Karbapenem Tedavisinden Vazgeçelim mi? Nasıl Vazgeçelim?

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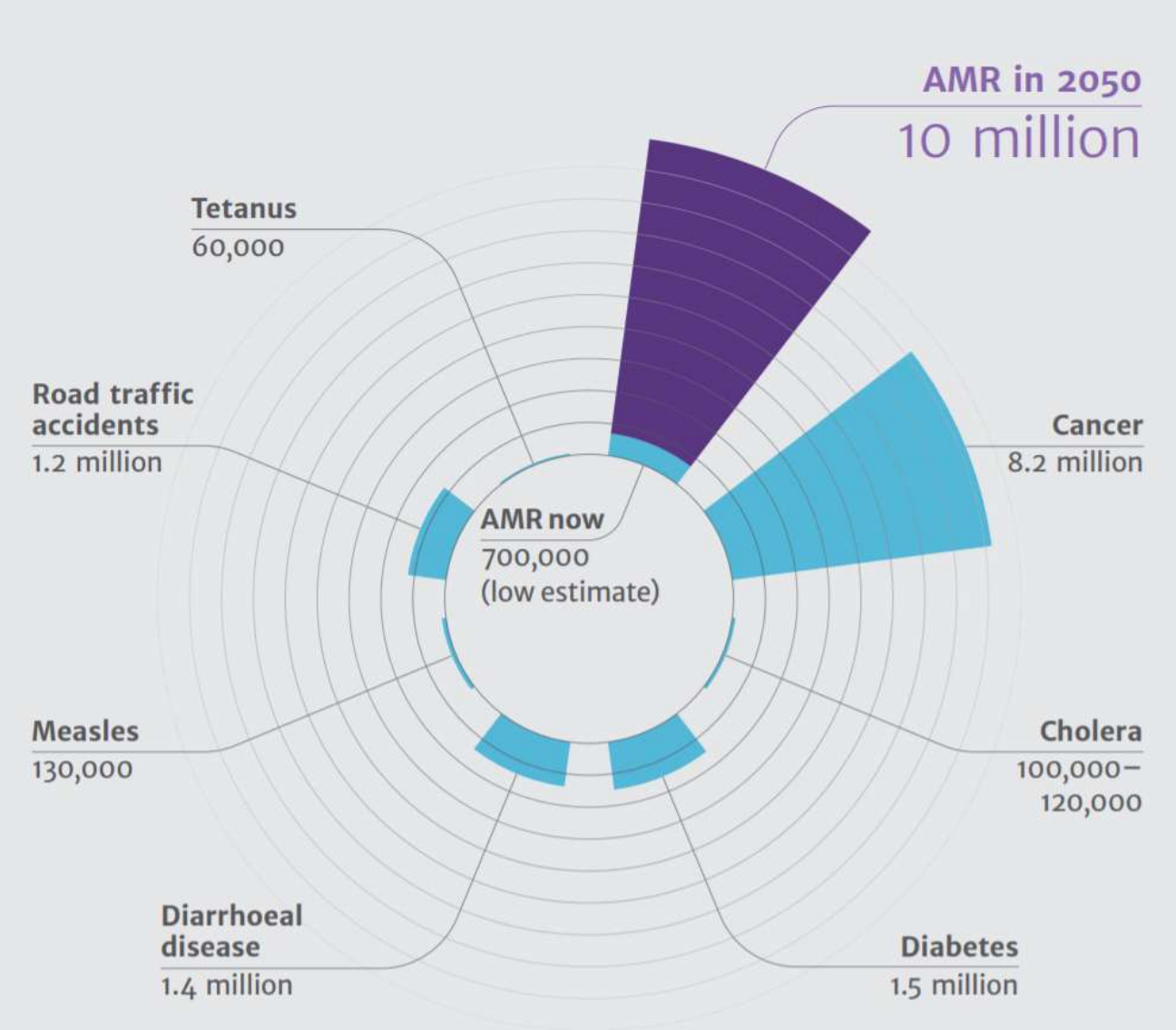
Enfeksiyon Hastalıkları ve Klinik Mikrobiyoloji Anabilim Dalı

