Şişli Hamidiye Etfal Training and Research Hospital, Istanbul, Türkiye;* [4] *Department of Infectious Diseases and Clinical Microbiology, Acibadem Maslak Hospital, Istanbul, Türkiye;* [5] *Department of Infectious Diseases and Clinical Microbiology, Acibadem Altunizade Hospital, Istanbul, Türkiye;* [6] *Department of Medical Microbiology, Prof. Dr. Cemil Tascioglu City Hospital,Istanbul Health Science University, Istanbul, Türkiye;* [7] *Department of Infectious Diseases and Clinical Microbiology, Prof. Dr. Cemil Tascioglu City Hospital,Istanbul Health Science University, Istanbul, Türkiye;* [8] *Department of Infectious Diseases and Clinical Microbiology, Faculty of Medicine, Mehmet Ali Aydinlar Acibadem University, Istanbul, Türkiye;* [9] *Department of Internal Medicine,Faculty of Medicine, Istanbul Medipol University, Istanbul, Türkiye*

Journal of Global Antimicrobial Resistance 39 (2024) 1-79

BACKGROUND-AIM: Ceftadizime-avibactam(CAZ-AVI) is recommended as the primary treatment for bloodstream infections (BSI) caused by OXA-48 β-Lactamase producing Carbapenem-resistant Enterobacterales (CRE), while polymyxin-based-combination-therapies(PBT) are considered a last resort if in-vitro susceptible and CAZ-AVI is unavailable.

Research comparing effectivenes of CAZ-AVI and PBT in CRE-BSI is limited, mostly focusing on KPC-producing isolates. In Turkey, OXA-48 is endemic and OXA-48-Like is common.Globally, there is limited studies on this topic. Therefore, our study aimed to compare the impact of these treatments on 30-day mortality in patients with CRE-BSI in this region.

METHODS: Retrospective data from January 2019 to May 2023 were collected from four tertiary healthcare centers in Istanbul. Demographic, clinical, and outcome data of ICU patients treated with CAZ-AVI monotherapy or PBT for CRE-BSI were analyzed. The effect on 30-day survival was evaluated using Cox regression analysis post propensity score matching (PSM) with R4.3.3 and Rstudio.

RESULTS: Out of 151 patients, 44.4% received CAZ-AVI and 55.6% received PBT. 30-day all-cause mortality rates were 20% with CAZ-AVI and 36.9% with PBT. Cox regression analysis post PSM indicated CAZ-AVI monotherapy significantly reduced the 30-day mortality risk compared to PBT(HR: 0.16,95%CI 0.07-0.37,p < 0.001), while age increased the risk(HR:1.02 per year, 95% CI 1.0-1.04, p: 0.01).

CONCLUSION: In regions endemic with OXA-48, CAZ-AVI demonstrated lower mortality rates in CRE-BSI compared to PBT. The results were attributed to the pharmacokinetic and pharmacodynamic disadvantages of polymyxins compared to CAZ-AVI and the impact of age-related physical conditions. Therefore,CAZ-AVI should be the preferred treatment for CRE-BSI in such endemic areas.

Efficacy and safety of ceftazidime-avibactam compared to other antimicrobials for the treatment of infections caused by carbapenem-resistant *Klebsiella pneumoniae* strains, a systematic review and meta-analysis

Theodoros Karampatakis [a,*], Katerina Tsergouli [b], Kinga Lowrie [c]

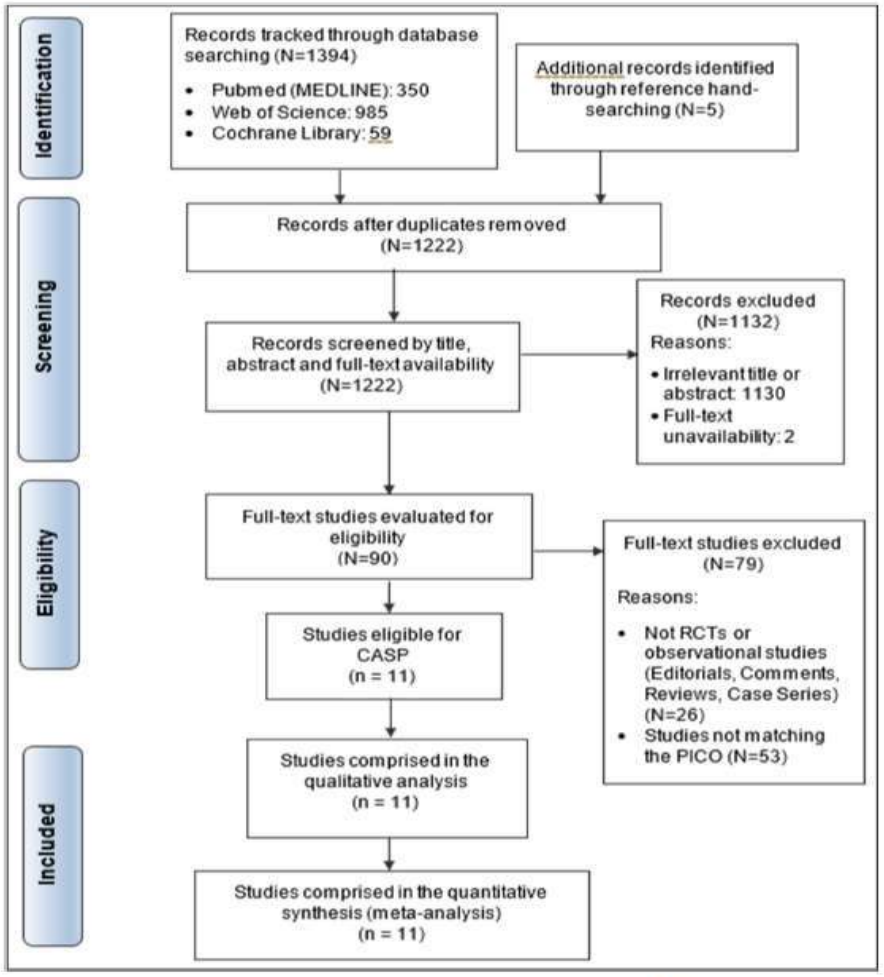


Fig. 1. PRISMA flow diagram of study retrieval and eligibility.

Efficacy and safety of ceftazidime-avibactam compared to other antimicrobials for the treatment of infections caused by carbapenem-resistant *Klebsiella pneumoniae* strains, a systematic review and meta-analysis

Theodoros Karampatakis [a,*], Katerina Tsergouli [b], Kinga Lowrie [c]

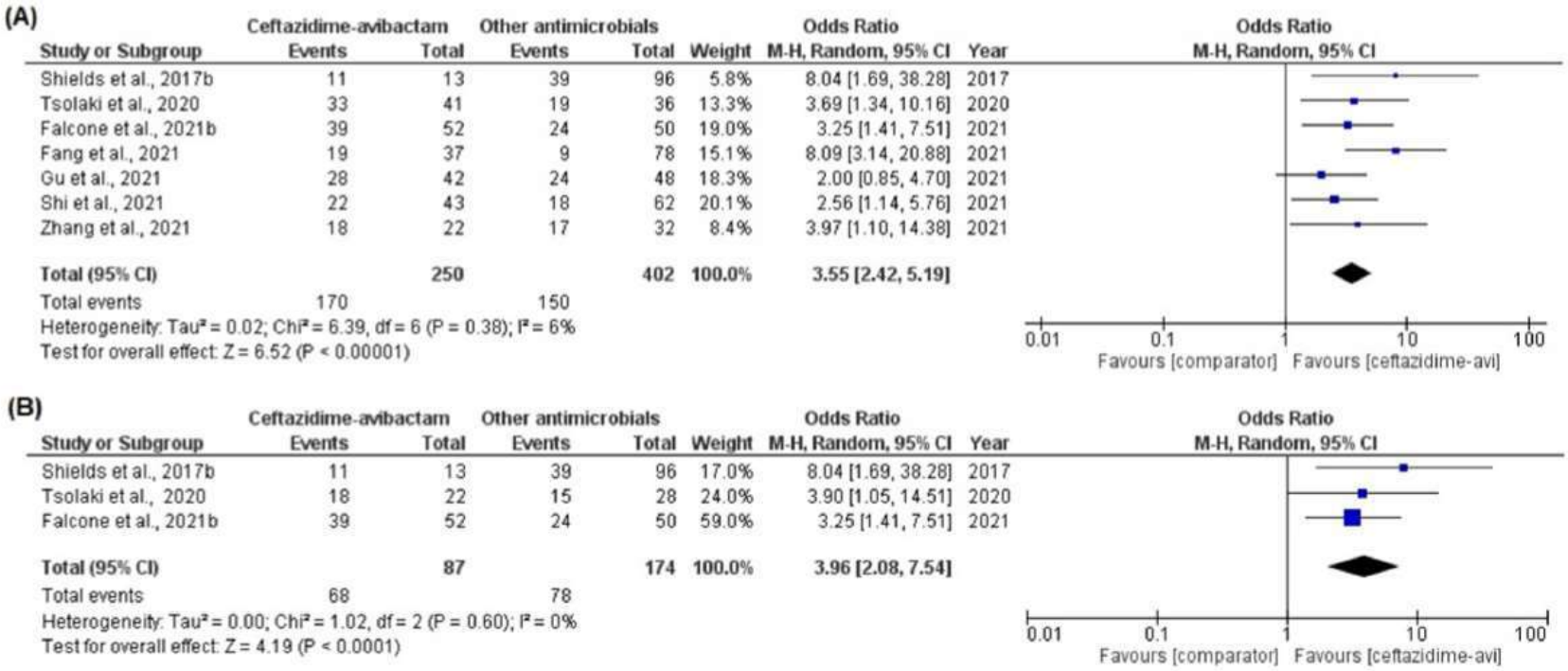


Fig. 2. (A) Clinical success of CAZ-AVI vs comparators in the treatment of CRKP infections (B) Clinical success of CAZ-AVI vs comparators in the treatment of CRKP BSIs.

Efficacy and safety of ceftazidime-avibactam compared to other antimicrobials for the treatment of infections caused by carbapenem-resistant *Klebsiella pneumoniae* strains, a systematic review and meta-analysis

Theodoros Karampatakis [a,*], Katerina Tsergouli [b], Kinga Lowrie [c]

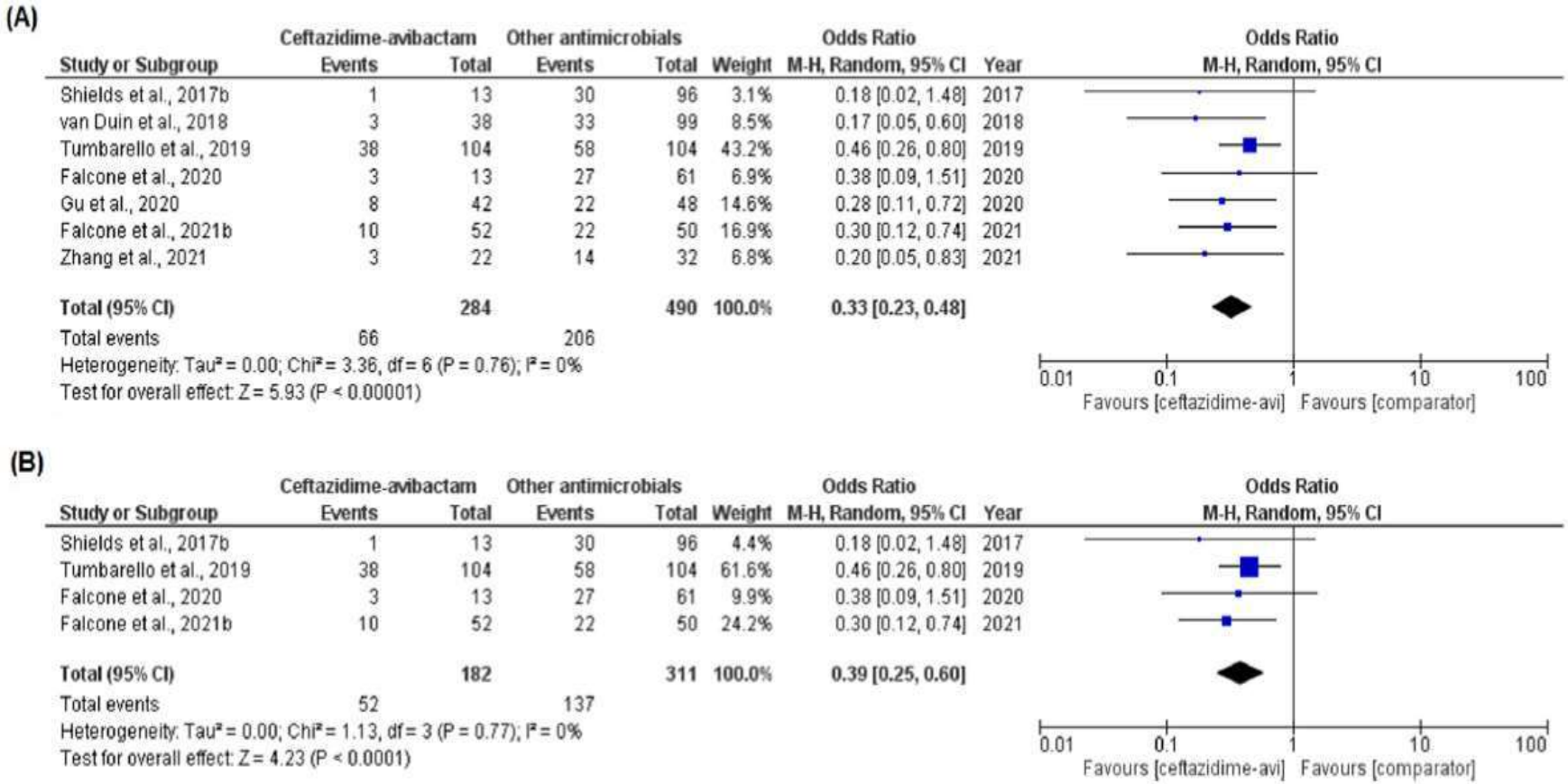


Fig. 4. (A) 30-day mortality of CAZ-AVI vs comparators in the treatment of CRKP infections (B) 30-day mortality of CAZ-AVI vs comparators in the treatment of CRKP BSIs.

Infection (2024) 52:19–28
https://doi.org/10.1007/s15010-023-02108-6

REVIEW

Ceftazidime–avibactam versus polymyxins in treating patients with carbapenem-resistant Enterobacteriaceae infections: a systematic review and meta-analysis

Jinglan Chen[1,2,3] · Qin Hu[1,3,6] · Pengxiang Zhou[4,5] · Sheng Deng[1,3]

Received: 17 July 2023 / Accepted: 3 October 2023 / Published online: 25 October 2023

Abstract

Objective Carbapenem-resistant Enterobacteriaceae (CRE) pose a significant threat to human health and have emerged as a major public health concern. We aimed to compare the efficacy and the safety of ceftazidime–avibactam (CAZ–AVI) and polymyxin in the treatment of CRE infections.

Methods A systematic review and meta-analysis was performed by searching the databases of EMBASE, PubMed, and the Cochrane Library. Published studies on the use of CAZ–AVI and polymyxin in the treatment of CRE infections were collected from the inception of the database until March 2023. Two investigators independently screened the literature according to the inclusion and exclusion criteria, evaluated the methodological quality of the included studies and extracted the data. The meta-analysis was performed using RevMan 5.4 software.

Results Ten articles with 833 patients were included (CAZ–AVI 325 patients vs Polymyxin 508 patients). Compared with the patients who received polymyxin-based therapy, the patients who received CAZ–AVI therapy had significantly lower 30-days mortality (RR = 0.49; 95% CI 0.01–2.34; $I^2 = 22\%$; $P < 0.00001$), higher clinical cure rate (RR = 2.70; 95% CI 1.67–4.38; $I^2 = 40\%$; $P < 0.00001$), and higher microbial clearance rate (RR = 2.70; 95% CI 2.09–3.49; $I^2 = 0\%$; $P < 0.00001$). However, there was no statistically difference in the incidence of acute kidney injury between patients who received CAZ–AVI and polymyxin therapy (RR = 1.38; 95% CI 0.69–2.77; $I^2 = 22\%$; $P = 0.36$). In addition, among patients with CRE bloodstream infection, those who received CAZ–AVI therapy had significantly lower mortality than those who received polymyxin therapy (RR = 0.44; 95% CI 0.27–0.69, $I^2 = 26\%$, $P < 0.00004$).

Conclusions Compared to polymyxin, CAZ–AVI demonstrated superior clinical efficacy in the treatment of CRE infections, suggesting that CAZ–AVI may be a superior option for CRE infections.

CAZ-AVI ve KPC-Kp

- İtalya, ÇM, Retrospektif, Gözlemsel
- 577 erişkin hasta
- 165 hasta monoterapi ve 462 hasta kombinasyon
- 30. gün mortalitesi %25(146/577)
- Mortalite açısından monoterapi ile kombinasyon arasında fark yok(%26.1 - %25, p=0.79)
- Mortalite için bağımsız risk faktörleri

  -Septik şok
  -Nötropeni
  -Increment skoru ≥ 8
  -Pnömoni
  -CAZ-AVI renal doz ayarı
  -CAZ-AVI uzamış infüzyon koruyucu faktör

Tumbarello M et al. Clin Infect Dis 2021

JAC Antimicrob Resist
https://doi.org/10.1093/jacamr/dlae201

JAC-Antimicrobial Resistance

Impact of renal-adjusted ceftazidime/avibactam in patients with KPC-producing *Klebsiella pneumoniae* bloodstream infection: a retrospective cohort study

A. Oliva [1]*†, L. Volpicelli [1]†, A. Gigante[2], M. Di Nillo[1], S. Trapani[1], A. Viscido[3], F. Sacco[3] and C. M. Mastroianni[1]

[1]*Department of Public Health and Infectious Diseases, Sapienza University of Rome, Piazzale Aldo Moro 5, Rome 00185, Italy;*
[2]*Department of Translational and Precision Medicine, Sapienza University of Rome, Viale dell'Università 37, Rome 00185, Italy;*
[3]*Microbiology and Virology Unit, University Hospital Policlinico Umberto I, Viale del Policlinico, 155, Rome 00161, Italy*

*Corresponding author. E-mail: alessandra.oliva@uniroma1.it
†These authors contributed equally.

Received 14 August 2024; accepted 18 November 2024

Background: Bloodstream infections (BSIs) caused by KPC-producing *Klebsiella pneumoniae* (KPC-Kp) are still associated with high mortality, and the game-changing drug ceftazidime/avibactam has shown suboptimal pharmacokinetics in some clinical settings. Ceftazidime/avibactam renal dose adjustment has recently been identified as an independent risk factor for mortality.

Objectives: To investigate the effect of ceftazidime/avibactam renal dose adjustment on mortality.

Methods: Patients with KPC-Kp BSI treated with a ceftazidime/avibactam-based regimen were retrospectively collected and analysed. The primary outcome was mortality at 7, 14 and 30 days after the start of definitive ceftazidime/avibactam antibiotic therapy. Renal function was estimated using the CKD-EPI equation.

Results: One hundred and ten patients with KPC-Kp BSI treated with a ceftazidime/avibactam-based regimen were included. Full-dose ceftazidime/avibactam (7.5 g daily) was prescribed to 82 patients (74.5%), while 28 patients (25.5%) received a renal-adjusted dose (17 patients due to chronic renal disease or haemodialysis, 11 patients due to infection-related acute kidney injury), with a median of 1.9 g daily. At multivariable analysis, receiving a reduced dose of ceftazidime/avibactam was independently associated with mortality (HR 4.47, 95% CI 1.09–18.03, $P=0.037$), along with intra-abdominal or lower respiratory tract infections as source of BSI (HR 5.42, 95% CI 1.77–16.55, $P=0.003$), septic shock (HR 6.99, 95% CI 1.36–35.87, $P=0.020$) and SARS-CoV-2 coinfection (HR 10.23, 95% CI 2.69–38.85, $P=0.001$).

Conclusions: Dose reduction of ceftazidime/avibactam according to renal function in patients with KPC-Kp BSI seems to be independently associated with higher mortality. This may be possibly due to inadequate exposure provided by the recommended doses for renal impairment.