KLİMİK
TÜRK KLİNİK MİKROBİYOLOJİ VE İNFEKSİYON HASTALIKLARI DERNEĞİ

ONDOKUZ MAYIS ÜNİVERSİTESİ

ADÇG
KLİMİK DERNEĞİ ANTİBİYOTİK DİRENCİ ÇALIŞMA GRUBU



The Review on Antimicrobial Resistance, Chaired by Jim O'Neill

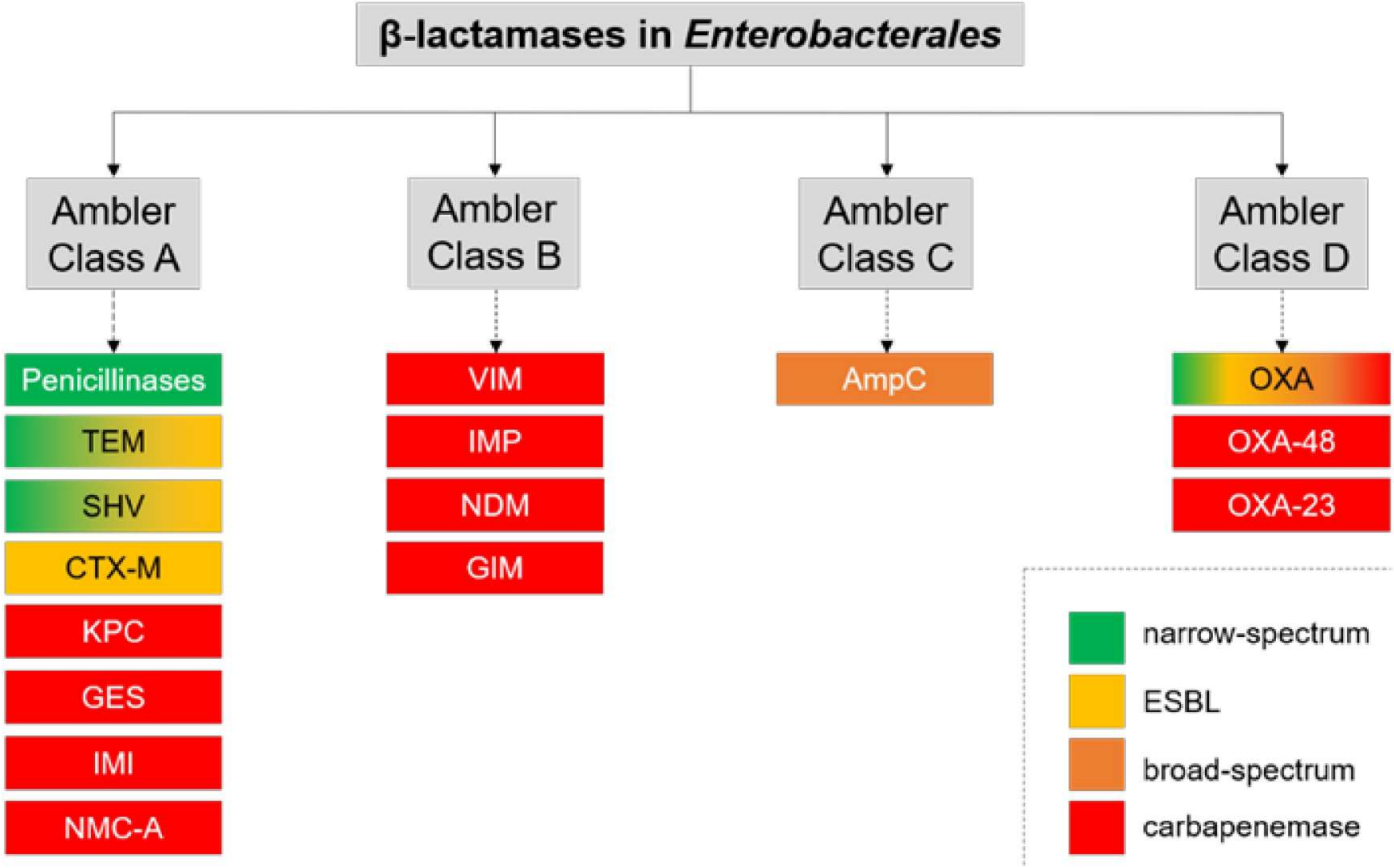
DSÖ İlk Kez Acil
Yeni Antibiyotik Gerektiren
Bakteriler Listesi Yayımladı

Priority 1: CRITICAL

Acinetobacter baumannii, carbapenem-resistant

Pseudomonas aeruginosa, carbapenem-resistant

Enterobacteriaceae, carbapenem-resistant, ESBL-producing


β-lactamases in *Enterobacterales*
Ambler Class A
Ambler Class B
Ambler Class C
Ambler Class D
Penicillinases
TEM
SHV
CTX-M
KPC
GES
IMI
NMC-A
VIM
IMP
NDM
GIM
AmpC
OXA
OXA-48
OXA-23
narrow-spectrum
ESBL
broad-spectrum
carbapenemase

Incidence and risk factors of carbapenem-resistant *Enterobacteriaceae* infection in intensive care units: a matched-case control study

Fahad A S Aleidan , Hind Alkhelaifi , Aljouharah Alsenaid , Haya Alromaizan , Fajer Alsalham , Alhanouf Almutairi , Khalid AlSulaiman & Abdel Galil Abdel Gadir

Table 2: Previous use of antimicrobial Classes in CRE and CSE patients

Antimicrobial Classes*	CRE no. (%)	CSE no. (%)	*P*-value
Aminoglycoside	39 (29.6)	11 (8.0)	<0.0001
Carbapenem	79 (64.4)	35 (26.1)	<0.0001
Cephalosporin	85 (59.9)	79 (55.6)	0.709
Penicillins	49 (34.5%)	41 (28.9)	0.462
Quinolones	18 (12.7)	14 (10.0)	0.501

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Published online 2020 Sep 14. doi: 10.3389/fcimb.2020.00462 PMID: 33042858

Epidemiology and Risk Factors for Carbapenem-Resistant *Klebsiella Pneumoniae* and Subsequent MALDI-TOF MS as a Tool to Cluster KPC-2-Producing *Klebsiella Pneumoniae*, a Retrospective Study

Lili Fang,[1,2,3,†] Heping Xu,[1,2,3,†] Xiaoying Ren,[1,2,3,†] Xun Li,[1,2,3] Xiaobo Ma,[1,2,3] Haijian Zhou,[4,5] Guolin Hong,[1,2,3,*] and Xianming Liang[6,7,*]

TABLE 1 | Comparison with patients' characteristics between CRKP and CSKP groups.

Characteristic[a]	CRKP group[b] (*n* = 35) *n*, %	CSKP group[b] (*n* = 70) *n*, %	*p*-value
Antimicrobial use prior to culture within 30 days			
One or more Antimicrobial uses	34 (97.1)	33 (47.1)	<0.001
Third- or fourth-generation cephalosporin use	6 (17.1)	15 (21.4)	0.605
Carbapenem use	16 (45.7)	5 (7.1)	<0.001
Quinolone use	14 (40.0)	6 (8.6)	<0.001

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Systematic review

Risk factors for carbapenem-resistant Gram-negative bacterial infections: a systematic review

Zaira R. Palacios-Baena [1,*], Maddalena Giannella [2], Davide Manissero [3], Jesus Rodríguez-Baño [4], Pierluigi Viale [2], Sara Lopes [5], Katy Wilson [6], Rachael McCool [6], Christopher Longshaw [7]