Impact of renal-adjusted ceftazidime/avibactam in patients with KPC-producing *Klebsiella pneumoniae* bloodstream infection: a retrospective cohort study

A. Oliva [1*†], L. Volpicelli [1†], A. Gigante[2], M. Di Nillo[1], S. Trapani[1], A. Viscido[3], F. Sacco[3] and C. M. Mastroianni[1]

- Retrospektif, tek merkez, İtalya
- KPC-Kp , Kan dolaşımı enfeksiyonları
- CAZ-AVİ
- Renal doz ayarı ile tam doz karşılaştırması
- 7,14 ve 30. gün mortalitesi

Impact of renal-adjusted ceftazidime/avibactam in patients with KPC-producing *Klebsiella pneumoniae* bloodstream infection: a retrospective cohort study

A. Oliva [1]*†, L. Volpicelli [1]†, A. Gigante[2], M. Di Nillo[1], S. Trapani[1], A. Viscido[3], F. Sacco[3] and C. M. Mastroianni[1]

- KPC Kp ile kolonizasyon %79.1
- YBÜ %30.9
- Septik şok %25.5
- KBY %30(5 hasta hemodiyalizde)
- COVID-19 9 hasta
- Uygun ampirik tedavi %38.2
- Kombinasyon %88.2(en sık meropenem veya fosfomisin)
- 30.gün mortalitesi %18.2

- 82(%74.5) hasta tam doz
- 28(%25.5) hasta azaltılmış doz
- 14. gün mortalitesi
  %6.1 ve %25, p=0,011
- 30.gün mortalitesi
  %13.4 ve %32.1, p=0,044
- Klinik iyileşme
  %64.6 ve %53.6

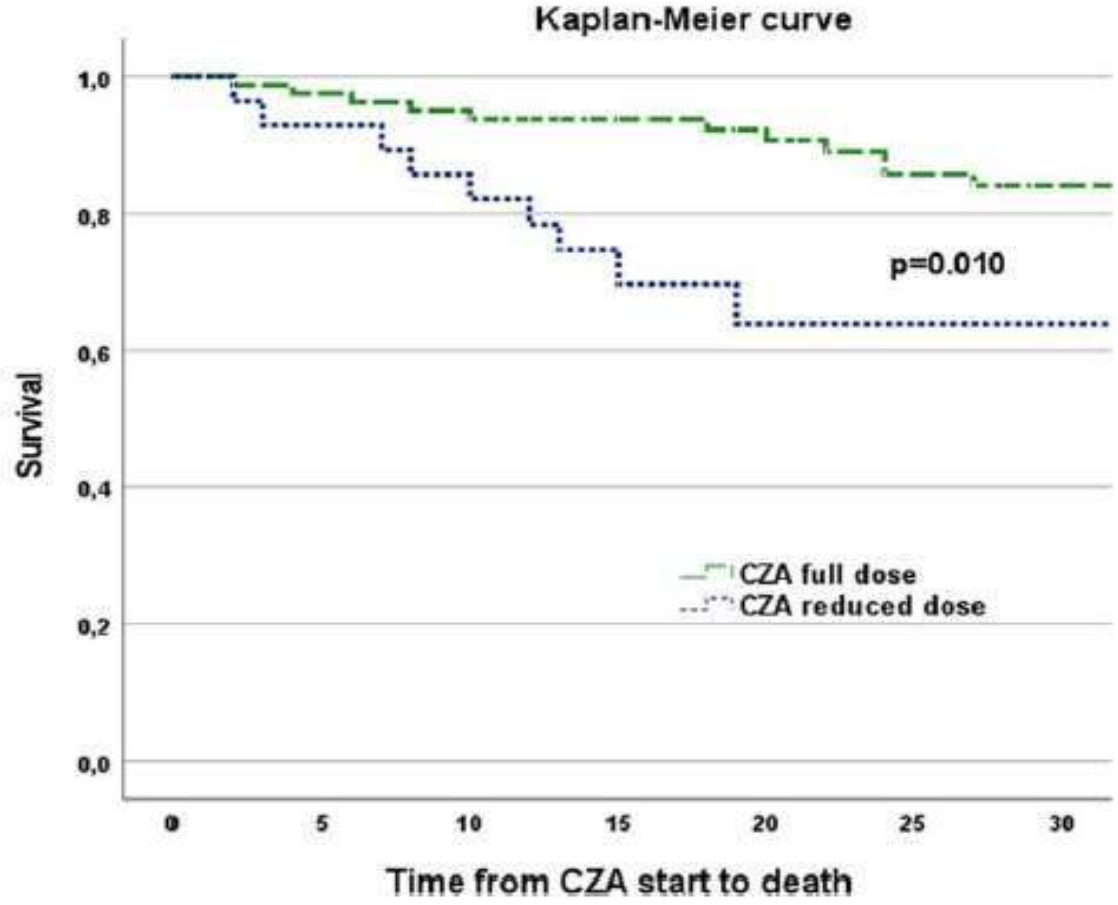


Figure 1. Kaplan–Meier survival curve comparing those treated with a full dose of ceftazidime/avibactam with those who received a dose reduced according to renal function. CZA, ceftazidime/avibactam.

Table 4. Multivariable analysis of independent predictors of 30 day mortality in patients with BSI from KPC-Kp

Variables	HR (95% CI)	*P* value
Adjusted dose of CZA	4.47 (1.09–18.03)	**0.037**
Source of BSI: IAI or LRTI	5.42 (1.77–16.55)	**0.003**
SARS-CoV-2 coinfection	10.23 (2.69–38.85)	**0.001**
Septic shock	6.99 (1.36–35.87)	**0.020**
CRRT required due to infection	2.27 (0.71–7.28)	0.165
CCI, one point increment	1.02 (0.84–1.23)	0.809
ICS, one point increment	0.90 (0.71–1.15)	0.419
Hospitalization in ICU	0.84 (0.28–2.51)	0.762
sCr at CZA prescription (0.1 mg/mL increment)	0.94 (0.62–1.45)	0.812

Values in bold indicate $P<0.05$.

BSI, bloodstream infection; CCI, Charlson comorbidity index; CRRT, continuous renal replacement therapy; CZA, ceftazidime/avibactam; IAI, intra-abdominal infection; ICS, increment CPE score; ICU, intensive care unit; LRTI, lower respiratory tract infection; sCr, serum creatinine.

Monoterapi - Kombinasyon

- Meta-analizlerde kombinasyon ile monoterapi arasında klinik iyileşme, mortalite ve mikrobiyolojik eradikasyon açısından anlamlı fark yok
- Direnç gelişimi monoterapide %4.1, kombinasyonda %3

Meini S et al. Infection 2021
Onorato L et al. Int J Antimicrob Agents 2019
Fiore M et al. Antibiotics 2020

Infection (2024) 52:2029–2042
https://doi.org/10.1007/s15010-024-02277-y

REVIEW

Ceftazidime-avibactam combination therapy versus monotherapy for treating carbapenem-resistant gram-negative infection: a systemic review and meta-analysis

Wei Hsu[1] · Min-Hsiang Chuang[1] · Wen-Wen Tsai[2] · Chih-Cheng Lai[3] · Hsin-Yu Lai[1] · Hung-Jen Tang[1]

Received: 27 February 2024 / Accepted: 18 April 2024 / Published online: 13 May 2024

Abstract

Background This meta-analysis was conducted to compare the efficacy of ceftazidime-avibactam combination therapy with that of monotherapy in the treatment of carbapenem-resistant Gram-negative bacterial (CR-GNB).

Methods A literature search of PubMed, Embase, the Cochrane Library, and ClinicalTrials.gov was conducted until September 1, 2023. Only studies that compared CZA combination therapy with monotherapy for CR-GNB infections were included.

Results A total of 25 studies (23 retrospective observational studies and 2 prospective studies) involving 2676 patients were included. There was no significant difference in 30-day mortality between the study group receiving combination therapy and the control group receiving monotherapy (risk ratio [RR] 0.91; 95% confidence interval [CI] 0.71–1.18). In addition, no significant differences were observed between the study and the control group in terms of in-hospital mortality (RR 1.00; 95% CI 0.79–1.27), 14-day mortality (RR 1.54; 95% CI 0.24–9.91), 90-day mortality (RR 1.18; 95% CI 0.62–2.22), and clinical cure rate (RR 0.95; 95% CI 0.84–1.08). However, the combination group had a borderline higher microbiological eradication rate than the control group (RR 1.15; 95% CI 1.00–1.32).

Conclusions Compared to monotherapy, CZA combination therapy did not yield additional clinical benefits. However, combination therapy may be associated with favorable microbiological outcomes.

Kombinasyon

- Kritik hastalarda(sepsis ve septik şoktaki) ekstraselüler volüm ve renal disfonksiyon sorunu CAZ-AVI'nin farmakokinetiğini etkileyebilir
- Pnömonide fosfomisin
- Kan dolaşımı enfeksiyonu, üriner ve intraabdominal kaynaklı bakteriyemilerde amikasin/gentamisin
- İntraabdominal enfeksiyon ve CYDE'de tigesiklin
- Duyarlılık sınırına yakın MİK'in olduğu ağır enfeksiyonlarda kolistin(sadece kolistin duyarlı ise)

Meini S et al. Infection 2021

Heliyon 10 (2024) e35757

Contents lists available at ScienceDirect

Heliyon

journal homepage: www.cell.com/heliyon

Research article

Ceftazidime-avibactam: Combination therapy versus monotherapy in the challenge of pneumonia caused by carbapenem-resistant *Klebsiella pneumoniae*

Chang-wei Liu [a,b], Qiang Chen [c,d], Nan Ding [e,**], Li-fen Hu [c,d,*]

[a] Department of Pharmacy, The First Affiliated Hospital of Anhui Medical University, Hefei, PR China
[b] The Grade 3 Pharmaceutical Chemistry Laboratory of State Administration of Traditional Chinese Medicine, The First Affiliated Hospital of Anhui Medical University, Hefei, PR China
[c] Department of Infectious Diseases, The First Affiliated Hospital of Anhui Medical University, Hefei, PR China
[d] Anhui Center for Surveillance of Bacterial Resistance, Hefei, PR China
[e] Department of Pharmacy, Shanghai Changhai Hospital, The First Affiliated Hospital of Naval Medical University, Shanghai, PR China

ARTICLE INFO

Keywords:
Ceftazidime-avibactam
Monotherapy
Combination therapy
Pneumonia
Carbapenem-resistant *Klebsiella pneumoniae*

ABSTRACT

This research focused on evaluating the clinical results of patients suffering from pneumonia caused by carbapenem-resistant *Klebsiella pneumoniae* (CRKP), who received treatment with either ceftazidime–avibactam (CZA) alone or in combination with other antibiotics. From January 2020 to December 2023, we retrospectively analyzed CRKP-related pneumonia patients treated in two Chinese tertiary hospitals. Mortality was measured at 14 and 30 days as the primary outcome. Secondary outcomes included the 14-day microbiological cure rate and the 14-day clinical cure rate. Factors contributing to clinical failure were evaluated via both univariate analysis and multivariate logistic regression. To account for confounding factors, propensity score matching (PSM) was utilized. Among the 195 patients with CRKP infections, 103 (52.8 %) received CZA combination therapy, and 92 (47.2 %) patients received CZA monotherapy. The combination therapy group exhibited superior clinical and microbiological cure rates compared to the monotherapy group, with a 14-day clinical cure rate of 60.1 % vs. 45.7 % ($P = 0.042$) and a 14-day microbiological cure rate of 72.8 % vs. 58.6 % ($P = 0.038$), respectively. Combination therapy reduced mortality rates at 14 days (7.8 % vs. 17.4 %, $P = 0.041$), but not at 30 days (14.6 % vs. 25.0 %, $P = 0.066$). Even after using PSM, the group treated with the CZA combination continued to had a lower mortality rate at 14 days (5.9 % vs. 17.6 %, $P = 0.039$). The 14-day clinical cure rate for the combination therapy group was 63.2 %, and the 14-day microbial cure rate was 77.9 %. Both of these statistics were notably greater than those observed in the monotherapy group. Furthermore, the multivariate logistic regression model indicated a significant link between combination therapy and a decrease in clinical failure. Carbapenems were noted to be the most effective class of concomitant agents. Our findings indicate that patients with pneumonia due to CRKP benefit from combination treatment of CZA rather than monotherapy; administering

Karbapenem Dirençli *Enterobacteriaceae* Enfeksiyonlarının Tedavisi

Treatment of Carbapenem-Resistant *Enterobacteriaceae* Infections

Halis AKALIN[a]

[a]Bursa Uludağ Üniversitesi Tıp Fakültesi, Enfeksiyon Hastalıkları ve Klinik Mikrobiyoloji ABD, Bursa, Türkiye

Yazışma Adresi/*Correspondence*:
Halis AKALIN
Bursa Uludağ Üniversitesi Tıp Fakültesi, Enfeksiyon Hastalıkları ve Klinik Mikrobiyoloji ABD, Bursa, Türkiye
halis@uludag.edu.tr

ÖZET Karbapenemlere karşı direnç gelişmesine karbapenemaz (beta-laktamaz enzimi) üretimi, dış membran proteinlerinin kaybı, penisilin bağlayan proteinlerdeki değişim, biyofilm oluşturma ve eflüks pompası ile atılım gibi birçok mekanizma aracılık etmektedir. Karbapenemazlar penisilinleri, sefalosporinleri, monobaktamları ve karbapenemleri hidroliz ederek inaktif hale getirirler. Karbapenem dirençli Enterobacterales takımında dünya çapında yaklaşık olarak %85 oranında karbapenemaz enzimi saptanmıştır. Ülkemiz "Sağlık Hizmeti ile İlişkili Enfeksiyonlarda Antimikrobiyal Direnç Oranları 2021 Yılı Raporunda" *Klebsiella pneumoniae* suşlarında genişlemiş spektrumlu beta-laktamaz oranı %66, karbapenem direnç oranı %63.57 ve kolistin direnci ise %31.93 olarak bildirilmiştir. Ülkemizde en yaygın karbapenemaz OXA-48 olmakla birlikte, KPC ve NDM enzimleri de giderek artmaktadır. OXA-48 ve NDM birlikteliği de %10'u geçmiştir. Karbapenem dirençli *Enterobacteriaceae* enfeksiyonları önemli bir morbidite ve mortalite nedeni olmaya devam etmektedir. Ülkemizde yapılan çalışmalarda 30.gün mortalitesi %44-52.8 arasında bulunmuştur. Seftazidim-avibaktam gibi yeni antibiyotikleri ve elimizdeki eski antibiyotikleri akılcı kullanmak zorundayız. Antibiyotik yönetiminin ve enfeksiyon kontrolünün birbirinin ayrılmaz parçaları olduğunu unutmamalıyız.

Anahtar Kelimeler: Karbapenem direnci; *Klebsiella*; *Enterobacteriaceae*; karbapenemazlar; meropenem; polimiksinler; Seftazidim-avibaktam

TABLO 2: Antibiyotiklerin karbapenemaz enzimlerine göre KRE üzerine aktiviteleri.

Antibiyotik	KRE-KÜ	KRE-KPC	KRE-OXA-48	KRE-MBL
Seftazidim-avibaktam	+/-	+	+	-
Meropenem-vaborbaktam	+/-	+	-	-
İmipenem-silastatin-relebaktam	+/-	+	-	-
Plazomisin	+	+	+	+/-
Eravasiklin	+	+	+	+
Sefiderokol	+	+	+	+
Polimiksinler	+	+	+	+
Aminoglikozidler	+/-	+/-	+/-	+/-
Fosfomisin İV	+/-	+/-	+/-	+/-
Aztreonam	-	-	-	+/-
Tigesiklin	+	+	+	+

KRE-KÜ: Karbapenemaz üretmeyen karbapenem dirençli Enterobacteriaceae; KRE-KPC: KPC pozitif karbapenem dirençli Enterobacteriaceae; KRE-OXA-48: OXA-48 pozitif karbapenem dirençli Enterobacteriaceae; KRE-MBL: Metallo-beta-laktamaz pozitif karbapenem dirençli Enterobacteriaceae; İV:İntravenöz; +: aktif; -: aktif değil; +/-: değişken.

Sinerji Çalışmaları

- 19 Kp
  - -CAZ-AVI + FOS Sinerjik
  - -CAZ-AVI + ERT Sinerjik

Ojdana D et al. Microb Drug Resistance 2019

- 24 CRE, Zaman-ölüm
  - -CAZ-AVI + COL Sinerjik %13
    Antagonist %46

Shields RK et al. Antimicrob Agents Chemother 2018

Sinerji Çalışmaları

- CAZ-AVI + Polimiksin B
  - -KPC-3(+) Kp
  - -İn vitro bakterisidal aktivitede iyileşme yok
  - -Galleria mellonella modelinde iyileşme yok

Borjan J et al. Int J Antimicrob Agents 2020

- ÇİD Kp ve Pa

-CAZ-AVI + AMI	Sinerjik
-CAZ-AVI + ATM	Sinerjik
-CAZ-AVI + MEM	Pa etkili
-CAZ-AVI + FOS	Kp etkili
-CAZ-AVI + COL	Sinerjik

Mikhail S et al. Antimicrob Agents Chemother 2019

Antimicrobial Original Research Paper

Evaluation of the synergy of ceftazidime/avibactam in combination with colistin, doripenem, levofloxacin, tigecycline, and tobramycin against OXA-48 producing Enterobacterales

Journal of Chemotherapy 2020 VOL. 32 NO. 4

Emel Mataraci Kara[1], Mesut Yilmaz[2], Ayşe Istanbullu Tosun[3], Berna Özbek Çelik[1]

[1]Department of Pharmaceutical Microbiology, Faculty of Pharmacy, Istanbul University, Beyazit, Istanbul, Turkey; [2]Department of Infectious Diseases and Clinical Microbiology, Faculty of Medicine, Istanbul Medipol University, Istanbul, Turkey; [3]Department of Medical Microbiology, Faculty of Medicine, Istanbul Medipol University, Istanbul, Turkey

This study aims to analyze the effect of ceftazidime/avibactam plus various antibiotics against OXA-48-producing Enterobacterales isolated from Intensive Care Units. Seventy-four non-duplicate OXA-48-producing Enterobacterales isolates were screened for their MICs by the microbroth dilution method. The in-vitro bactericidal and synergistic activities of ceftazidime/avibactam alone or in combination with other antibiotics were determined by time-kill curve assays. According to our results, colistin was the most active drug with higher susceptibility rates in the strains. Colistin, levofloxacin, tobramycin, and doripenem showed bactericidal effects against different isolates. The best synergistic interactions were achieved with ceftazidime/avibactam + colistin, ceftazidime/avibactam + tobramycin, and ceftazidime/avibactam + tigecycline against studied strains used at 1xMIC concentrations at 24 h. No antagonism was observed against studied OXA-48-producing Enterobacterales strains. The findings of this study suggest that ceftazidime/avibactam plus colistin, tobramycin, or tigecycline were more effective against OXA-48-producing Enterobacterales strains. This combination therapy could be an alternative antibiotic therapy for carbapenemase-producing Enterobacterales strains.

Synergistic antibacterial activity of ceftazidime–avibactam in combination with colistin, gentamicin, amikacin, and fosfomycin against carbapenem-resistant *Klebsiella pneumoniae*

Nazmiye Ülkü Tüzemen[1], Uğur Önal[2], Osman Merdan[1,3], Bekir Akca[1], Beyza Ener[1], Cüneyt Özakın[1] & Halis Akalın[2]

Results

Bacterial isolates

Our research involved 55 CRKP strains, each belonging to a different patient. These strains were grown from clinical specimens collected between November 2020 and November 2022. The patients were of varying ages (ranging from 23–86) and genders (35 males and 20 females). The strains were collected from different parts of the body, such as blood (n:25, 45.5%), deep tracheal aspirate (n:18, 32.7%), wound pus (n:6, 10.9%), sputum (n:3, 5.5%), urine (n:2, 3.6%), and cerebrospinal fluid (n:1, 1.8%). OXA-48 production was the most common (49.1%), followed by KPC production (29.1%), co-production of KPC and OXA-48 (10.9%), NDM production (3.7%), co-production of VIM and NDM (1.8%), co-production of OXA-48 and NDM (1.8%), co-production of KPC, OXA-48, and NDM (1.8%), and the absence of any gene (1.8%).

55 CRKP, 2020-2022

OXA-48	%49.1
KPC	%29.1
OXA-48-KPC	%10.9
NDM	%3.7
VIM-NDM	%1.8
OXA-48 - NDM	%1.8
KPC-OXA-48 -NDM	%1.8

Combination			Checkerboard assay			
CZA+COL	CZA	COL	Total	Synergy (%)	Additive (%)	Indifference (%)
	S	S	6	0	4 (66.7)	2 (33.3)
	R	S	3	1(33.3)	1(33.3)	1(33.3)
	S	R	43	41 (95.3)	2 (4.7)	0
	R	R	3	1 (33.3)	0	2 (66.7)
	Total		55	43 (78.2)	7 (12.7)	5 (9.1)
CZA+GEN	CZA	GEN				
	S	S	11	6 (54.5)	4 (36.4)	1 (9.1)
	R	S	1	0	0	1(100)
	S	R	38	4 (10.5)	4 (10.5)	30 (79)
	R	R	5	0	0	5(100)
	Total		55	10 (18.2)	8 (14.5)	37 (67.3)
CZA+AK	CZA	AK				
	S	S	13	5 (38.5)	6 (46.2)	2 (15.3)
	R	S	3	0	2(66.7)	1(33.3)
	S	R	36	7 (19.4)	11 (30.6)	18 (50)
	R	R	3	0	0	3 (100)
	Total		55	12 (21.8)	19 (34.6)	24 (43.6)
CZA+FOS	CZA	FOS				
	S	S	23	22 (95.7)	1 (4.3)	0
	R	S	3	2 (66.7)	1(33.3)	0
	S	R	26	11 (42.3)	2 (7.7)	13 (50)
	R	R	3	0	0	3 (100)
	Total		55	35 (63.6)	4 (7.3)	16 (29.1)

Table 3. Results of checkerboard assay in CRKP isolates. *CRKP* carbapenem-resistant *K. pneumoniae*, *CZA* ceftazidime–avibactam, *COL* colistin, *AK* amikacin, *GEN* gentamicin, *FOS* fosfomycin.

J Antimicrob Chemother 2024; **79**: 1069–1080
https://doi.org/10.1093/jac/dkae074 Advance Access publication 25 March 2024

Journal of Antimicrobial Chemotherapy

Synergistic effects of ceftazidime/avibactam combined with meropenem in a murine model of infection with KPC-producing *Klebsiella pneumoniae*

Mei Zheng[1,2,3], Fu-Hao Li[1,2,3], Juan Liu[1,2,3], Wen-Jie Li[1,2,3], Ruo-Xi Yin[1,2,3], Da-Tong Cai[1,2], Diego O. Andrey[4], Si-Lin Zheng[1,2], Ana C. Gales[5], Wan-Jiang Zhang[6], Jian Sun[1,2,3], Xiao-Ping Liao[1,2,3] and Yang Yu[1,2,3]*

[1]State Key Laboratory for Animal Disease Control and Prevention, South China Agricultural University, Guangzhou, China; [2]Guangdong Provincial Key Laboratory of Veterinary Pharmaceutics Development and Safety Evaluation, South China Agricultural University, Guangzhou, China; [3]Guangdong Laboratory for Lingnan Modern Agriculture, National Risk Assessment Laboratory for Antimicrobial Resistance of Animal Original Bacteria, College of Veterinary Medicine, South China Agricultural University, Guangzhou, China; [4]Service of Infectious Diseases, Geneva University Hospitals and Faculty of Medicine, Geneva, 1211, Switzerland; [5]Infectious Diseases Division, Federal University of Sao Paulo–UNIFESP, Escola Paulista de Medicina, São Paulo, Brazil; [6]State Key Laboratory of Veterinary Biotechnology, Harbin Veterinary Research Institute, Chinese Academy of Agricultural Sciences, Harbin, China

*Corresponding author. E-mail: graceyyu@scau.edu.cn

Received 11 September 2023; accepted 27 February 2024

Objectives: The emergence and expansion of carbapenem-resistant *Klebsiella pneumoniae* infections is a concern due to the lack of 'first-line' antibiotic treatment options. The ceftazidime/avibactam is an important clinical treatment for carbapenem-resistant *K. pneumoniae* infections but there is an increasing number of cases of treatment failure and drug resistance. Therefore, a potential solution is combination therapies that result in synergistic activity against *K. pneumoniae* carbapenemase: producing *K. pneumoniae* (KPC-Kp) isolates and preventing the emergence of KPC mutants resistant to ceftazidime/avibactam are needed in lieu of novel antibiotics.

Methods: To evaluate their synergistic activity, antibiotic combinations were tested against 26 KPC-Kp strains. Antibiotic resistance profiles, molecular characteristics and virulence genes were investigated by susceptibility testing and whole-genome sequencing. Antibiotic synergy was evaluated by *in vitro* chequerboard experiments, time-killing curves and dose–response assays. The mouse thigh model was used to confirm antibiotic combination activities *in vivo*. Additionally, antibiotic combinations were evaluated for their ability to prevent the emergence of ceftazidime/avibactam resistant mutations of bla_{KPC}.

Results: The combination of ceftazidime/avibactam plus meropenem showed remarkable synergistic activity against 26 strains and restored susceptibility to both the partnering antibiotics. The significant therapeutic effect of ceftazidime/avibactam combined with meropenem was also confirmed in the mouse model and bacterial loads in the thigh muscle of the combination groups were significantly reduced. Furthermore, ceftazidime/avibactam plus meropenem showed significant activity in preventing the occurrence of resistance mutations.

Conclusions: Our results indicated that the combination of ceftazidime/avibactam plus meropenem offers viable therapeutic alternatives in treating serious infections due to KPC-Kp.

J Antimicrob Chemother 2025; **80**: 334–346
https://doi.org/10.1093/jac/dkae451 Advance Access publication 17 December 2024

Journal of Antimicrobial Chemotherapy 50 years

A systematic review and individual bacterial species level meta-analysis of *in vitro* studies on the efficacy of ceftazidime/avibactam combined with other antimicrobials against carbapenem-resistant Gram-negative bacteria

Getnet M. Assefa[1,2], Jason A. Roberts[1,3,4,5,6], Abdullah T. Aslan[1], Solomon A. Mohammed[1,2] and Fekade B. Sime [1]*

[1]*Centre for Clinical Research, Faculty of Medicine, The University of Queensland, Brisbane, QLD, Australia;* [2]*Department of Pharmacy, College of Medicine and Health Sciences, Wollo University, Dessie, Ethiopia;* [3]*Pharmacy Department, Royal Brisbane and Women's Hospital, Brisbane, QLD, Australia;* [4]*Department of Intensive Care Medicine, Royal Brisbane and Women's Hospital, Brisbane, QLD, Australia;* [5]*Herston Infectious Disease Institute (HeIDI), Metro North Health, Brisbane, QLD, Australia;* [6]*Division of Anaesthesiology Critical Care Emerging and Pain Medicine, Nimes University Hospital, University of Montpellier, Nimes, France*

*Corresponding author. E-mail: f.sime@uq.edu.au

Received 1 September 2024; accepted 2 December 2024

Background: Carbapenem-resistant Gram-negative bacteria (CR-GNB) develop resistance to many antimicrobials. To effectively manage infections caused by these organisms, novel agents and/or combinations of antimicrobials are required.

Objectives: Evaluated the *in vitro* efficacy of ceftazidime/avibactam in combination with other antimicrobials against CR-GNB.

Methods: PubMed, Web of Science, Embase and Scopus were searched. Study outcomes were quantified by counting the number of isolates exhibiting synergy, defined as a fractional inhibitory concentration index ≤ 0.5 for checkerboard and Etest, and a >2 log cfu/mL reduction for time-kill studies. The proportion of synergy was calculated as the ratio of isolates exhibiting synergy to the total number of isolates tested. These proportions were analysed using a random-effects model, following the Freeman–Tukey double-arcsine transformation.

Results: Forty-five *in vitro* studies were included. A total of 734 isolates were tested, and 69.3% of them were resistant to ceftazidime/avibactam. The combination of ceftazidime/avibactam with aztreonam showed a high synergy rate against carbapenem-resistant *Klebsiella pneumoniae* (effect size, ES= 0.91–0.98) and *Escherichia coli* (ES= 0.75–1.00). Ceftazidime/avibactam also demonstrated a high synergy rate (ES= 1) in time-kill studies when combined with azithromycin, fosfomycin and gentamicin against *K. pneumoniae*. Compared to ceftazidime/avibactam alone, a higher bactericidal rate was reported when ceftazidime/avibactam was combined with other antimicrobials against carbapenem-resistant *K. pneumoniae* (57% versus 31%) and *E. coli* (93% versus 0%).

Conclusions: Ceftazidime/avibactam frequently demonstrates synergistic bactericidal activity when combined with various antimicrobials against CR-GNB in *in vitro* tests. Further pre-clinical and clinical studies are warranted to validate the utility of ceftazidime/avibactam-based combination regimens for CR-GNB infections.

Table 2. *In vitro* synergy and antagonism of ceftazidime/avibactam in combination with other antimicrobials against *K. pneumoniae* by test method

Tests method used	Antimicrobials combined with CZA	Number of studies	Number of the isolates tested	ES (95% CI)	Synergy rate	ES (95% CI)	Antagonism rate
Time-kill	Amikacin	5	23	0.43 [0.23; 0.66]	Moderate	0.09 [0.01; 0.28]	Low
	Azithromycin	1	2	1.00 [0.16; 1.00]	High	0.00 [0.00; 0.84]	No antagonism
	Aztreonam	4	11	0.91 [0.59; 1.00]	High	0.00 [0.00; 0.28]	No antagonism
	Colistin	4	23	0.35 [0.16; 0.57]	Low	0.35 [0.16; 0.57]	Low
	Doripenem	1	4	0.25 [0.01; 0.81]	Low	0.00 [0.00; 0.60]	No antagonism
	Fosfomycin	2	3	1.00 [0.29; 1.00]	High	0.00 [0.00; 0.71]	No antagonism
	Gentamicin	2	5	1.00 [0.48; 1.00]	High	0.00 [0.00; 0.52]	No antagonism
	Levofloxacin	1	4	0.50 [0.07; 0.93]	Moderate	0.00 [0.00; 0.60]	No antagonism
	Meropenem	2	6	0.50 [0.12; 0.88]	Moderate	0.33 [0.04; 0.78]	Low
	Polymyxin B	4	20	0.35 [0.15; 0.59]	Low	0.20 [0.06; 0.44]	Low
	Tigecycline	2	14	0.07 [0.00; 0.34]	Positive trend	0.00 [0.00; 0.23]	No antagonism
	Tobramycin	1	4	0.50 [0.07; 0.93]	Moderate	0.00 [0.00; 0.60]	No antagonism
Checkerboard	Amikacin	3	46	0.41 [0.27; 0.57]	Moderate	0.02 [0.00; 0.12]	Positive trend
	Aztreonam	4	131	0.95 [0.89; 0.98]	High	0.00 [0.00; 0.03]	No antagonism
	Colistin	1	30	0.00 [0.00; 0.12]	No synergy	0.00 [0.00; 0.12]	No antagonism
	Fosfomycin	1	3	0.00 [0.00; 0.71]	No synergy	0.02 [0.00; 0.71]	Positive trend
	Meropenem	2	15	1.00 [0.78; 1.00]	High	0.00 [0.00; 0.22]	No antagonism
	Polymyxin B	1	12	0.50 [0.21; 0.79]	Moderate	0.00 [0.00; 0.26]	No antagonism
	Tigecycline	3	45	0.02 [0.00; 0.12]	Positive trend	0.02 [0.00; 0.12]	Positive trend
Etest	Aztreonam	8	153	0.98 [0.94; 1.00]	High	0.01 [0.00; 0.05]	Positive trend
	Cefiderocol	3	11	0.55 [0.23; 0.83]	Moderate	0.00 [0.00; 0.28]	No antagonism
	Ciprofloxacin	1	13	0.00 [0.00; 0.25]	No synergy	0.00 [0.00; 0.25]	No antagonism
	Ertapenem	3	42	0.71 [0.55; 0.84]	Moderate	0.02 [0.00; 0.13]	Positive trend
	Fosfomycin	2	19	0.47 [0.24; 0.71]	Moderate	0.00 [0.00; 0.18]	No antagonism
	Gentamicin	1	13	0.00 [0.00; 0.25]	No synergy	0.00 [0.00; 0.25]	No antagonism
	Imipenem	2	23	1.00 [0.85; 1.00]	High	0.00 [0.00; 0.15]	No antagonism
	MER/VAB	1	18	0.72 [0.47; 0.90]	Moderate	0.00 [0.00; 0.19]	No antagonism
	Meropenem	2	23	1.00 [0.85; 1.00]	High	0.00 [0.00; 0.15]	No antagonism
	Sulbactam	1	2	0.50 [0.01; 0.99]	Moderate	0.00 [0.00; 0.84]	No antagonism
	Tigecycline	3	33	0.06 [0.01; 0.20]	Low	0.00 [0.00; 0.11]	No antagonism

CZA, ceftazidime/avibactam; ES, effect size, ES = 0—the absence of the outcome, ES ≤ 0.35—low, 0.35 < ES < 0.75—moderate, ES ≥ 0.75—high; MER/VAB, meropenem/vaborbactam.

JAC Antimicrob Resist
https://doi.org/10.1093/jacamr/dlac121

JAC-Antimicrobial Resistance

Effect of ceftazidime/avibactam plus fosfomycin combination on 30 day mortality in patients with bloodstream infections caused by KPC-producing *Klebsiella pneumoniae*: results from a multicentre retrospective study

A. Oliva [1]*†, L. Volpicelli[1]†, S. Di Bari[1], A. Curtolo[1], C. Borrazzo[2], F. Cogliati Dezza[1], A. Cona[3], S. Agrenzano[3], A. Mularoni [3], M. Trancassini[1], F. Mengoni[1], S. Stefani[4], G Raponi [1] and M. Venditti[1]

[1]Department of Public Health and Infectious Diseases, Sapienza University of Rome, Piazzale Aldo Moro 5, Rome 00185, Italy; [2]Department of Medico-Surgical Sciences and Biotechnologies, Sapienza University of Rome, Piazzale Aldo Moro 5, Rome 00185, Italy; [3]Unit of Infectious Diseases, ISMETT-IRCCS Istituto Mediterraneo per i Trapianti e Terapie ad Alta Specializzazione, Via E. Tricomi, 5, Palermo 90127, Italy; [4]Department of Biomedical and Biotechnological Sciences. Policlinico Hospital, University of Catania, Via Androne 81, Catania 95124, Italy

*Corresponding author. E-mail: alessandra.oliva@uniroma1.it
†Alessandra Oliva and Lorenzo Volpicelli contributed equally to this work.

Received 11 June 2022; accepted 5 November 2022

Introduction: The primary outcome of the study was to evaluate the effect on 30 day mortality of the combination ceftazidime/avibactam + fosfomycin in the treatment of bloodstream infections (BSIs) caused by KPC-producing *Klebsiella pneumoniae* (KPC-*Kp*).

Materials and methods: From October 2018 to March 2021, a retrospective, two-centre study was performed on patients with KPC-*Kp* BSI hospitalized at Sapienza University (Rome) and ISMETT-IRCCS (Palermo) and treated with ceftazidime/avibactam-containing regimens. A matched cohort (1:1) analysis was performed. Cases were patients receiving ceftazidime/avibactam + fosfomycin and controls were patients receiving ceftazidime/avibactam alone or in combination with *in vitro* non-active drugs different from fosfomycin (ceftazidime/avibactam ± other). Patients were matched for age, Charlson comorbidity index, ward of isolation (ICU or non-ICU), source of infection and severity of BSI, expressed as INCREMENT carbapenemase-producing Enterobacteriaceae (CPE) score.

Results: Overall, 221 patients were included in the study. Following the 1:1 match, 122 subjects were retrieved: 61 cases (ceftazidime/avibactam + fosfomycin) and 61 controls (ceftazidime/avibactam ± other). No difference in overall mortality emerged between cases and controls, whereas controls had more non-BSI KPC-*Kp* infections and a higher number of deaths attributable to secondary infections. Almost half of ceftazidime/avibactam + fosfomycin patients were prescribed fosfomycin without MIC fosfomycin availability. No difference in the outcome emerged after stratification for fosfomycin susceptibility availability and dosage. SARS-CoV-2 infection and ICS ≥ 8 independently predicted 30 day mortality, whereas an appropriate definitive therapy was protective.

Conclusions: Our data show that fosfomycin was used in the treatment of KPC-*Kp* BSI independently from having its susceptibility testing available. Although no difference was found in 30 day overall mortality, ceftazidime/avibactam + fosfomycin was associated with a lower rate of subsequent KPC-*Kp* infections and secondary infections than other ceftazidime/avibactam-based regimens.

Efficacy and Safety of Ceftazidime–Avibactam Alone versus Ceftazidime–Avibactam Plus Fosfomycin for the Treatment of Hospital-Acquired Pneumonia and Ventilator-Associated Pneumonia: A Multicentric Retrospective Study from the SUSANA Cohort

Marco Fois [1], Andrea De Vito [1,*], Francesca Cherchi [1], Elena Ricci [2], Michela Pontolillo [3], Katia Falasca [3], Nicolò Corti [4,5], Agnese Comelli [6], Alessandra Bandera [6], Chiara Molteni [7], Stefania Piconi [7], Francesca Colucci [8], Paolo Maggi [8], Vincenzo Boscia [9], Aakash Fugooah [9], Sara Benedetti [10], Giuseppe Vittorio De Socio [10], Paolo Bonfanti [4,5] and Giordano Madeddu [1,*]

[1] Unit of Infectious Diseases, Department of Medicine, Surgery and Pharmacy, University of Sassari, 07100 Sassari, Italy; m.fois63@studenti.uniss.it (M.F.); f.cherchi25@studenti.uniss.it (F.C.)
[2] Fondazione ASIA Onlus, 20090 Buccinasco, Italy; ed.ricci@libero.it
[3] Clinic of Infectious Diseases, Department of Medicine and Science of Aging, G. D'Annunzio University, Chieti-Pescara, 66100 Chieti, Italy; michypontolillo@hotmail.it (M.P.); k.falasca@unich.it (K.F.)
[4] Infectious Disease Unit, Fondazione IRCCS San Gerardo dei Tintori, 20900 Monza, Italy; n.corti7@campus.unimib.it (N.C.); paolo.bonfanti@unimib.it (P.B.)
[5] School of Medicine and Surgery, University of Milano-Bicocca, 20900 Monza, Italy
[6] Infectious Diseases Unit, Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, 20122 Milan, Italy; agnese.comelli@policlinico.mi.it (A.C.); alessandra.bandera@policlinico.mi.it (A.B.)
[7] Unit of Infectious Diseases, "A. Manzoni" Hospital, 23900 Lecco, Italy; c.molteni@asst-lecco.it (C.M.); s.piconi@asst-lecco.it (S.P.)
[8] Infectious Diseases Unit, AORN Sant'Anna e San Sebastiano, 81100 Caserta, Italy; f.colucci16@studenti.unisa.it (F.C.); paolo.maggi@unicampania.it (P.M.)
[9] Unit of Infectious Diseases, Garibaldi Hospital, 95124 Catania, Italy; enzoboscia@libero.it (V.B.)
[10] Unit of Infectious Diseases, Santa Maria Hospital, 06129 Perugia, Italy; sara.benedetti@ao-siena.toscana.it (S.B.); giuseppe.desocio@ospedale.perugia.it (G.V.D.S.)
* Correspondence: andreadevitoaho@gmail.com (A.D.V.); giordano@uniss.it (G.M.); Tel.: +39-3404704834 (A.D.V.)

check for updates

Citation: Fois, M.; De Vito, A.; Cherchi, F.; Ricci, E.; Pontolillo, M.; Falasca, K.; Corti, N.; Comelli, A.; Bandera, A.; Molteni, C.; et al. Efficacy and Safety of Ceftazidime–Avibactam Alone versus Ceftazidime–Avibactam Plus Fosfomycin for the Treatment of Hospital-Acquired Pneumonia and Ventilator-Associated Pneumonia: A Multicentric Retrospective Study from the SUSANA Cohort. *Antibiotics* **2024**, *13*, 616. https://doi.org/10.3390/antibiotics13070616

Academic Editor: Eduardo Rodríguez-Noriega

Received: 17 May 2024
Revised: 24 June 2024
Accepted: 29 June 2024
Published: 2 July 2024

Abstract: Hospital-acquired pneumonia (HAP) and ventilation-associated pneumonia (VAP) are challenging clinical conditions due to the challenging tissue penetrability of the lung. This study aims to evaluate the potential role of fosfomycin (FOS) associated with ceftazidime/avibactam (CZA) in improving the outcome in this setting. We performed a retrospective study including people with HAP or VAP treated with CZA or CZA+FOS for at least 72 h. Clinical data were collected from the SUSANA study, a multicentric cohort to monitor the efficacy and safety of the newer antimicrobial agents. A total of 75 nosocomial pneumonia episodes were included in the analysis. Of these, 34 received CZA alone and 41 in combination with FOS (CZA+FOS). People treated with CZA alone were older, more frequently male, received a prolonged infusion more frequently, and were less frequently affected by carbapenem-resistant infections ($p = 0.01$, $p = 0.06$, $p < 0.001$, $p = 0.03$, respectively). No difference was found in terms of survival at 28 days from treatment start between CZA and CZA+FOS at the multivariate analysis (HR = 0.32; 95% CI = 0.07–1.39; $p = 0.128$), while prolonged infusion showed a lower mortality rate at 28 days (HR = 0.34; 95% CI = 0.14–0.96; $p = 0.04$). Regarding safety, three adverse events (one acute kidney failure, one multiorgan failure, and one urticaria) were reported. Our study found no significant association between combination therapy and mortality. Further investigations, with larger and more homogeneous samples, are needed to evaluate the role of combination therapy in this setting.