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[2] *Infectious Diseases Unit, Department of Medical and Surgical Sciences, Policlinico Sant'Orsola Malpighi, Bologna, Italy*
[3] *Medical Affairs for Infection and Immune Diagnostics, QIAGEN, London, UK*
[4] *Department of Medicine, University of Seville, Seville, Spain*
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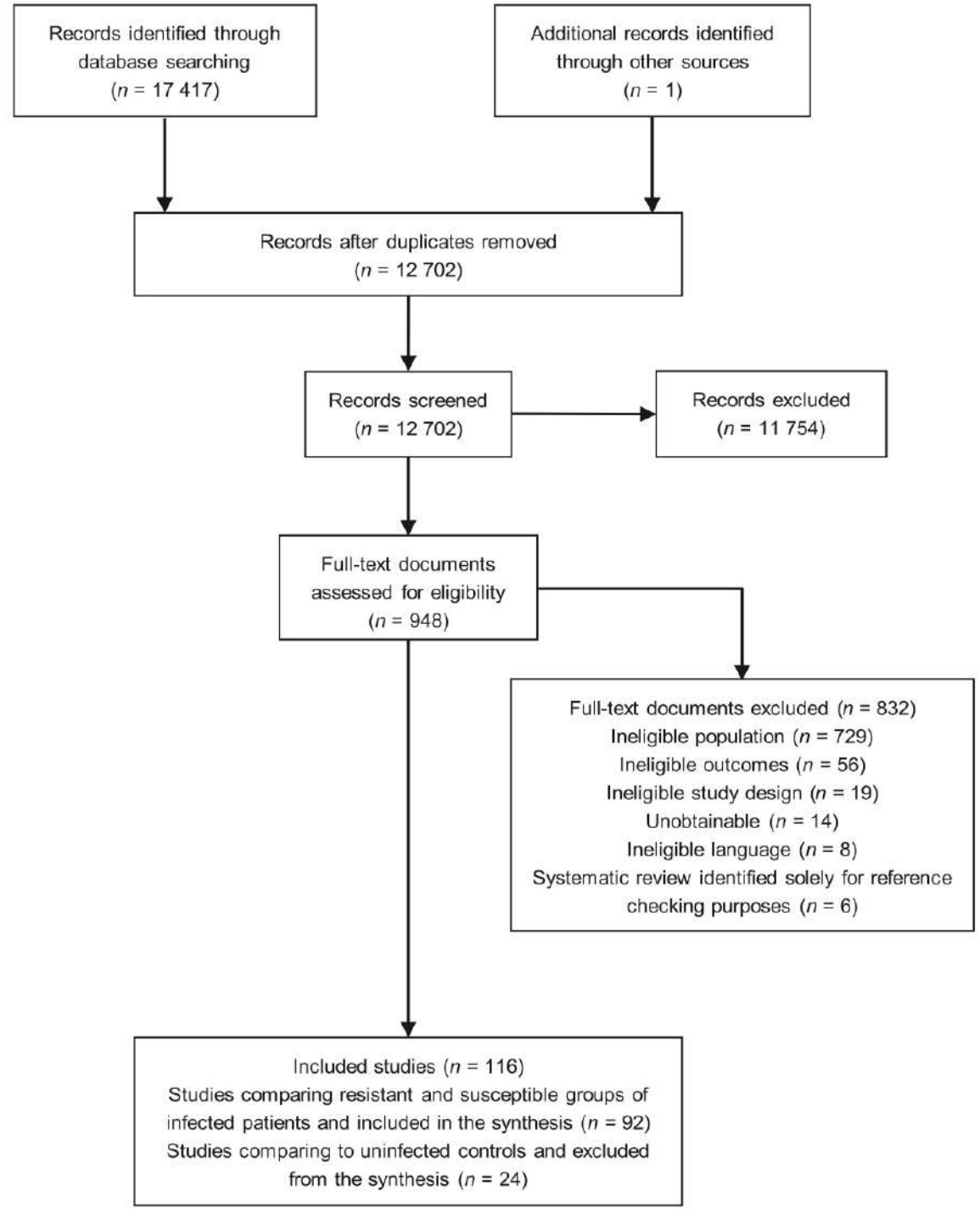
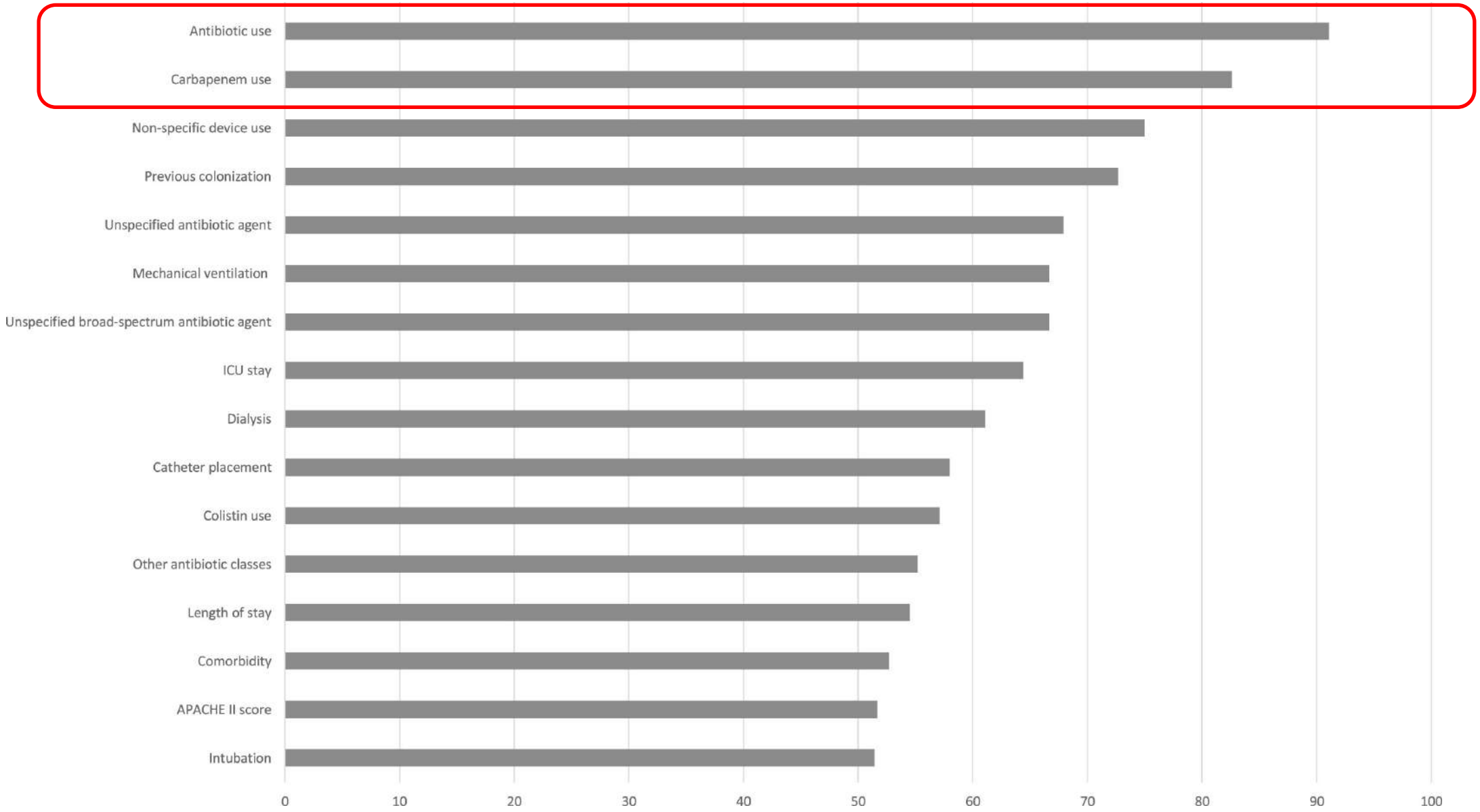
ABSTRACT