Zheng et al. BMC Infectious Diseases (2023) 23:709
https://doi.org/10.1186/s12879-023-08715-w

BMC Infectious Diseases

RESEARCH Open Access

Ceftazidime/avibactam combined with colistin: a novel attempt to treat carbapenem-resistant Gram-negative bacilli infection

Zihao Zheng[1†], Ziqiang Shao[2†], Lihai Lu[1], Siyu Tang[3], Kai Shi[4], Fangxiao Gong[2] and Jingquan Liu[2*]

Abstract

Background The rapid global emergence and spread of carbapenem-resistant Gram-negative bacilli (CR-GNB) is recognized as a major public health concern, and there are currently few effective treatments for CR-GNB infection. The aim of this study was to investigate the clinical characteristics and outcomes of patients with CR-GNB infections treated with ceftazidime/avibactam (CAZ/AVI) combined with colistin from October 2019 to February 2023 in China.

Methods A total of 31 patients with CR-GNB infections were retrospectively identified using the electronic medical record system of Zhejiang Provincial People's Hospital.

Results Thirty-one patients were treated with CAZ/AVI combined with colistin. Respiratory tract infections (87%) were most common. The common drug-resistant bacteria encompass Klebsiella pneumonia (54.8%), Acinetobacter baumannii (29.0%), and Pseudomonas aeruginosa (16.1%). The 30-day mortality rate was 29.0%, and the 7-day microbial clearance rate was 64.5%. The inflammatory marker CRP changes, but not PCT and WBC, were statistically significant on days 7 and 14 after combination therapy. There were seven patients developing acute renal injury (AKI) after combination therapy and treating with continuous renal replacement therapy (CRRT). Two patients developed diarrhea.

Conclusion The combination of CAZ/AVI and colistin has potential efficacy in patients with CR-GNB infection, but more studies are needed to determine whether it can reduce 30-day mortality rates and increase 7-day microbial clearance. At the same time, the adverse reactions of combination therapy should not be ignored.

Keywords Ceftazidime/avibactam, Colistin, Combination therapy, Carbapenem-resistant Gram-negative bacilli

Journal of Global Antimicrobial Resistance 33 (2023) 321–327

Contents lists available at ScienceDirect

Journal of Global Antimicrobial Resistance

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

Ceftazidime/avibactam-resistant meropenem-susceptible KPC-producing *Klebsiella pneumoniae*: Analysis of cases and evaluation of in vitro activity of fosfomycin-containing combinations

A. Oliva[a,*], D. Al Ismail[a], G. Arcari[b], MC. Miele[a], E. Casali[a], F. Sacco[c], L. Volpicelli[a], M. De Angelis[a], M.T. Mascellino[a], F. Cancelli[a], G. Raponi[a,c], A. Carattoli[b], M Venditti[a]

[a] *Department of Public Health and Infectious Diseases, Sapienza University of Rome, Rome, Italy*
[b] *Department of Molecular Medicine, Sapienza University of Rome, Rome, Italy*
[c] *Microbiology and Virology Unit, University Hospital Policlinico Umberto I, Rome, Italy*

ARTICLE INFO

Article history:
Received 12 January 2023
Revised 18 March 2023
Accepted 26 March 2023
Available online 21 April 2023

Editor: Stefania Stefani

Keywords:
Ceftazidime/avibactam-resistant
meropenem-susceptible KPC-producing
Klebsiella pneumoniae KPC-variant
Fosfomycin
Synergism
Carbapenems
Meropenem/vaborbactam

ABSTRACT

Objectives: Little is known regarding outcomes and optimal therapeutic regimens of infections caused by *Klebsiella pneumoniae* carbapenemase-producing *Klebsiella pneumoniae* (KPC-Kp) resistant to ceftazidime/avibactam (CZA) and susceptible to meropenem (MEM). Although susceptible to MEM in vitro, the possibility of developing MEM resistance overtime is a concern. We describe the clinical characteristics of patients with colonization/infection due to KPC variants with a focus on the in vitro activity of fosfomycin (FOS)-containing combinations.

Methods: Patients with colonization/infection due to a KPC variant were included. Fosfomycin susceptibility was performed by agar dilution method. Synergistic activity of FOS-based combinations was evaluated by gradient strip-agar diffusion method. The emergence of in vitro MEM resistance was also tested.

Results: Eleven patients were included: eight with infection [four with ventilator-associated pneumonia and four with bloodstream infections] and three with colonization. Previous therapy with CZA was administered to all patients (with a mean cumulative duration of 23 days). All subjects with infection received meropenem, in monotherapy (n = 4) or with amikacin (n = 2) or fosfomycin (n = 2), and achieved clinical cure. A new CZA-susceptible and MEM-resistant KPC-Kp strain was subsequently isolated in three patients (27.3%). Meropenem/vaborbactam (MVB) showed high in vitro activity, while FOS+MEM combination was synergistic in 40% of cases. In vitro resistance to MEM was observed with maintenance of CZA resistance.

Conclusions: Detection of KPC variants may occur within the same patient, especially if CZA has been previously administered. Although clinical success has been obtained with carbapenems, the emergence of MEM resistance is a concern. Fosfomycin plus meropenem is synergistic and may be a valuable combination option for KPC variants, while MVB may be considered in monotherapy. The detection of KPC variants in an endemic setting for KPC-Kp represents a worryingly emerging condition. The optimal therapeutic approach is still unknown and the development of meropenem resistance is of concern, which may lead to therapeutic failure in clinical practice. In these cases, the addition of fosfomycin to meropenem, or a more potent antibiotic, such as meropenem/vaborbactam, may be valuable therapeutic options.

Eski Antibiyotikler Enterobacterales

Karbapenem Dirençli Enterobacterales Ağır Enfeksiyonlar

- Seftazidim-Avibaktam
- Seftazidim-Avibaktam
  - -Temin edilemezse
  - -Alerji varsa
  - -Tolere edilemiyorsa
  - -Direnç varsa
- Eski antibiyotiklerin kombinasyonu
- MBL(+) ise Seftazidim-avibaktam + Fosfomisin veya Polimiksin veya AG veya Tigesiklin (Aztreonam ülkemizde yok)

Eski Antibiyotikler

(MDR-Gram Negatifler İçin İntravenöz Kullanılabilen)

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

TABLO 5: KRE enfeksiyonlarının eski antibiyotiklerle tedavisi.*

Klinik Tablo	Ağır enfeksiyonlar**	Ağır olmayan enfeksiyonlar
Piyelonefrit veya Komplike ÜSE		
Ertapenem dirençli-Meropenem dirençli ve Meropenem MİK ≤8 mg/L ise	Meropenem (YD,Uİ) + Kolistin	
	Meropenem (YD,Uİ) + Aminoglikozid veya Fosfomisin veya Tigesiklin***	Aminoglikozidler*****
		Kolistin
		Tigesiklin***
Meropenem MİK >8 mg/L ise	Fosfomisin + Aminoglikozid	
	Tigesiklin*** + Kolistin veya Gentamisin	
Seçenekler çok sınırlı ise	Çift karbapenem****	
Kan Dolaşımı Enfeksiyonları		
Meropenem MİK ≤8 mg/L ise	Meropenem (YD, Uİ) + Polimiksin	
	Meropenem (YD,Uİ) +	
	Fosfomisin****** veya Tigesiklin*******	
Meropenem MİK >8 mg/L ise	Polimiksin******* + Tigesiklin*******	
	Polimiksin******* + Fosfomisin	
	Tigesiklin******* + Aminoglikozid	
İntraabdominal Enfeksiyonlar		
Meropenem MİK ≤8 mg/L ise	Meropenem(YD,Uİ) + Tigesiklin	
		Tigesiklin
Meropenem MİK >8 mg/L ise	Polimiksin + Tigesiklin	
	Fosfomisin + Tigesiklin	
	Polimiksin + Fosfomisin********	
	Tigesiklin + Aminoglikozid*********	
Hastanede Gelişen Pnömoni veya Ventilatörle İlişkili Pnömoni		
Meropenem MİK ≤8 mg/L ise	Meropenem (YD,Uİ) + Polimiksin	
	Meropenem + Fosfomisin******	
Meropenem MİK >8 mg/L ise	Meropenem********** + Fosfomisin******	
	Fosfomisin + Tigesiklin (YD)**********	
	Polimiksin + Tigesiklin (YD)**********	

*Yeni antibiyotiklerin temin edilemediği, yeni antibiyotiklere direnç varlığı ya da yeni antibiyotiklerin tolere edilemediği durumlarda tedavi klinik tablonun ağırlığına, in vitro duyarlılık ve sinerji testleri sonuçlarına, seçilecek ajanın farmakokinetik ve farmakodinamik özelliklerine, enfeksiyon yerine ve konağın özelliklerine göre bireyselleştirilmelidir. Eski antibiyotiklerin kombinasyonlarının klinik açıdan birbirlerine üstünlükleri konusundaki bilgilerimiz yeterli değildir.[43] Meropenem + kolistin dışındaki diğer kombinasyonlarda klinik deneyim azdır ve kanıtların önemli bir kısmı in vitro sinerji testlerinden gelmektedir. Genellikle kombinasyonlarda antagonizma gösterilememiştir.[95]

**Mümkünse in vitro etkili 2 antibiyotik kombinasyonu yapılmalıdır.[43]

***Sadece tigesikline duyarlı ve alternatifin olmadığı durumlarda tigesiklin mümkünse yüksek dozda verilmelidir. Üriner sistem enfeksiyonlarında ve ürosepsisde klinik deneyim oldukça azdır.[43-45] IDSA klavuzunda monoterapi şeklinde kullanılması desteklenmemektedir.[44]

****Deneyimin önemli bir kısmı üriner sistem enfeksiyonlarındadır. Tek karbapeneme üstünlüğü gösterilememiştir. Yeni çalışmalara ihtiyaç vardır, Seçeneklerin sınırlı olduğu durumlarda alternatif olabilir.[61,70,73,91]

*****IDSA klavuzunda alternatif olarak monoterapi önerisi mevcuttur. Bununla birlikte piyelonefrit tedavisinde kanıtlar güçlü değildir.[44,74-76]

******Meropenem + fosfomisin kombinasyonu(izole edilen suş her iki antibiyotiğe dirençli bile olsa) ülkemizde yapılan bir çalışmada sinerjik etkili bulunmuştur.[72]

*******Polimiksin içeren kombinasyonlar tigesiklin içeren kombinasyonlara göre daha başarılı bulunmuştur.[97] IDSA klavuzunda kan dolaşımı enfeksiyonlarında monoterapi şeklinde kullanımı önerilmemektedir.[44] ESCMID klavuzunda kan dolaşımı enfeksiyonlarında kullanılması desteklenmemektedir.[43]

********Bu kombinasyona metronidazol eklenmelidir.

*********Başka alternatif yoksa seçilmelidir(Uluslararası intraabdominal enfeksiyon tedavi klavuzlarında ağır enfeksiyonlarda tigesiklin önerilmemektedir).

**********Meropenem MİK >8 mg/L olsa bile fosfomisin(fosfomisin dirençli bile olsa) ile sinerjiktir. Alternatifin olmadığı durumlarda kullanılabilir.[72]

**********Başka alternatif yoksa tigesiklin yüksek dozda kullanılmalıdır.[43]

KPC(+) *K. pneumoniae* - Tedavi

- 2010-2011, ÇM(3), İtalya
- 125 Kan Dolaşımı Enfeksiyonu – KPC-Kp
- 30 günlük mortalite %41.6
- Monoterapide(tigesiklin, kolistin, gentamisin) mortalite %54.3
- Kombinasyonda(2 veya 3 AB) mortalite %34.1, p=0.02

Tumbarello M et al. Clin Infect Dis 2012

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

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

Journal of Global Antimicrobial Resistance 15 (2018) 127–135

Contents lists available at ScienceDirect

Journal of Global Antimicrobial Resistance

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

Prospective, comparative clinical study between high-dose colistin monotherapy and colistin–meropenem combination therapy for treatment of hospital-acquired pneumonia and ventilator-associated pneumonia caused by multidrug-resistant *Klebsiella pneumoniae*

Mohamed Farouk Ahmed Abdelsalam[a,*], Maged Salah Abdalla[b,1], Hanan Salah El-Din El-Abhar[c]

[a] Clinical Pharmacy Department, The Teachers' Hospital, Al-Jazeera, Cairo, Egypt
[b] Anesthesia Department, Faculty of Medicine, Cairo University, Cairo, Egypt
[c] Department of Pharmacology and Toxicology, Faculty of Pharmacy, Cairo University, Cairo, Egypt

ARTICLE INFO

Article history:
Received 11 May 2018
Received in revised form 4 July 2018
Accepted 6 July 2018
Available online 11 October 2018

Keywords:
Multidrug-resistant
Klebsiella pneumoniae
Hospital-acquired pneumonia
Ventilator-associated pneumonia
Hospital mortality
Procalcitonin

ABSTRACT

Objectives: In clinical practice, colistin is used as combination therapy to improve its antibacterial activity, despite the consequent increase in toxicity. This prospective, comparative study evaluated the effectiveness and adverse effects of using colistin alone at a loading dose of 9 million international units (MIU) followed by 3 MIU every 8 h (q8 h) versus colistin + meropenem 1 g q8 h in treating multidrug-resistant (MDR) *Klebsiella pneumoniae*-induced hospital-acquired pneumonia (HAP) or ventilator-associated pneumonia (VAP). The primary outcome measure was in-hospital mortality. The secondary measure was the occurrence of colistin toxicity.

Methods: A total of 60 patients were divided into two groups (30 patients each); the first group received intravenous colistin at a mean daily dose of 8.304 MIU and the second group received colistin 8.58 MIU combined with meropenem (mean daily dose of 2.88 g for 15 days).

Results: The colistin–meropenem combination group showed a significant decrease in mortality versus colistin alone [16.7% (5/30) vs. 43.3% (13/30); $P = 0.047$]. The improved clinical response mediated by combination therapy was not associated with any significant nephrotoxicity, hepatotoxicity or neurotoxicity. Moreover, the 42 surviving patients showed normal procalcitonin values associated with a decrease in SOFA score, whilst 12 of them showed significantly elevated C-reactive protein (CRP) ($P = 0.0002$).

Conclusions: This study revealed the superiority of colistin–meropenem combination therapy over colistin monotherapy in the treatment of MDR *K. pneumoniae*-induced HAP or VAP and highlights the advantage of procalcitonin over CRP as a marker for eradication of sepsis and suspension of therapy.

KDE – Polimiksin - Metaanaliz

- 19 kontrollu ve 6 tek kollu çalışma
- 1086 hasta
- Kontrollu çalışmalarda polimiksin ile tedavi edilen gruplarla kontrol grupları arasında mortalite, klinik yanıt ve mikrobiyolojik yanıt açısından fark yok

Ni W et al. Braz J Infect Dis 2015

KDE – Polimiksin - Metaanaliz

- Alt grup analizinde polimiksin kombinasyonunda, polimiksin monoterapisine ve kontrol grubuna göre mortalite(28. veya 30.gün) düşük (OR, 0.36,p<0.01 ve OR,0.49,p<0.01)

Ni W et al. Braz J Infect Dis 2015

KDE – Kombinasyon - Metaanaliz

- 20 randomize olmayan çalışma
- 692 hasta
- Bakteriyemi, pnömoni, ÜSE
- Kombinasyon - Mortalite

-Tigesiklin + Gentamisin	%50
-Tigesiklin + Kolistin	%64
-Karbapenem + Kolistin	%67

Falagas ME et al. Antimicrob Agents Chemother 2014

KDE – Kombinasyon - Metaanaliz

- Monoterapi – Mortalite
  - -Kolistin %57
  - -Tigesiklin %80
- 194 Bakteriyemi
  - -Kombinasyonda mortalite daha az

Falagas ME et al. Antimicrob Agents Chemother 2014

Karbapenem Dirençli GNB

- Gözlemsel çalışmalarda polimiksin monoterapisinde mortalite yüksek
- *Klebsiella pneumoniae* bakteriyemilerinde bu fark daha belirgin
- Kanıt kalitesi?

Zusman O et al. J Antimicrob Chemother 2017

Kolistin ve MDR Gram Negatifler: Kombinasyon? Monoterapi?

- Gözlemsel çalışmalarda kombinasyon daha yüksek sağkalım ile birlikte
- RKÇ ise bu etki yok
- Mortalite oranlarında fark yok
- Asya'daki çalışmalarda *Acinetobacter* spp. bakteriyemilerinde yüksek doz kolistin ile kombinasyon etkili görünüyor

Vardakas KZ et al. Int J Antimicrob Agents 2018

Journal of Global Antimicrobial Resistance 23 (2020) 197–202

Contents lists available at ScienceDirect

Journal of Global Antimicrobial Resistance

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

Polymyxin monotherapy versus polymyxin-based combination therapy against carbapenem-resistant *Klebsiella pneumoniae*: A systematic review and meta-analysis

Si-Yuan Hou[a,*], Dan Wu[b], Xing-Huo Feng[a,*]

[a] *Intensive Care Unit, The People's Hospital of Liaoning Province, NO. 33 Wenyi Road, Shenhe District, Shenyang, Liaoning 110016, China*
[b] *Second Department of Rheumatology, Shengjing Hospital of China Medical University, 39 Huaxiang Road, Tiexi District, Shenyang, Liaoning 110022, China*

ARTICLE INFO

Article history:
Received 22 October 2018
Received in revised form 21 July 2020
Accepted 31 August 2020
Available online 19 October 2020

Keywords:
Polymyxin
Monotherapy
Combination therapy
Carbapenem-resistant *Klebsiella pneumoniae*

ABSTRACT

Objectives: This meta-analysis was performed to compare polymyxin monotherapy and polymyxin-based combination therapy for carbapenem-resistant *Klebsiella pneumoniae* (CR-KP) infections.
Methods: We conducted searches on MEDLINE, Embase and Cochrane Collaborative database for both observational studies and randomised controlled trials (RCTs) comparing polymyxin monotherapy with polymyxin-based combination therapy in patients with CR-KP infection. The primary outcome was mortality. We divided all included studies into several groups according to different combination-combination and different infection types. The odds ratio (OR) and 95% confidence intervals (CI) were calculated for outcome analysis.
Results: Ten studies with 481 patients were included. Polymyxin monotherapy was associated with higher mortality than polymyxin-based combination therapy in treatment of CR-KP bloodstream infections (BSI) (OR 1.93, 95% CI 1.14–3.27, $P = 0.01$) and ventilator-associated pneumonia (VAP)/hospital-acquired pneumonia (HAP) (OR 3.82, 95% CI 1.15–12.71, $P = 0.03$). In subgroup analysis of different combinations, mortality was significantly higher with polymyxin monotherapy compared with combination therapy with tigecycline (OR 1.88, 95% CI 1.05–3.37, $P = 0.03$), or with cabapenem (OR 3.11, 95% CI 1.25–7.74, $P = 0.01$), but no differences were found in combinations with aminoglycosides (OR 1.29, 95% CI 0.72–2.29, $P = 0.38$). Three-drug combination therapy including polymyxin was also associated with significant survival benefit (OR 3.86, 95% CI 1.60–9.32, $P = 0.003$).
Conclusions: Polymyxin-based combination therapy provides significant survival benefit in treatment of CR-KP, which appears to be more pronounced when a carbapenem or tigecycline is included in the regimen.

- PDR Kp(CAZ-AVİ henüz yok)
  -Ertapenem + Meropenem + Kolistin

  Oliva A et al. Int J Infect Dis 2015
- PDR Kp(CAZ-AVİ henüz yok)
  -Çift Karbapenem ± Kolistin

  Emre S ve ark. KLİMİK Derg 2018

European Journal of Clinical Microbiology & Infectious Diseases (2023) 42:1269–1273
https://doi.org/10.1007/s10096-023-04660-3

BRIEF REPORT

Ertapenem plus meropenem combination treatment in carbapenem-resistant *Klebsiella pneumoniae* bacteremia: an analysis of 53 cases

Uğur Önal[1,2] · Deniz Akyol[1,3] · Arda Kaya[1] · Dilşah Başkol[1] · Buse Kenanoglu[1] · Gamze Şanlıdağ[1] · Ayşe Uyan Önal[1,4] · Cansu Bulut Avşar[1,5] · Merve Mert[1] · Seichan Memetali[1] · Hüseyin Aytaç Erdem[1] · Devrim Bozkurt[6] · Adnan Şimşir[7] · Osman Bozbıyık[8] · Ümit Kahraman[9] · Erkin Özgiray[10] · Pervin Korkmaz[11] · Feriha Çilli[12] · Hüsnü Pullukçu[1] · Tansu Yamazhan[1] · Meltem Işıkgöz Taşbakan[1] · Bilgin Arda[1] · Sercan Ulusoy[1] · Oğuz Reşat Sipahi[1,13]

Received: 16 May 2023 / Accepted: 3 September 2023 / Published online: 7 September 2023

Abstract

Herein, we aimed to describe the outcomes of patients with blood stream infections due to carbapenem-resistant *Klebsiella pneumoniae* (CR-Kp) who received ertapenem plus meropenem combination treatment (EMCT). A total of 53 patients with culture proven CR-Kp bacteremia treated with ertapenem + meropenem were included. The patients with secondary bacteremia due to urinary tract infection exhibited a significantly lower 1-month mortality (OMM), particularly in those with microbiological eradication and those with end-of-treatment success. Salvage EMCT resulted in 49% 1-month survival.

Table 1 Analysis of study variables in terms of one month mortality (*p* values show comparison of that regimen versus others)

Treatment regimens after culture results		Day-30 mortality		*p* value
		Present	Absent	
Gender	Female	8 (62%)	5 (38%)	0.379
	Male	19 (52%)	21 (48%)	
Age (years)		62.19 ± 2.76	58.92 ± 2.91	0.420
Day 3–5 microbiological success	Present	4 (20%)	16 (80%)	0.002*
	Absent	19 (65%)	10 (35%)	
End of treatment microbiological success	Present	12(32%)	25 (68%)	< 0.001*
	Absent	11 (92%)	1 (8%)	
Pneumonia subgroup	Present	7 (70%)	3 (30%)	0.293
	Absent	20 (46%)	23 (54%)	
Urinary tract infection subgroup	Present	0 (0%)	8 (100%)	0.002*
	Absent	27 (60%)	18 (40%)	
Only receiving EMCT	Present	7 (37%)	12 (63%)	0.920
	Absent	13 (38%)	21 (62%)	
End of therapy clinical success	Present	2 (7%)	25 (93%)	< 0.001*
	Absent	25 (96%)	1 (4%)	

*$p<0.05$

J Antimicrob Chemother 2022; **77**: 3118–3125
https://doi.org/10.1093/jac/dkac292 Advance Access publication 1 September 2022

Journal of Antimicrobial Chemotherapy

Double-, single- and none-carbapenem-containing regimens for the treatment of carbapenem-resistant Enterobacterales (CRE) bloodstream infections: a retrospective cohort

Maria Helena Rigatto[1,2,3]*†, Fabiano Ramos[1,4]†, Andressa Barros[1], Silvia Pedroso[4], Isabelli Guasso[4], Luciana Gonçalves[5], Pedro Bergo[5] and Alexandre P. Zavascki[2,3]

[1]*Medical Sciences Post-Graduation Program, Universidade Federal do Rio Grande do Sul, Porto Alegre, Brazil;* [2]*Department of Internal Medicine, Medical School, Universidade Federal do Rio Grande do Sul, Porto Alegre, Brazil;* [3]*Infectious Diseases Service, Hospital de Clínicas de Porto Alegre, Porto Alegre, Brazil;* [4]*Infection Control Service, Hospital São Lucas da PUCRS, Porto Alegre, Brazil;* [5]*Pontificia Universidade Católica do Rio Grande do Sul, Medical School, Porto Alegre, Brazil*

*Corresponding author. E-mail: mrigatto@hcpa.edu.br
†These authors contributed equally to this study.

Received 27 April 2022; accepted 19 July 2022

Objectives: To investigate the effect of double-, single- and none-carbapenem-containing antimicrobial regimens in the treatment of patients with carbapenem-resistant Enterobacterales (CRE) bloodstream infections (BSIs).

Methods: We conducted a retrospective cohort study from 2013 to 2020 in two Brazilian hospitals. Patients ≥18 years old with CRE BSI were included and excluded if death or treatment duration for ≤48 h after BSI or non-Class A-producing carbapenemase isolates. We evaluated the impact of different carbapenem-containing regimens on 30 day mortality through a propensity score adjusted model and a Cox proportional hazards model.

Results: Two-hundred and seventy-nine patients were included for analyses: 47 (16.9%), 149 (53.4%) and 83 (29.8%) were treated with double-, single- and none-carbapenem-containing regimens, respectively. One-hundred and seventeen (41.9%) patients died in 30 days. Treatment with a single-carbapenem regimen was associated with a lower risk of death in 30 days compared with therapies containing no carbapenem [adjusted HR (aHR) 0.66, 95% CI 0.44–0.99, $P=0.048$], when adjusted for Charlson score and ICU admission at baseline, while double-carbapenem regimens were not associated with a lower risk of death (aHR 0.78, 95% CI 0.46–1.32, $P=0.35$). Propensity score adjusted model results went in the same direction.

Conclusions: Double-carbapenem- was not superior to single-carbapenem-containing regimens in patients with CRE BSIs. Single-carbapenem-containing schemes were associated with a lower mortality risk.

Tigesiklin + Kolistin

- OXA-48(+) Kp: Sinerjik
- KPC-3(+) Kp: İntermediate veya Aditif
- VIM-1 ve KPC-2(+) Kp: İntermediate veya Aditif

Betts JW et al. Antimicrob Agents Chemother 2014

- KPC-Kp, İntraabdominal enf
  -Normal doz Tigesiklin + Kolistin: Başarılı
  -Suşun MİK değerleri düşük

  Camargo JF et al. Antimicrob Agents Chemother 2015

- PDR Kp bakteriyemi(CAZ-AVİ henüz yok)
  -Yüksek doz Tigesiklin + Kolistin: Başarılı

  Humphries RM et al. J Med Microbiol 2010

Tigecycline Treatment for Carbapenem-Resistant *Enterobacteriaceae* Infections

A Systematic Review and Meta-Analysis

Wentao Ni, MD, Yuliang Han, MD, Jie Liu, MD, Chuanqi Wei, MD, Jin Zhao, MD, Junchang Cui, MD, Rui Wang, PhD, and Youning Liu, MD

Abstract: Carbapenem-resistant *Enterobacteriaceae* (CRE) infections are prevalent worldwide; they have few effective treatments and this jeopardizes public health. Clinicians often use tigecycline to combat CRE, but its clinical efficacy remains controversial. Therefore, to compare the efficacy and safety of tigecycline in treating CRE infections compared with that of other antimicrobial agents, and to evaluate whether combination therapy and high-dose regimens are beneficial, we performed a systematic review and meta-analysis.

PubMed and Embase were searched for controlled trials or cohort studies reporting the efficacy and/or safety of tigecycline-based regimens to treat CRE infections. Statistical analyses were performed using the Comprehensive Meta-Analysis V2.2. All meta-analyses were performed based on fixed- or random-effects model, and the I^2 method was used to assess heterogeneity.

Twenty-one controlled studies and 5 single-arm studies were included in this systematic review. With regard to the controlled studies, the tigecycline groups did not differ significantly from the control groups in terms of overall mortality (Odds ratio (OR) = 0.96 [95% confidence interval (CI) = 0.75–1.22; $P = 0.73$]), clinical response rate (OR = 0.58 [95% CI = 0.31–1.09; $P = 0.09$]), or microbiological response rate (OR = 0.46 [95% CI = 0.15–1.44; $P = 0.18$]). Subgroup analyses showed that 30-day mortality was significantly lower in patients who received tigecycline combination therapy than in those who received monotherapy (OR = 1.83 [95% CI = 1.07–3.12; $P = 0.03$]) and other antibiotic regimens (OR = 0.59 [95% CI = 0.39–0.88; $P = 0.01$]), respectively. In addition, high-dose tigecycline regimens differed significantly from standard dose schedules in terms of ICU mortality (OR = 12.48 [95% CI = 2.06–75.43; $P = 0.006$]). The results of the 5 single-arm studies corroborated the findings of the controlled studies.

Our results indicated that the efficacy of tigecycline in treating CRE infections is similar to that of other antibiotics. Tigecycline combination therapy and high-dose regimens may be more effective than monotherapy and standard-dose regimens, respectively. Nonetheless, considering that the current available evidence is limited, well-designed randomized controlled trials are urgently needed to clarify the comparative efficacy of tigecycline in treating CRE infections.

(*Medicine* 95(11):e3126)

Abbreviations: CI = confidence interval, CRE = carbapenem-resistant *Enterobacteriaceae*, ICU = intensive care unit, NOS = Newcastle–Ottawa scale, OR = odds ratio, RCT = randomized controlled trial.

INTRODUCTION

Enterobacteriaceae, such as *Klebsiella pneumoniae*, *Escherichia coli*, and *Enterobacter cloacae*, are frequently involved in hospital-associated infections. In particular, strains that produce extended-spectrum β-lactamases are common.[1] Carbapenems are the most broadly used first-line antibiotics for such infections. However, widespread use of these drugs has resulted in the emergence of carbapenem-resistant strains, most of which produce carbapenemases and are, therefore, resistant to the drug.[2] In recent years, these versatile carbapenemases have spread worldwide among the *Enterobacteriaceae*, especially *K pneumoniae*. For this reason, nosocomial outbreaks of carbapenem-resistant *Enterobacteriaceae* (CRE) are frequent worldwide, leading to prolonged hospital stays and higher mortality rates.[3]

frontiers | Frontiers in Medicine

ORIGINAL RESEARCH

Polymyxin B/Tigecycline Combination vs. Polymyxin B or Tigecycline Alone for the Treatment of Hospital-Acquired Pneumonia Caused by Carbapenem-Resistant *Enterobacteriaceae* or Carbapenem-Resistant *Acinetobacter baumannii*

OPEN ACCESS

Edited by:
Leonardo Neves Andrade,
University of São Paulo, Brazil

Reviewed by:
Clara Stanciulescu,
Carol Davila University of Medicine and Pharmacy, Romania
Jocelyn Tan,
Singapore General Hospital, Singapore

Kang Chang[†], Haibo Wang[†], Jianping Zhao[2], Xianghong Yang[4], Bo Wu[5], Wenkui Sun[6], Man Huang[7], Zhenshun Cheng[8], Hong Chen[9], Yuanlin Song[10], Ping Chen[11], Xianggi Chen[12], Xin Gan[13], Wanli Ma[14], Lihua Xing[15], Yimin Wang[16], Xiaoying Gu[16], Xiaohui Zou[1] and Bin Cao[1,16,17,18]*

Introduction: It is not clear whether polymyxin B/tigecycline (PMB/TGC) combination is better than PMB or TGC alone in the treatment of hospital-acquired pneumonia (HAP) caused by carbapenem-resistant organisms (CROs).

Methods: We conducted a multicenter, retrospective cohort study in patients with HAP caused by CROs. The primary outcome was 28-day mortality, and the secondary outcomes included clinical success and the incidence of acute kidney injury (AKI). Multivariate Cox regression analysis was performed to examine the relationship between antimicrobial treatments and 28-day mortality by adjusting other potential confounding factors.

Results: A total of 364 eligible patients were included in the final analysis, i.e., 99 in the PMB group, 173 in the TGC group, and 92 in the PMB/TGC combination group. The 28-day mortality rate was 28.3% (28/99) in the PMB group, 39.3% (68/173) in the TGC group, and 48.9% (45/92) in the PMB/TGC combination group ($p = 0.014$). The multivariate Cox regression model showed that there was a statistically significant lower risk of 28-day mortality among participants in the PMB group when compared with the PMB/TGC combination group [hazard ratio (HR) 0.50, 95% confidence interval (CI) 0.31–0.81, $p = 0.004$] and that participants in the TGC group had a lower risk of 28-day mortality than in the PMB/TGC combination group but without statistical significance. The incidence of AKI in the PMB group (52.5%) and the PMB/TGC combination group (53.3%) was significantly higher than that in the TGC group (33.5%, $p = 0.001$).

Conclusion: The appropriate PMB/TGC combination was not superior to appropriate PMB therapy in the treatment of HAP caused by carbapenem-resistant *Enterobacteriaceae*/carbapenem-resistant *Acinetobacter baumannii* (CRE/CRAB) in terms of 28-day mortality.

De Pascale et al. Ann. Intensive Care (2020) 10:94
https://doi.org/10.1186/s13613-020-00715-2

Annals of Intensive Care

RESEARCH Open Access

Pharmacokinetics of high-dose tigecycline in critically ill patients with severe infections

Gennaro De Pascale[1,2*†], Lucia Lisi[3,4†], Gabriella Maria Pia Ciotti[3,4], Maria Sole Vallecoccia[1,2], Salvatore Lucio Cutuli[1,2], Laura Cascarano[1,2], Camilla Gelormini[1,2], Giuseppe Bello[1,2], Luca Montini[1,2], Simone Carelli[1,2], Valentina Di Gravio[1,2], Mario Tumbarello[5,6], Maurizio Sanguinetti[7,8], Pierluigi Navarra[3,4†] and Massimo Antonelli[1,2†]

Abstract

Background: In critically ill patients, the use of high tigecycline dosages (HD TGC) (200 mg/day) has been recently increasing but few pharmacokinetic/pharmacodynamic (PK/PD) data are available. We designed a prospective observational study to describe the pharmacokinetic/pharmacodynamic (PK/PD) profile of HD TGC in a cohort of critically ill patients with severe infections.

Results: This was a single centre, prospective, observational study that was conducted in the 20-bed mixed ICU of a 1500-bed teaching hospital in Rome, Italy. In all patients admitted to the ICU between 2015 and 2018, who received TGC (200 mg loading dose, then 100 mg q12) for the treatment of documented infections, serial blood samples were collected to measure steady-state TGC concentrations. Moreover, epithelial lining fluid (ELF) concentrations were determined in patients with nosocomial pneumonia. Amongst the 32 non-obese patients included, 11 had a treatment failure, whilst the other 21 subjects successfully eradicated the infection. There were no between-group differences in terms of demographic aspects and main comorbidities. In nosocomial pneumonia, for a target $AUC_{0\text{-}24}$/MIC of 4.5, 75% of the patients would be successfully treated in presence of 0.5 mcg/mL MIC value and all the patients obtained the PK target with MIC $\leq$ 0.12 mcg/mL. In intra-abdominal infections (IAI), for a target $AUC_{0\text{-}24}$/MIC of 6.96, at least 50% of the patients would be adequately treated against bacteria with MIC $\leq$ 0.5 mcg/mL. Finally, in skin and soft-tissue infections (SSTI), for a target $AUC_{0\text{-}24}$/MIC of 17.9 only 25% of the patients obtained the PK target at MIC values of 0.5 mcg/mL and less than 10% were adequately treated against germs with MIC value $\geq$ 1 mcg/mL. HD TGC showed a relevant pulmonary penetration with a median and IQR ELF/plasma ratio (%) of 152.9 [73.5–386.8].

Conclusions: The use of HD TGC is associated with satisfactory plasmatic and pulmonary concentrations for the treatment of severe infections due to fully susceptible bacteria (MIC < 0.5 mcg/mL). Even higher dosages and combination strategies may be suggested in presence of difficult to treat pathogens, especially in case of SSTI and IAI.

Keywords: Tigecycline, High dose, Pharmacokinetics, Epithelial lining fluid, Critically ill patients, Severe infections

Table 1 Baseline patients' characteristics

	Total cohort ($n=32$)	Treatment failure ($n=11$)	Treatment success ($n=21$)	p value
Demographics and comorbidities				
Age, years	56 [46–68.5]	55 [49.75–71]	56 [45–68.25]	0.75
Male sex, N (%)	17 (53.1)	5 (45.5)	12 (57.1)	0.8
Weight, (kg)	76.5 [60–90]	75 [67.8–80]	90 [60–100]	0.45
Albumin, (g/dL)*	23 [21.5–26.5]	22 [19.25–26.25]	24 [22.75–26.5]	0.17
Fluid balance, (mL)*	+762.9 [−393 to +3703.5]	+3332 [−1124.2 to +4112]	616.3 [−358.5 to +2592.7]	0.5
SAPS II score	53.5 [44.5–67.5]	61 [44.7–66.5]	52 [43.5–67.5]	0.92
Cardiovascular diseases, N (%)	6 (18.75)	3 (27.3)	3 (14.3)	0.39
COPD, N (%)	5 (15.6)	1 (9.1)	4 (19.1)	0.64
Chronic renal failure, N (%)	7 (21.9)	3 (27.3)	4 (19.1)	0.4
Diabetes, N (%)	3 (9.4)	0	3 (14.3)	0.53
Neoplasm, N (%)	7 (21.9)	4 (36.4)	3 (14.3)	0.2
Presenting features and outcomes				
ICU LOS before TGC, (days)	7.5 [2.5–16]	5 [0.5–11.25]	12 [3.75–18.25]	0.13
MV duration before TGC (days)	8 [3–12]	5 [0.5–11.25]	8 [3.75–14.75]	0.19
Vasopressors duration before TGC (days)	4.5 [0–8.5]	5 [0.25–8.25]	4 [0–8.25]	0.89
SOFA score*	7 [4–10]	8 [4.75–12]	6 [4–9]	0.2
Septic shock, N (%)*	18 (56.3)	7 (63.6)	11 (52.4)	0.71
ARF requiring MV, N (%)*	28 (87.5)	10 (90.9)	18 (85.7)	1
AKI requiring CRRT, N (%)*	11 (34.4)	3 (27.3)	8 (38.1)	0.7
Creatinine clearance (ml/min)*	97.3 [32–150.8]	63.2 [32–155]	104 [30–142]	0.85
VAP, N (%)	19 (59.4)	3 (27.3)	16 (76.2)	*0.02*
Non-pulmonary infections, N (%)#	13 (40.6)	8 (72.7)	5 (23.8)	*0.02*
Secondary bacteraemia, N (%)	13 (40.6)	4 (36.4)	9 (42.9)	1
Source control, N (%)	13 (40.6)	7 (63.6)	6 (28.6)	*0.07*
TGC therapy duration,(days)	12 [9–15]	12 [10–15]	11 [8–17]	0.69
TGC empirical therapy, N (%)	17 (53.1)	7 (63.6)	10 (47.6)	0.47
Gram-positive bacteria N (%)**	11 (34.4)	4 (36.4)	7 (33.3)	1
Gram-negative bacteria N (%)***	29 (90.6)	10 (90.9)	19 (90.5)	1
ICU LOS after TGC, (days)	15 [10.5–27]	14.5 [12–19]	16 [10–31.4]	0.42
MV duration after TGC (days)	10 [5–15]	14 [9.75–15.75]	8 [2–13.5]	0.04
Vasopressors duration after TGC (days)	3 [1.5–13]	8 [2.25–13]	3 [0–10.75]	0.12
30-day mortality	9 (28.1)	8 (72.7)	1 (4.8)	<0.001

Data are presented as median [IQR], unless otherwise indicated

Pts patients, *VAP* ventilator-associated pneumonia; *TGC* tigecycline, *SAPS II* Simplified Acute Physiology Score, *COPD* chronic obstructive pulmonary disease, *LOS* length of stay, *ICU* Intensive Care Unit, *MV* mechanical ventilation, *SOFA* Sequential Organ Failure Assessment, *AKI* acute kidney injury; *CRRT* continuous renal replacement therapy, *ARF* acute respiratory failure, *MV* mechanical ventilation; *kg* kilogram, *IQR* interquartile range

* Evaluated at TGC starting day

** i.e. *Staphylococcus aureus* ($n=6$), *enterococci* ($n=3$), *streptococcus* spp. ($n=2$)

*** i.e. *Acinetobacter baumannii* ($n=10$), carbapenem-resistant *Klebsiella pneumonia* ($n=6$), *Escherichia coli* ($n=6$), *Proteus* spp. ($n=5$), *Bacteroides* spp. ($n=2$)

\# Ten intra-abdominal infections and three skin and soft-tissue infections

Table 2 Steady-state serum and alveolar TGC PK parameters in the 32 enrolled patients

Parameter	Patients ($n=32$)
Vd, L	438.6
CL, L/h	42.1
$t_{1/2}$, h	7.2
C_{max}, mcg/mL	0.34 [0.15–1.03]
C_{min}, mcg/mL	0.09 [0.05–0.26]
ELF C_{max}, mcg/mL*	0.42 [0.15–1.2]
ELF C_{min}, mcg/mL*	0.32 [0.17–0.43]
ELF/plasma ratio (%), median [IQR]*	152.9 [73.5–386.8]
$AUC_{0\text{-}24}$, mcg h/mL	3.61 [2.55–10.39]
$AUC_{0\text{-}24}$/0.12 mcg/mL MIC ≥ 4.5, (%)	100
$AUC_{0\text{-}24}$/0.25 mcg/mL MIC ≥ 4.5, (%)	94
$AUC_{0\text{-}24}$/0.5 mcg/mL MIC ≥ 4.5, (%)	75
$AUC_{0\text{-}24}$/1 mcg/mL MIC ≥ 4.5, (%)	40.6
$AUC_{0\text{-}24}$/2 mcg/mL MIC ≥ 4.5, (%)	28.1
$AUC_{0\text{-}24}$/0.12 mcg/mL MIC ≥ 6.96, (%)	100
$AUC_{0\text{-}24}$/0.25 mcg/mL MIC ≥ 6.96, (%)	91
$AUC_{0\text{-}24}$/0.5 mcg/mL MIC ≥ 6.96, (%)	50
$AUC_{0\text{-}24}$/1 mcg/mL MIC ≥ 6.96, (%)	34.4
$AUC_{0\text{-}24}$/2 mcg/mL MIC ≥ 6.96, (%)	15.6
$AUC_{0\text{-}24}$/0.12 mcg/mL MIC ≥ 17.9, (%)	78
$AUC_{0\text{-}24}$/0.25 mcg/mL MIC ≥ 17.9, (%)	44
$AUC_{0\text{-}24}$/0.5 mcg/mL MIC ≥ 17.9, (%)	25
$AUC_{0\text{-}24}$/1 mcg/mL MIC ≥ 17.9, (%)	9.4
$AUC_{0\text{-}24}$/2 mcg/mL MIC ≥ 17.9, (%)	3.1

Data are expressed as median [IQR] and N (%)

TGC tigecycline; *PK* pharmacokinetic; *Vd* volume of drug distribution, *IQR* interquartile range; *CL* drug clearance; $t_{1/2}$ elimination half-life; C_{max} peak plasmatic concentration; C_{min} trough plasmatic concentration; *ELF* epithelial lining fluid; *MIC* minimum inhibitory concentration; *AUC* total drug area under the time–concentration curve

*TGC ELF concentrations were measured in 12 (1 h) and 7 (12 h) samples, respectively

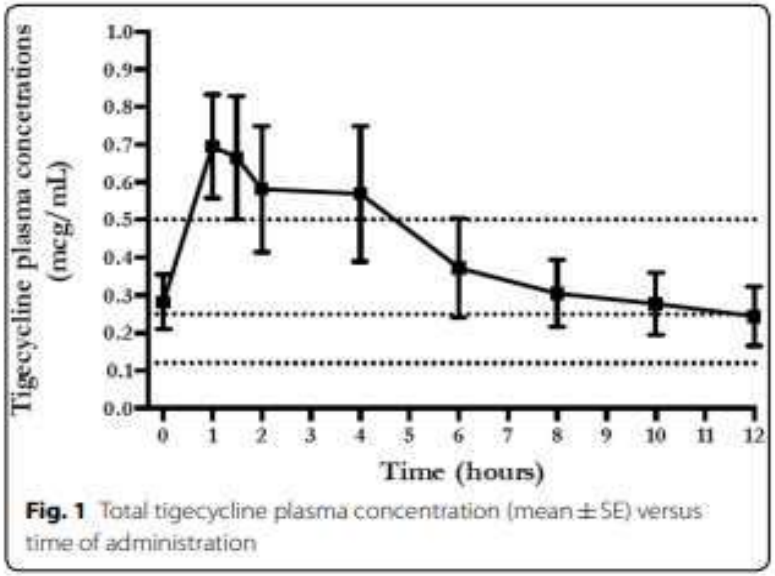


Fig. 1 Total tigecycline plasma concentration (mean ± SE) versus time of administration

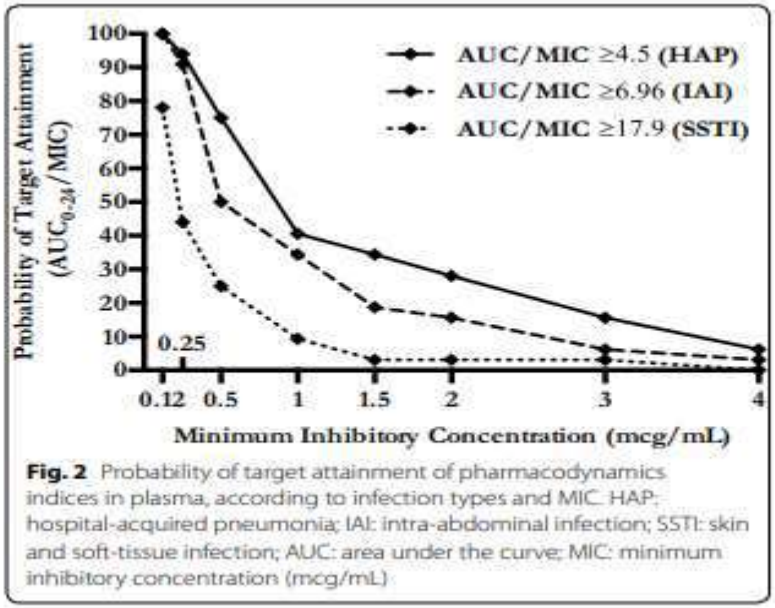


Fig. 2 Probability of target attainment of pharmacodynamics indices in plasma, according to infection types and MIC. HAP: hospital-acquired pneumonia; IAI: intra-abdominal infection; SSTI: skin and soft-tissue infection; AUC: area under the curve; MIC: minimum inhibitory concentration (mcg/mL)

Journal of Chemotherapy

ISSN: (Print) (Online) Journal homepage: https://www.tandfonline.com/loi/yjoc20

In-vitro activity of fosfomycin against *Escherichia coli* and *Klebsiella pneumoniae* bloodstream isolates and frequency of OXA-48, NDM, KPC, VIM, IMP types of carbapenemases in the carbapenem-resistant groups

Pınar Zarakolu, Özgen Köseoğlu Eser, Barış Otlu, Öznur Gürpınar, Cüneyt Özakın, Halis Akalın, İftihar Köksal & Serhat Ünal

Table 2. In-vitro fosfomycin susceptibility of *E. coli* isolates.

Bacteria	n of the isolates	Fosfomycin susceptibility[a] n (%)	Fosfomycin MIC_{50} (µg/ml)	Fosfomycin MIC_{90} (µg/ml)	Range (µg/ml)
Escherichia coli					
Carbapenem-susceptible	85	84/85 (98.8%)	0.5	8	0.5-128
Carbapenem-resistant*	41	39/41 (95.1%)	1	32	0.5-256
Total	126	**122/126 (96.8%)**			

[a]Fisher's exact test p-value=0.786
*32/41 were carbapenemase-producing

Table 3. In-vitro fosfomycin susceptibility of *K. pneumoniae* isolates.

Bacteria	n of the isolates	Fosfomycin susceptibility[a] n (%)	Fosfomycin MIC_{50} (µg/ml)	Fosfomycin MIC_{90} (µg/ml)	Range (µg/ml)
Klebsiella pneumoniae					
Carbapenem-susceptible	76	69/76 (90.7%)	16	32	1-256
Carbapenem-resistant*	144	100/144 (69.4%)	16	128	0.5-256
Total	220	**169/220 (76.8%)**			

[a]CMH Chi-sq. test p-value=0.0004
*131/144 were carbapenemase-producing

Table 4. Distribution of types of carbapenemases in fosfomycin-resistant and fosfomycin-susceptible *E. coli* and *K. pneumoniae* isolates.

	Oxa-48	NDM	KPC	VIM	IMP	Oxa-48, NDM	Oxa-48, NDM, KPC	Oxa-48, NDM, VIM	OXA-48, IMP	NDM, KPC, VIM	NDM, KPC	VIM, IMP
Escherichia coli Carbapenemase-positive ($n=32$)	30	–	–	1	–	1	–	–	–	–	–	–
Fosfomycin-resistant ($n=1$)	1	–	–	–	–	–	–	–	–	–	–	–
Fosfomycin-susceptible ($n=31$)	29	–	–	1	–	1	–	–	–	–	–	–
Klebsiella pneumoniae Carbapenemase-positive ($n=131$)	82	12	14	5	–	9	1	–	1	2	3	2
Fosfomycin-resistant ($n=40$)	24	4	2	2	–	6	–	–	–	1	1	–
Fosfomycin-susceptible ($n=91$)	58	8	12	3	–	3	1	–	1	1	2	2

Retrospective analysis of fosfomycin combinational therapy for sepsis caused by carbapenem-resistant *Klebsiella pneumoniae*

YUN LIAO[1*], GUANG-HUI HU[2*], YUN-FEI XU[2], JIAN-PING CHE[2], MING LUO[2], HAI-MIN ZHANG[2], BO PENG[2], XU-DONG YAO[2], JUN-HUA ZHENG[2] and MIN LIU[2]

Çin, 2012-2014

Erişkin hastalar(104)

Karb-R *K.pneumoniae*

Sepsis/Ağır sepsis/Septik şok

10 suş fosfomisin dirençli

Table II. Antimicrobial susceptibility test result of 104 patients with severe infection caused by carbapenem-resistant *Klebsiella pneumoniae*.

Drug	Sensitive	Intermediary	Resistance
Tigecycline	68 (65.4)	1 (1.0)	35 (33.7)
Minocyline	79 (76.0)	17 (16.3)	8 (7.7)
Colistin	97 (93.3)	0 (0)	7 (6.7)
Gentamicin	14 (13.5)	0 (0)	91 (86.5)
Amikacin	28 (26.9)	0 (0)	76 (73.1)
Meropenem	1 (1.00	0 (0)	103 (99.0)
Imipenem	1 (1.00	0 (0)	103 (99.0)
Ertapenem	1 (1.00	0 (0)	103 (99.0)
Cefepime	9 (8.7)	0 (0)	95 (91.3)
Fosfomycin	40 (38.5)	54 (51.9)	10 (9.6)

Abstract. The aim of the present study was to compare the efficacy and safety of fosfomycin combinational therapy with other antibiotics for the treatment of infections caused by carbapenem-resistant *Klebsiella pneumoniae* (CRKP). This retrospective cohort study examined 104 cases of sepsis caused by CRKP occurring between January 2012 and November 2014 in Shanghai Tenth People's Hospital. Three categories of patient outcome were assessed: Survival/mortality, duration of intensive care unit stays and duration of medical ventilation. Univariate ordinal analyses were adopted to evaluate the correlations between outcome and treatment. A total of 104 patients with physician-diagnosed CRKP were involved in the study. The overall mortality rate was 25.0%. The majority of the infections (84; 80.8%) were hospital acquired. Critical infections received more than one active antibiotic as therapy. Patients treated with fosfomycin combinational therapy were less likely to fail therapy (OR: 4.71, 95% CI: 1.03-21.65, P=0.034) and tended to have a shorter duration of mechanical ventilation. Gender (OR: 4.35, 95% CI: 1.08-3.60, P=0.037), history of chronic obstructive pulmonary disease (OR: 9.35, 95% CI: 0.06-0.19, P=0.007) and peripheral catheter use (OR: 3.00, 95% CI: 0.07-0.19, P=0.002) are risk factors for clinical outcome. Therefore, the use of fosfomycin combinational therapy for treatment of infection due to CRKP appears to be associated with improved survival rate.

Table I. Baseline characteristics of 104 patients with severe infection caused by carbapenem-resistant *Klebsiella pneumoniae*. Univariate analysis of factors associated with clinical outcome, N (%).

Demographic variables	Total (104)	Mortality (26)	Survivors (78)	P-value	OR (95% CI)
Age (mean ± SD)	67.2±15.7	68.4±15.5	66.8±15.9	0.641	
Gender					
Male	79 (76.0)	16 (61.5)	63 (80.8)	**0.047**	**2.63 (1.00-6.93)**
Female	25 (24.0)	10 (38.5)	15 (19.2)		
Type of infection					
CAP	28 (26.9)	6 (23.1)	22 (28.2)	0.610	1.31 (0.46-3.69)
HAP	84 (80.8)	21 (80.8)	63 (80.8)	1.000	1.00 (0.32-3.08)
Urinary tract infection	17 (16.3)	5 (19.2)	12 (15.4)	0.646	0.76 (0.24-2.42)
Surgical site infection	11 (10.6)	2 (7.7)	9 (11.5)	0.581	1.57 (0.32-7.76)
Intra-abdominal infecton	4 (3.8)	1 (3.8)	3 (3.8)	1.000	1.04 (1.00-1.08)
Primary bacteraemia	9 (8.7)	3 (11.5)	6 (7.7)	0.546	0.64 (0.15-2.76)
Central venous catheter bacteraemia	0 (0)	0 (0)	0 (0)		
Ventilator associated pneumonia	1 (1.0)	0 (0)	1 (1.3)	1.000	0.75 (067-0.83)
Targeted treatment					
Monotherapy	32 (30.8)	11 (42.3)	21 (26.9)	0.141	0.50 (0.20-1.27)
Combination therapy	72 (69.2)	15 (57.7)	57 (73.1)		
Fosfomycin combination	**24 (23.1)**	**2 (7.7)**	**22 (28.2)**	**0.034**	**4.71 (1.03-21.65)**
Other treatment regimens	**65 (61.9)**	**16 (24.6)**	**49 (75.4)**		
Length of ICU stays		15.2±10.5	17.6±12.2	0.355	
Duration of mechanical ventilation		10.7±10.6	10.9±10.9	0.958	

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.

JOURNAL OF CHEMOTHERAPY
https://doi.org/10.1080/1120009X.2024.2349439

Taylor & Francis
Taylor & Francis Group

ANTIMICROBIAL ORIGINAL RESEARCH PAPER

A comparative study of ceftazidime/avibactam-based and fosfomycin plus meropenem-based regimens for managing infections caused by carbapenem-resistant *Klebsiella pneumoniae* in critically ill patients

Uğur Önal[a], Ülkü Tüzemen[b], Pınar Küçükdemirci Kaya[c], Remzi İşçimen[c], Nermin Kelebek Girgin[c], Cüneyt Özakın[b], Ferda Kahveci[c] and Halis Akalın[a]

[a]Department of Infectious Diseases and Clinical Microbiology, Uludag University, Bursa, Türkiye; [b]Department of Medical Microbiology, Uludag University, Bursa, Türkiye; [c]Department of Anesthesiology and Reanimation, Uludag University, Bursa, Türkiye

ABSTRACT

The main aim of this study was to compare and analyze the effectiveness of treatment regimens using ceftazidime/avibactam (CAZ/AVI) versus fosfomycin plus meropenem (FOS/MER) for managing bloodstream infections (BSI) or ventilator-associated pneumonia (VAP) caused by carbapenem-resistant *Klebsiella pneumoniae* (CRKP) in critically ill patients. Between 4 January 2019, and 16 July 2023, adult patients (≥18 years old) diagnosed with BSI or VAP due to culture confirmed CRKP in ICU of a tertiary care hospital were investigated retrospectively. A total of 71 patients were categorized into two groups: 30 patients in CAZ/AVI-based, and 41 patients in FOS/MER-based group. No substantial disparities were found in the total duration of ICU hospitalization, as well as the 14- and 30-day mortality rates, between patients treated with CAZ/AVI-based and FOS/MER-based therapeutic regimens. We consider that our study provides for the first time a comprehensive understanding of treatment outcomes and associated risk factors among patients with CRKP-related infections.

ARTICLE HISTORY
Received 9 November 2023
Revised 22 April 2024
Accepted 24 April 2024

KEYWORDS
Ceftazidime-avibactam; fosfomycin; meropenem; carbapenem-resistant *Klebsiella pneumoniae*

Table 1. Characteristics of patients receiving CAZ/AVI-based and fosfomycin plus meropenem-based therapeutic regimen.

Variable	CAZ/AVI ($n = 30$)	FOS/MER ($n = 41$)	Chi-square or *t*-test *p*-values
Age	59.40 ± 3.49	58.76 ± 2.76	0.884
Gender (Female)	10 (33%)	17 (41%)	0.486
Hypertension	14 (47%)	19 (46%)	0.978
Diabetes mellitus	8 (27%)	16 (39%)	0.277
COPD	5 (17%)	4 (10%)	0.387
Chronic Renal Failure	4 (13%)	12 (29%)	0.112
Immunosuppression	7 (23%)	13 (32%)	0.438
APACHE-II score (at admission)	22.93 ± 1.32	23.15 ± 1.52	0.916
APACHE-II score (at diagnosis)	23.9 ± 1.31	21.9 ± 1.05	0.235
SOFA score (at the time of culture collection)	7.87 ± 0.64	8.56 ± 0.54	0.414
SOFA score (at diagnosis)	8.33 ± 0.64	8.66 ± 0.54	0.700
INCREMENT-CPE score (at diagnosis of BSI)	9.48 ± 0.87	11.12 ± 0.57	0.110
Bloodstream infection	17 (57%)	24 (59%)	0.875
Combination treatment[a]	19 (63%)	29 (71%)	0.511
CRRT	7 (23%)	13 (32%)	0.438
Duration (in days) from index culture to initiation of treatment[b]	4.2 ± 0.52	3.37 ± 0.45	0.235
Polymicrobial infection	19 (63%)	21 (51%)	0.309
Polymicrobial BSI	8 (27%)	10 (24%)	0.828
Polymicrobial infection with *Acinetobacter* spp.	9 (30%)	11 (27%)	0.769
Polymicrobial infection with *Pseudomonas aeruginosa*	5 (17%)	4 (10%)	0.387
Polymicrobial infection with Staphylococci	3 (10%)	6 (15%)	0.562
Polymicrobial infection with other pathogens[c]	4 (13%)	2 (5%)	0.206

All data are exhibited as number (%), Mean ± standard deviation (SD), COPD: Chronic obstructive pulmonary disease, CRRT: Continuous renal replacement therapy, CAZ/AVI: Ceftazidime/avibactam-based, FOS/MER: Fosfomycin plus meropenem-based.

[a]Rather than FOS/MER combination.

[b]CAZ/AVI- based or FOS/MER-based treatment.

[c]*Escherichia coli* ($n = 2$), *Citrobacter koseri* ($n = 2$), *Stenotrophomonas maltophilia* ($n = 1$), *Enterococcus faecium* ($n = 1$).

Table 2. Mortality rates and length of ICU hospitalization for CAZ/AVI-based and fosfomycin plus meropenem-based therapeutic regimens.

Variable	CAZ/AVI ($n = 30$)	FOS/MER ($n = 41$)	Chi-square or *t*-test *p*-values
14-day mortality	10 (33%)	17 (42%)	0.486
30-day mortality	15 (50%)	25 (61%)	0.357
14-day mortality within the BSI subgroup	5 (29%)	7 (29%)	0.986
30-day mortality within the BSI subgroup	8 (47%)	13 (54%)	0.654
14-day mortality within the VAP subgroup	5 (39%)	10 (59%)	0.269
30-day mortality within the VAP subgroup	7 (54%)	12 (71%)	0.346
Total duration of ICU hospitalization (days)	59.93 ± 9.98	45.27 ± 7.29	0.228

All data are exhibited as number (%), Mean ± standard deviation (SD), CAZ/AVI: Ceftazidim/avibactam-based, FOS/MER: Fosfomycin plus meropenem-based.

Karbapenem ve Kolistin Dirençli Enterobacterales
Eski Antibiyotikler

Journal of Hospital Infection 98 (2018) 260–263

Available online at www.sciencedirect.com

Journal of Hospital Infection

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

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

M. Aydın [a,*], Ö. Ergönül [b], A. Azap [c], H. Bilgin [d], G. Aydın [c,e], S.A. Çavuş [f], Y.Z. Demiroğlu [g], H.E. Alışkan [h], O. Memikoğlu [c], Ş. Menekşe [i], Ş. Kaya [j], N.A. Demir [k], İ. Karaoğlan [l], S. Başaran [m], Ç. Hatipoğlu [n], Ş. Erdinç [n], E. Yılmaz [o], A. Tümtürk [p], Y. Tezer [p], H. Demirkaya [q], Ş.E. Çakar [r], Ş. Keske [b], S. Tekin [b], C. Yardımcı [s], Ç. Karakoç [t], P. Ergen [u], Ö. Azap [q], L. Mülazımoğlu [d], O. Ural [k], F. Can [v], H. Akalın [o], Turkish Society of Clinical M

G

S U M M A R Y

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

Table I
Antibiotic resistance rates in 1556 episodes of healthcare-associated Gram-negative bacteraemia

Species	*N* (%) of isolates that were resistant to:				
	Carbapenems	Fluoroquinolones	Third-generation cephalosporins	Aminoglycosides	Colistin
Acinetobacter baumannii N = 437	401 (91.8)	389 (89.0)	410 (93.8)	310 (70.9)	9 (2.1)
Klebsiella pneumoniae N = 416	216 (51.9)	266 (63.9)	320 (76.9)	200 (48.1)	67 (16.1)
Escherichia coli N = 339	34 (10.0)	189 (55.8)	203 (59.9)	103 (30.4)	3 (0.9)
Pseudomonas aeruginosa N = 205	88 (42.9)	102 (49.8)	103 (50.2)	65 (31.7)	18 (8.8)
Enterobacter cloacae N = 159	37 (23.3)	46 (28.9)	59 (37.1)	51 (32.1)	9 (5.7)

The most common primary diagnosis in the study patients was cardiovascular disease, followed by solid organ and haematological malignancies (Table II). On univariate analysis, numerous factors were found to be associated with fatality (Table II). On multi-variate analysis, age >70 years, central-catheter-related infections, ventilator-associated pneumonia, APACHE II score, MIC of carbapenems and MIC of colistin were included as the independent variables. The MICs of carbapenems [odds ratio (OR) 1.02, 95% confidence interval (CI) 1.01—1.04; $P = 0.002$] and colistin (OR 1.1, 95% CI 1.03—1.17, $P = 0.001$) were the only factors that were significantly associated with fatality. The logistic regression model predicted fatality with sensitivity of 74% (area under receiver operating characteristic curve was 74%).

Kolistin-R ve Karbapenem-R Kp

- Kolistin + Tigesiklin sinerjik

  Betts Jwet al. Antimicrob Agents Chemother 2014

- Kolistin + Ertapenem + Meropenem hızlı bakterisidal etki

  Oliva A et al. Int J Infect Dis 2015
  Oliva A et al. J Infect 2016

AMERICAN SOCIETY FOR MICROBIOLOGY | Microbiology Spectrum

a | Antimicrobial Chemotherapy | Research Article

Effect of colistin-tigecycline combination on colistin-resistant and carbapenem-resistant *Klebsiella pneumoniae* and *Acinetobacter baumannii*

Suyeon Park,[1] Yanhong Jin,[1] Kwan Soo Ko[1]

TABLE 1 Antimicrobial susceptibility profiles of *K. pneumoniae* and *A. baumannii* strains

Species	Strain	Minimum inhibitory concentration (mg/L)[a]			
		Tigecycline	Colistin	Meropenem	Imipenem
K. pneumoniae	742	1 (S)	64 (R)	64 (R)	64 (R)
	777	1 (S)	64 (R)	64 (R)	64 (R)
A. baumannii	F-1629	2 (S)	>64 (R)	>64 (R)	>64 (R)
	SCH2203-16	2 (S)	64 (R)	>64 (R)	>64 (R)

[a]R, resistant; S, susceptible.

Zaman-Ölüm Eğrisi

Kolistin 2 mg/L + Tigesiklin 4-8 mg/L Sinerjik etkili

Galleria mellonella larva modelinde etkili

AMERICAN SOCIETY FOR MICROBIOLOGY | Antimicrobial Agents and Chemotherapy®

Synergistic Activity of Colistin-Containing Combinations against Colistin-Resistant *Enterobacteriaceae*

Thea Brennan-Krohn,[a,b,d] Alejandro Pironti,[c] James E. Kirby[a,d]

TABLE 2 Rates of synergy by drug using checkerboard array

Drug tested in combination with colistin	% synergy[a] (95% confidence interval) for:	
	All strains	Strains excluding species intrinsically resistant to colistin
Linezolid	95.0 (73.1–99.7)	100 (78.1–100.0)
Rifampin	94.7 (71.9–99.7)	100 (77.1–100.0)
Azithromycin	90.0 (66.9–98.2)	100 (78.1–100.0)
Fusidic acid	90.0 (66.9–98.2)	94.4 (70.6–99.7)
Minocycline	85.0 (61.1–96.0)	88.9 (63.9–98.1)
Clindamycin	80.0 (55.7–93.4)	88.9 (63.9–98.1)
Erythromycin	80.0 (55.7–93.4)	88.9 (63.9–98.1)
Chloramphenicol	75.0 (50.6–90.4)	77.8 (51.9–92.6)
Levofloxacin	70.0 (36.4–80.0)	66.7 (41.2–85.6)
Doxycycline	60.0 (36.4–80.0)	66.7 (41.2–85.6)
Ceftazidime-avibactam	41.2 (19.4–66.5)	46.7 (22.3–72.6)
Tigecycline	25.0 (9.6–49.4)	27.8 (10.7–53.6)
Vancomycin	25.0 (9.6–49.4)	27.8 (10.7–53.6)
Tetracycline	20.0 (6.6–44.3)	22.2 (7.4–48.1)
Meropenem	15.0 (4.0–38.9)	11.1 (1.9–36.1)
Amikacin	15.0 (4.0–38.9)	16.7 (4.4–42.3)
Trimethoprim-sulfamethoxazole	15.0 (4.0–38.9)	11.1 (1.9–36.1)
Apramycin	10.0 (1.8–33.1)	11.1 (1.9–36.1)
Daptomycin	0.0 (0–22.9)	0.0 (0.0–25.3)

[a]Synergy percentages represent the results of testing of 20 isolates for each combination, except rifampin (results of testing of 19 isolates were used because 1 trial had skipped wells), daptomycin (results for testing of 17 isolates were used because 1 trial had skipped wells and 2 trials had colistin MICs >±1 2-fold dilution from the modal MIC), and ceftazidime-avibactam (results for 17 isolates were used because 3 trials had colistin MICs >±1 2-fold dilution from the modal MIC).

TABLE 3. Univariate analysis of risk factors for in-hospital mortality among 91 patients infected by carbapenem-resistant *Klebsiella pneumoniae* (CR-KP)

	Survivors (n = 66), n (%)	Non-survivors (n = 25), n (%)	p
Demographic data			
Age (years, median, IQR)	68, 45.7–75.2	75, 60–77.5	0.05
Male sex	40 (60.6)	15 (60)	1
Underlying conditions			
Immunosuppression[a]	27 (40.9)	15 (60)	0.15
Diabetes	23 (34.8)	8 (32)	0.81
Chronic obstructive pulmonary disease	18 (27.3)	13 (52)	0.04
Chronic kidney disease	15 (22.7)	12 (48)	0.02
Cancer	13 (19.7)	6 (24)	0.77
Chronic liver disease	4 (6.1)	2 (8)	1
Charlson score (median, IQR)	5, 2–8	6, 4–10	0.03
Days of stay before isolation (median, IQR)	12.5, 7–37	17, 13–25	0.29
Ward of hospitalization			
Intensive-care unit	23 (34.8)	21 (84)	<0.001
APACHE II score (median, IQR)[b]	14, 12–17	18, 12–22	0.12
Medical	34 (51.5)	2 (8)	<0.001
Surgical	9 (13.6)	2 (8)	0.51
Mechanism of carbapenem resistance			
K. pneumoniae carbapenemases	59 (89.4)	24 (96)	0.69
Verona integron-encoded metallo-β-lactamase	3 (4.5)	0	
Extended spectrum β-lactamases + OmpKs	4 (6.1)	1 (4)	
Antibiotic resistance			
Imipenem	64 (97)	24 (96)	1
Meropenem	57 (86.4)	24 (96)	0.27
Gentamicin	51 (77.3)	21 (84)	0.57
Colistin	19 (28.8)	13 (52)	0.05
Tigecycline	15 (22.7)	2 (8)	0.14
Fosfomycin	8/14 (57.1)	3/9 (33.3)	0.40
Type of infection			
Urinary tract infection	29 (43.9)	0	<0.001
Bloodstream infection (BSI)	18 (27.3)	16 (64)	0.002
Low-risk BSI	10 (15.2)	6 (24)	0.36
High-risk BSI	8 (12.1)	10 (40)	0.006
Lower respiratory tract infection	8 (12.1)	6 (24)	0.19
Skin and soft tissues infection[c]	9 (13.6)	2 (8)	1
Intra-abdominal infection	2 (3)	1 (4)	1
Septic shock	0	15 (60)	<0.001
Therapeutic management			
Appropriate antibiotic therapy	50 (75.8)	17 (68)	0.59
Antibiotic therapy with two or more agribiotics	37 (56.1)	17 (68)	0.34
Gentamicin monotherapy	15 (22.7)	1 (4)	0.03
Colistin monotherapy	6 (9.1)	4 (16)	0.45
Colistin plus tigecycline	12 (18.2)	4 (16)	1
Colistin plus fosfomycin	5 (7.6)	0	0.32
Colistin plus gentamicin	3 (4.5)	2 (8)	0.61
Tigecycline plus fosfomycin	4 (6.1)	2 (8)	1
Removal of the infectious source	19 (28)	7 (28)	1

IQR, interquartile range; ICU, intensive care unit; OmpKs, outer membrane proteins.
[a]Immunosuppression includes patients with solid organ transplantation, corticosteroid therapy, and human immunodeficiency virus infection.
[b]APACHE II score at the ICU admission was calculated for the 46 patients hospitalized in ICU at the time of CR-KP isolation.
[c]Skin and soft tissues infection includes surgical site infections.

High rate of colistin resistance among patients with carbapenem-resistant *Klebsiella pneumoniae* infection accounts for an excess of mortality

A. Capone[1], M. Giannella[1], D. Fortini[2], A. Giordano[3], M. Meledandri[4], M. Ballardini[4], M. Venditti[5], E. Bordi[6], D. Capozzi[7], M. P. Balice[8], A. Tarasi[9], G. Parisi[10], A. Lappa[10], A. Carattoli[2], N. Petrosillo[1] and on behalf of the SEERBIO-GRAB

TABLE 4. Multivariate analysis of risk factors for in-hospital mortality in patients with infection due carbapenem-resistant *Klebsiella pneumoniae* (CR-KP), adjusted for appropriate antibiotic treatment, combination therapy and removal of the infectious source

	OR (95% CI)	p
Charlson comorbidity score	1.42 (1.15–1.76)	0.001
Hospitalization in intensive-care unit	18.05 (3.90–83.51)	<0.001
Bloodstream infection	4.92 (1.35–17.28)	0.01
Infection due to a colistin-resistant strain	4.15 (1.17–14.74)	0.02

J Antimicrob Chemother 2015; **70**: 905–913
doi:10.1093/jac/dku432 Advance Access publication 25 October 2014

Journal of Antimicrobial Chemotherapy

Gentamicin therapy for sepsis due to carbapenem-resistant and colistin-resistant *Klebsiella pneumoniae*

Marcelino Gonzalez-Padilla[1]†, Julián Torre-Cisneros[1,2]*†, Francisco Rivera-Espinar[3], Antonio Pontes-Moreno[3], Lorena López-Cerero[2,4,5], Alvaro Pascual[2,4,5], Clara Natera[1], Marina Rodríguez[3], Inmaculada Salcedo[6], Fernando Rodríguez-López[2,7], Antonio Rivero[1] and Jesús Rodríguez-Baño[2,4,5]

[1]*Clinic Unit of Infectious Diseases, Hospital Universitario Reina Sofia-IMIBIC-Universidad de Córdoba, Córdoba, Spain;* [2]*Spanish Network for Research in Infectious Diseases (REIPI RD12/0015), Instituto de Salud Carlos III, Madrid, Spain;* [3]*Intensive Care Unit, Hospital Universitario Reina Sofia, Córdoba, Spain;* [4]*Clinic Unit of Infectious Diseases, Microbiology and Preventive Medicine, Hospitales Universitarios Virgen Macarena y Virgen del Rocio, Seville, Spain;* [5]*Departamento de Medicina, Universidad de Sevilla, Seville, Spain;* [6]*Clinic Unit of Preventive Medicine, Hospital Universitario Reina Sofia, Córdoba, Spain;* [7]*Clinic Unit of Microbiology, Hospital Universitario Reina Sofia, Universidad de Córdoba, Córdoba, Spain*

*Corresponding author. Unidad Clinica de Enfermedades Infecciosas, Hospital Universitario Reina Sofia-IMIBIC-Universidad de Córdoba, Avenida Menendez Pidal s/n, 14004-Córdoba, Spain. Tel: +34957011636; Fax: +34957011636; E-mail: julian.torre.sspa@juntadeandalucia.es
†M. G.-P. and J. T.-C. contributed equally to this work.

Received 24 June 2014; returned 4 August 2014; revised 11 September 2014; accepted 29 September 2014

Objectives: Antimicrobial therapy for sepsis caused by carbapenem- and colistin-resistant *Klebsiella pneumoniae* is not well established. We hypothesized that the early use of gentamicin in cases due to susceptible organisms would decrease the crude mortality rate of this infection.

Methods: This retrospective cohort study examined 50 cases of sepsis caused by carbapenem-resistant *K. pneumoniae* occurring between June 2012 and February 2013 during an outbreak of *K. pneumoniae* ST512 producing KPC-3, SHV-11 and TEM-1. Survival curves categorized by the use of gentamicin were constructed using the Kaplan–Meier method and compared using the log-rank test. Eight multivariate models using Cox regression were designed to study the risk factors for mortality and test the hypothesis.

Results: The 30 day crude mortality rate was 38%. The use of targeted gentamicin was associated with reduced mortality (20.7% versus 61.9%, $P=0.02$). In all multivariate regression models, the use of gentamicin was independently associated with lower mortality until Day 30 (HR 0.17–0.29, $P=0.03$–0.002 depending on the model) after controlling for other potential confounding variables such as age, optimal treatment, renal function, severity of infection, underlying disease, use of tigecycline and previous hospitalization.

Conclusions: Gentamicin reduced the mortality from sepsis caused by this *K. pneumoniae* ST512 clone producing KPC-3, SHV-11 and TEM-1.

Keywords: *K. pneumoniae*, carbapenem resistance, mortality

Table 1. Baseline characteristics of 50 patients with severe infection caused by carbapenem-resistant and colistin-resistant *K. pneumoniae*: univariate analysis of factors associated with crude mortality at 30 days

	Number (%) of patients (unless otherwise stated)				
	total ($n=50$)	no survivors ($n=19$)	survivors ($n=31$)	P	HR (95% CI)
Demographic variables					
age (years), median (range)	**60.5 (19–86)**	**67 (41–86)**	**55 (19–85)**	**0.046**	**1.03 (1.00–1.06)**
male	32 (64.0)	12 (63.2)	20 (64.5)	0.971	0.98 (0.38–2.49)
Comorbidities					
Charlson index, median (range)	4 (0–11)	4 (0–11)	3 (0–8)	0.178	1.13 (0.95–1.35)
renal failure[a]	**16 (32.0)**	**10 (52.6)**	**6 (19.4)**	**0.008**	**3.44 (1.39–8.54)**
Previous hospitalization (3 previous months)	**16 (32.0)**	**10 (52.6)**	**6 (19.4)**	**0.022**	**2.88 (1.16–7.14)**
Admission to the ICU	22 (44.0)	8 (42.1)	14 (45.2)	0.671	1.16 (0.59–2.59)
Invasive procedures (in previous week)					
mechanical ventilation	26 (52.0)	10 (52.6)	16 (51.6)	0.644	1.24 (0.49–3.16)
central venous catheter	36 (72.0)	11 (57.9)	25 (80.6)	0.349	0.62 (0.23–1.68)
urinary catheter	46 (92.0)	17 (89.5)	29 (93.5)	0.893	0.90 (0.21–3.92)
Prior antibiotic therapy (in the previous month)					
quinolones	**21 (42.0)**	**12 (63.2)**	**9 (29.0)**	**0.043**	**2.63 (1.03–6.71)**
amoxicillin/clavulanic acid	14 (28.0)	3 (15.8)	11 (35.5)	0.132	0.42 (0.12–1.43)
meropenem	23 (46.0)	9 (47.4)	14 (45.2)	0.764	1.14 (0.46–2.82)
cephalosporins	12 (24.0)	7 (36.8)	5 (16.1)	0.071	2.36 (0.93–6.02)
piperacillin/tazobactam	13 (26.0)	6 (31.6)	7 (22.6)	0.461	1.44 (0.55–3.79)
Type of infection					
pneumonia	24 (48.0)	8 (42.1)	16 (51.6)	0.356	1.07 (0.93–1.23)
purulent tracheobronchitis	4 (8.0)	1 (5.3)	3 (9.7)		
urinary tract infection	10 (20.0)	5 (26.3)	5 (16.1)		
surgical wound infection	4 (8.0)	1 (5.3)	3 (9.7)		
intra-abdominal infection	1 (2.0)	1 (5.3)	0 (0)		
infection of skin and soft tissue	1 (2.0)	0 (0)	1 (3.2)		
endocarditis	1 (2.0)	1 (5.3)	0		
primary or catheter-related bacteraemia	4 (8.0)	2 (10.5)	2 (6.5)		
infection of the CNS	1 (2.0)	0	1 (3.2)		
Bacteraemia	18 (36.0)	7 (36.8)	11 (35.5)	0.866	1.08 (0.43–2.57)
Severe sepsis/septic shock	**30 (60.0)**	**18 (94.7)**	**12 (38.7)**	**0.006**	**16.6 (2.21–125.1)**
CL_{CR} at start of antibiotic treatment (mL/min), mean ± SD	**96.2 ± 53.2**	**69.4 ± 38.0**	**112.6 ± 55.0**	**0.005**	**0.98 (0.97–0.99)**

Active empirical treatment	6 (12.0)	2 (10.5)	4 (12.9)	0.857	0.87 (0.20–3.78)
Time to initiation of optimal targeted treatment (days), mean (range)	2.1 (0–5)	1.7 (0–5)	2.2 (0–5)	0.405	0.86 (0.61–1.22)
Optimal targeted treatment	**37 (74.0)**	**9 (47.4)**	**28 (90.3)**	**0.001**	**0.18 (0.07–0.45)**
monotherapy	16 (32.0)	4 (21.1)	12 (38.7)	0.258	0.53(0.18–1.60)
tigecycline	8 (16.0)	3 (15.8)	5 (16.1)		
gentamicin	8 (16.0)	1 (5.3)	7 (22.6)		
combination therapy	21 (42.0)	5 (26.3)	16 (51.6)	0.058	0.37 (0.13–1.03)
tigecycline + gentamicin	21 (42.0)	5 (26.3)	16 (51.6)		
Optimal targeted treatment with tigecycline	29 (58.0)	8 (42.1)	21 (67.7)	0.059	0.41 (0.16–1.03)
Optimal targeted treatment with high-dose tigecycline	10 (20.0)	1 (5.3)	9 (29.0)	0.098	0.18 (0.20–1.37)
	total (n=50)	no survivors (n=19)	survivors (n=31)	P	HR (95% CI)
Targeted treatment with meropenem	11 (22.0)	9 (47.4)	2 (6.4)	<0.001	6.02 (2.37–15.28)
Optimal targeted treatment with gentamicin	**29 (58.0)**	**6 (31.6)**	**23 (74.2)**	**0.002**	**0.21 (0.08–0.57)**
MIC ≤2 mg/L	**13 (26.0)**	**1 (5.3)**	**12 (38.7)**	**0.009**	**0.05 (0.01–0.47)**
MIC >2 to ≤4 mg/L	16 (32.0)	5 (26.3)	11 (35.5)	0.133	0.42 (0.14–1.30)

Variables with a statistically significant different distribution between survivors and non-survivors are shown in bold.
[a]CL_{CR} calculated using the Cockroft–Gault formula.

Klebsiella pneumoniae Bakteriyemisi

- Kartal Koşuyolu Hastanesi
- 2011-2017, retrospektif
- 210 Kp bakteriyemisi
- 111 Karbapenem dirençli
- 60 Kolistin dirençli(OXA-48 %78, NDM %35)
- 30.gün mortalitesi %58
- Mortalite için bağımsız risk faktörleri
  -Karbapenem direnci, APACHE II skoru yüksekliği
- Tedaviye amikasin eklenmesi koruyucu

Menekse S et al. Int J Infect Dis 2019

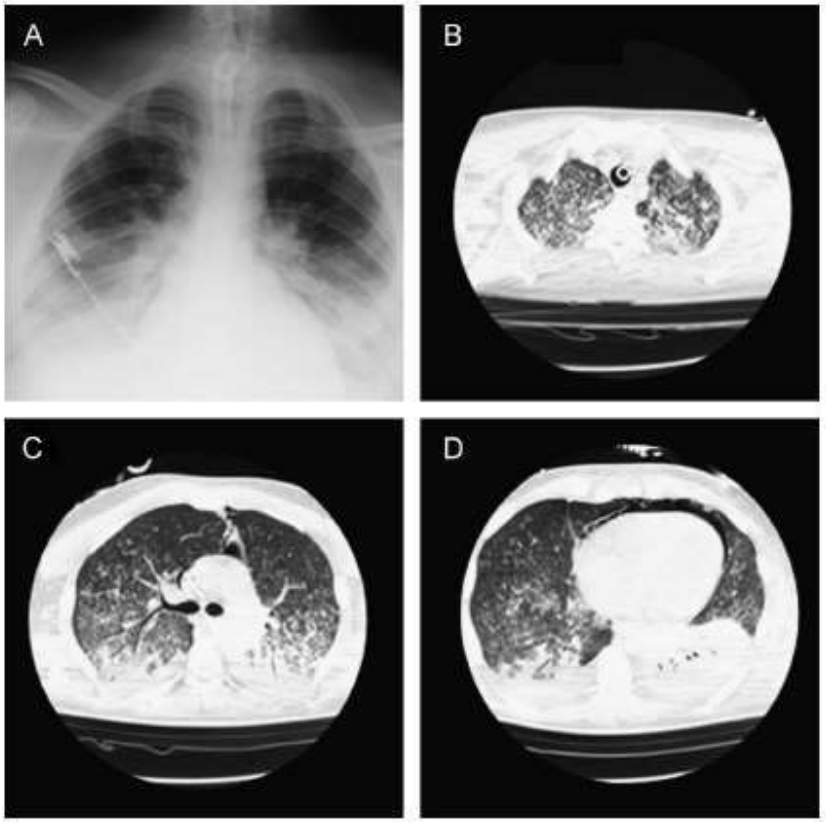
Kolistin Dirençli Kp - VİP

Table 2 – Antibiotic susceptibility test on bronchoalveolar lavage positive for KPC-Kp.

Antibiotic[a]	Vitek-2® (MIC μg/ml)	E-test (MIC μg/ml)
Amikacin	>16	32
Colistin	>16	4
Cotrimoxazole	–	>32
Fosfomycin	–	16
Gentamicin	4	2
Imipenem	>16	16
Meropenem	>16	8
Tigecycline	2	2

KPC-Kp, *Klebsiella pneumoniae* producing KPC-type carbapenemase; MIC, minimum inhibitory concentration.

[a] Susceptibility was determined in accordance to European Committee on Antimicrobial Susceptibility Testing (EUCAST) clinical breakpoints.



Kolistin Dirençli Kp - VİP

- Tigesiklin 2x100 mg
  + Fosfomisin 3x3 g
  + Kolistin 2x4.5 MIU
- 9 günlük tedavi ile iyileşme

Viaggi B et al. Respir Invest 2015

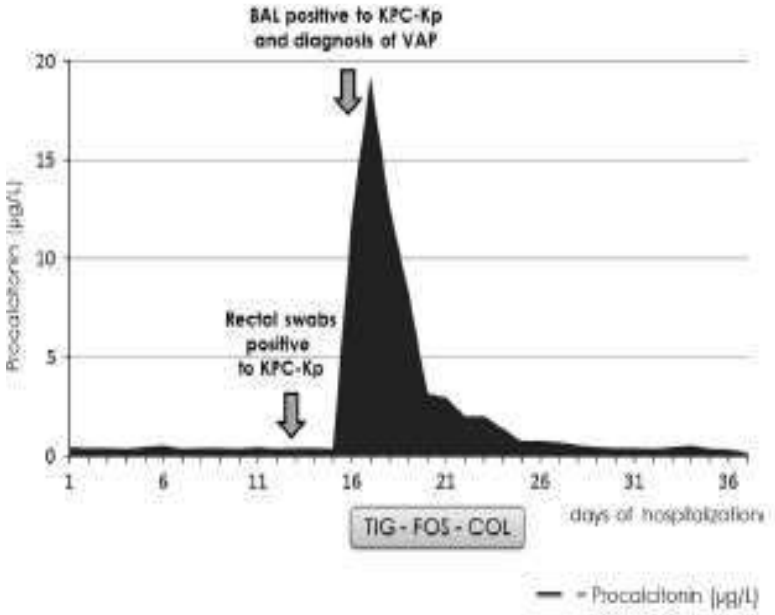


Fig. 2 – Time-course of serum procalcitonin concentration and antibiotic administrations in the intensive care unit. COL: colistin, FOS: fosfomycin, TIG: tigecycline, BAL: bronchoalveolar lavage, KPC-Kp: *Klebsiella pneumoniae* producing KPC-type carbapenemase.

Mortality Associated with Bacteremia Due to Colistin-Resistant *Klebsiella pneumoniae* with High-Level Meropenem Resistance: Importance of Combination Therapy without Colistin and Carbapenems

Isabel Machuca,[a] Belén Gutiérrez-Gutiérrez,[b] Irene Gracia-Ahufinger,[c] Francisco Rivera Espinar,[d] Ángela Cano,[a] Julia Guzmán-Puche,[c] Elena Pérez-Nadales,[a] Clara Natera,[a] Marina Rodríguez,[d] Rafael León,[d] Juan J. Castón,[a] Fernando Rodríguez-López,[c] Jesús Rodríguez-Baño,[b] Julián Torre-Cisneros[a]

August 2017 Volume 61 Issue 8 e00406-17 Antimicrobial Agents and Chemotherapy

ABSTRACT Combination therapy including colistin and a carbapenem has been found to be associated with lower mortality in the treatment of bloodstream infections (BSI) due to KPC-producing *Klebsiella pneumoniae* when the isolates show a meropenem or imipenem MIC of <16 mg/liter. However, the optimal treatment of BSI caused by colistin- and high-level carbapenem-resistant KPC-producing *K. pneumoniae* is unknown. A prospective cohort study including episodes of bacteremia caused by colistin-resistant and high-level meropenem-resistant (MIC ≥ 64 mg/liter) KPC-producing *K. pneumoniae* diagnosed from July 2012 to February 2016 was performed. The impact of combination therapy on crude 30-day mortality was analyzed by Cox regression using a propensity score as a covariate to control for indication bias and in an inverse probability of treatment weighting (IPTW) cohort. The study sample comprised 104 patients, of which 32 (30.8%) received targeted monotherapy and 72 (69.2%) received targeted combination therapy; none of them received either colistin or a carbapenem. The 30-day crude mortality rate was 30.8% (43.8% in patients treated with monotherapy and 25% in patients receiving combination therapy). In the Cox regression analysis, 30-day mortality was independently associated with septic shock at BSI onset (hazard ratio [HR], 6.03; 95% confidence interval [CI], 1.65 to 21.9; $P = 0.006$) and admission to the critical care unit (HR, 2.87; 95% CI, 0.99 to 8.27; $P = 0.05$). Targeted combination therapy was associated with lower mortality only in patients with septic shock (HR, 0.14; 95% CI, 0.03 to 0.67; $P = 0.01$). These results were confirmed in the Cox regression analysis of the IPTW cohort. Combination therapy is associated with reduced mortality in patients with bacteremia due to colistin-resistant KPC-producing *K. pneumoniae* with high-level carbapenem resistance in patients with septic shock.

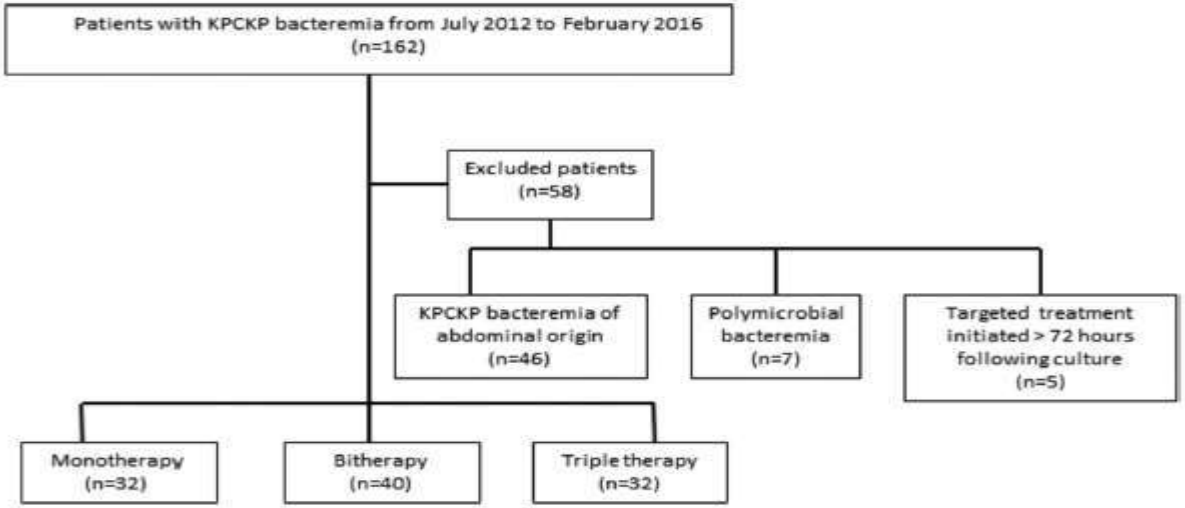


FIG 1 Study flow diagram.

TABLE 3 Outcome of patients with bacteremia due to colistin-resistant *Klebsiella pneumoniae* with high-level meropenem resistance according to treatment regimen

Treatment regimen	No. dead/treated	Mortality (%)
Monotherapy		
Tigecycline	8/15	53.3
Gentamicin	4/9	44.4
Fosfomycin	2/8	25
Total for monotherapy	14/32	43.8
Combination therapy		
Tigecycline + gentamicin	3/13	23.1
Tigecycline + fosfomycin	6/16	37.5
Gentamicin + fosfomycin	3/11	27.3
Tigecycline + fosfomycin + gentamicin	6/32	18.8
Total for combination therapy	18/72	25

Kolistin-R ve Yüksek Düzeyde Meropenem Dirençli Kp Bakteriyemisi

- Kolistin ve karbapenem içermeyen kombinasyonlar
- Monoterapi 14/32(%43.8 mortalite)
  - -Tigesiklin
  - -Gentamisin
  - -Fosfomisin
- Kombinasyon 18/72(%25 mortalite)
  - -Tigesiklin + Gentamisin
  - -Tigesiklin + Fosfomisin
  - -Gentamisin + Fosfomisin
  - -Tigesiklin + Fosfomisin + Gentamisin
- Septik şoklu hastalarda kombinasyon yararlı($p<0.001$)

Machura I et al. Antimicrob Agents Chemother 2017

European Journal of Clinical Microbiology & Infectious Diseases (2020) 39:965–970
https://doi.org/10.1007/s10096-019-03784-9

ORIGINAL ARTICLE

Check for updates

Treatment pattern, prognostic factors, and outcome in patients with infection due to pan-drug-resistant gram-negative bacteria

Diamantis P. Kofteridis[1] · Angeliki M. Andrianaki[1] · Sofia Maraki[2] · Anna Mathioudaki[1] · Marina Plataki[1] · Christina Alexopoulou[3] · Petros Ioannou[1] · George Samonis[1] · Antonis Valachis[4]

- PDR Gram Negatif, Retrospektif, Yunanistan
- 2010-2018, 65 PDR izolat
- *Klebsiella pneumoniae* 31(%48)
- *Acinetobacter baumannii* 28(%43)
- *Pseudomonas aeruginosa* 6(%9)
- Ampirik tedavi

  Kolistin içeren kombinasyonlar 32(%49)
  Kolistin ve tigesiklin içermeyen kombinasyonlar 25(%39)
  Karbapenem + Tigesiklin 8(%12)

Table 2 Infection-related in-hospital mortality in study cohort according to antibiotic treatment strategy

Treatment strategy	Total number of patients (%)	Mortality rate, in %
Empirical therapy	65 (100)	32
Colistin combination	32 (49)	16
Colistin + carbapenemes	7 (11)	29
Colistin + tigecycline + carbapenemes	7 (11)	0
Colistin + 1 other antibiotic	7 (11)	0
Colistin + 2 other antibiotics (non-tigecycline)	6 (9)	33
Colistin + tigecycline	5 (7)	20
Non-colistin, non-tigecycline combination	25 (39)	56
Carbapenemes + tigecycline	8 (12)	25
Subsequent therapy	38 (59)	47
Colistin combination	26 (68)	58
Colistin + 2 other antibiotics (non-tigecycline)	14 (37)	64
Colistin + tigecycline + carbapenemes	7 (18)	57
Colistin + 1 other antibiotic	4 (11)	50
Non-colistin, non-tigecycline combination	8 (21)	25
Carbapenemes + tigecycline	4 (11)	25
Colistin + tigecycline	1 (2)	0

Table 3 Predictive factors for infection-related in-hospital mortality in patients with infection due to PDR pathogens

Variables	Odds ratio	95% confidence interval	*p* value
Charlson comorbidity index	1.5	1.0–2.3	0.030
Prior steroid use	4.1	1.0–17.0	0.049
Non-colistin, non-tigecycline empirical therapy	7.5	1.7–32.8	0.008

antibiotics

MDPI

Article

Meropenem plus Ertapenem and Ceftazidime–Avibactam plus Aztreonam for the Treatment of Ventilator Associated Pneumonia Caused by Pan-Drug Resistant *Klebsiella pneumonia*

Konstantinos Mantzarlis [1,*], Efstratios Manoulakas [1], Kyriaki Parisi [1], Evaggelia Sdroulia [1], Nikolaos Zapaniotis [2], Vassiliki Tsolaki [1], Epaminondas Zakynthinos [1] and Demosthenes Makris [1]

[1] Department of Critical Care, University Hospital of Larissa, School of Medicine, University of Thessaly, 41110 Thessaly, Greece; emanoulakas@uth.gr (E.M.); parisi@uth.gr (K.P.); buchbox1973@gmail.com (E.S.); vastsolaki@uth.gr (V.T.); ezakynth@uth.gr (E.Z.); dimomakris@med.uth.gr (D.M.)

[2] Department of Microbiology, University Hospital of Larissa, School of Medicine, University of Thessaly, 41110 Thessaly, Greece; nzapaniotis@yahoo.com

* Correspondence: mantzk@outlook.com

Abstract: Introduction: Gram-negative bacteria (GNB) account for about 70% of infections in the intensive care unit (ICU) setting and are associated with significant morbidity and mortality. In recent years, pan-drug resistant (PDR) strains, strains that are not susceptible to any antibiotic, have been emerged and new treatment strategies are required. Results: Fifty eligible patients were recruited in the three groups. A statistically significant reduction in the Sequential Organ Failure Assessment (SOFA) score was observed in the control group on day 4 in comparison to day 0 of VAP ($p = 0.005$). The Clinical Pulmonary Infection Score (CPIS) was also reduced on day 4 ($p = 0.0016$) and day 7 in comparison to day 0 ($p = 0.001$). Patients that received combination therapy, CAZ–AVI + ATM and DCT, presented with a lower SOFA score and CPIS on day 7 in comparison to day 0 ($p = 0.0288$ and $p = 0.037$, respectively). No differences in the ΔSOFA score and ΔCPIS were found between the groups. The control group presented with a significantly lower ICU stay and duration of mechanical ventilation ($p = 0.03$ and $p = 0.02$, respectively). There was no difference in mortality. Materials and methods: This is a retrospective analysis. This study was conducted in a mixed ICU in the University Hospital of Larissa, Thessaly, Greece during a three-year period (2020-2022). Patients suffering from ventilator associated pneumonia (VAP) due to carbapenem-resistant *K. pneumonia* (CR-KP) were divided in three different groups: the first one was treated using ceftazidime–avibactam plus aztreonam (CAZ–AVI + ATM group), the second was treated using double carbapenems (DCT group), and the last one (control group) received appropriate therapy since the strain was susceptible in vitro to at least to one antibiotic. Conclusions: Treatment with CAZ–AVI +ATM or DCT may offer a clinical benefit in patients suffering with infections due to PDR *K. pneumoniae*. Larger studies are required to

Citation: Mantzarlis, K.; Manoulakas, E.; Parisi, K.; Sdroulia, E.; Zapaniotis, N.; Tsolaki, V.; Zakynthinos, E.; Makris, D. Meropenem plus Ertapenem and Ceftazidime–Avibactam plus Aztreonam for the Treatment of Ventilator Associated Pneumonia Caused by Pan-Drug Resistant *Klebsiella pneumonia*. *Antibiotics* **2024**, *13*, 141. https://doi.org/10.3390/antibiotics13020141

Journal of
Clinical Medicine

MDPI

Review

Treatment Options for Colistin Resistant *Klebsiella pneumoniae*: Present and Future

Nicola Petrosillo *, Fabrizio Taglietti and Guido Granata

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.