Background: Rapid and widespread increases in carbapenem resistance (CR) necessitate identification of risk factors to guide appropriate interventions.
Objectives: We aimed to identify risk factors for CR Gram-negative infection through a systematic literature review.
Data sources: We searched MEDLINE (via OvidSP and PubMed) and Embase (via OvidSP) databases and the Cochrane Central Register of Controlled Trials.
Study eligibility criteria: Prospective or retrospective cohort and case–control studies reporting quantitative data on risk factors associated with infections due to CR Gram-negative pathogens in hospitalized patients were eligible.
Participants: Studies included hospitalized patients with CR infection caused by Gram-negative bacterial pathogens (Enterobacterales and non-fermenters).
Methods: Searches were conducted in January 2018/December 2019 to identify studies published since 2007. Risk factor data were extracted and grouped by factor. The primary metric was proportion of studies reporting a significant association with CR infection for each factor.
Results: In total, 92 studies were identified. Risk factors most frequently reported as significantly associated with CR infection (>10 studies) were previous antibiotic use (91.1%; 72/79 studies); previous carbapenem use (82.6%; 57/69); previous colonization (72.7%; 8/11); mechanical ventilation (66.7%; 36/54); previous intensive care unit stay (64.4%; 38/59); dialysis (61.1%; 11/18); catheter (58.0%; 40/69); length of stay in hospital (54.5%; 30/55); comorbidities (52.7%; 39/74); APACHE II (51.7%; 15/29); and intubation (51.4%; 18/35). Risk factors were mostly consistent across different species and sites of infection.
Conclusions: Several variables, particularly previous antibiotic use, are strong risk factors for CR infection. Interventions to mitigate against CR infection should target these factors.

Zaira R. Palacios-Baena, Clin Microbiol Infect 2021;27:228



Tek değişkenli analiz ile en sık olarak CR enfeksiyonu ile anlamlı bir ilişkiye sahip olduğu bildirilen bireysel risk faktörleri



https://doi.org/10.1016/j.cmi.2020.10.016

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

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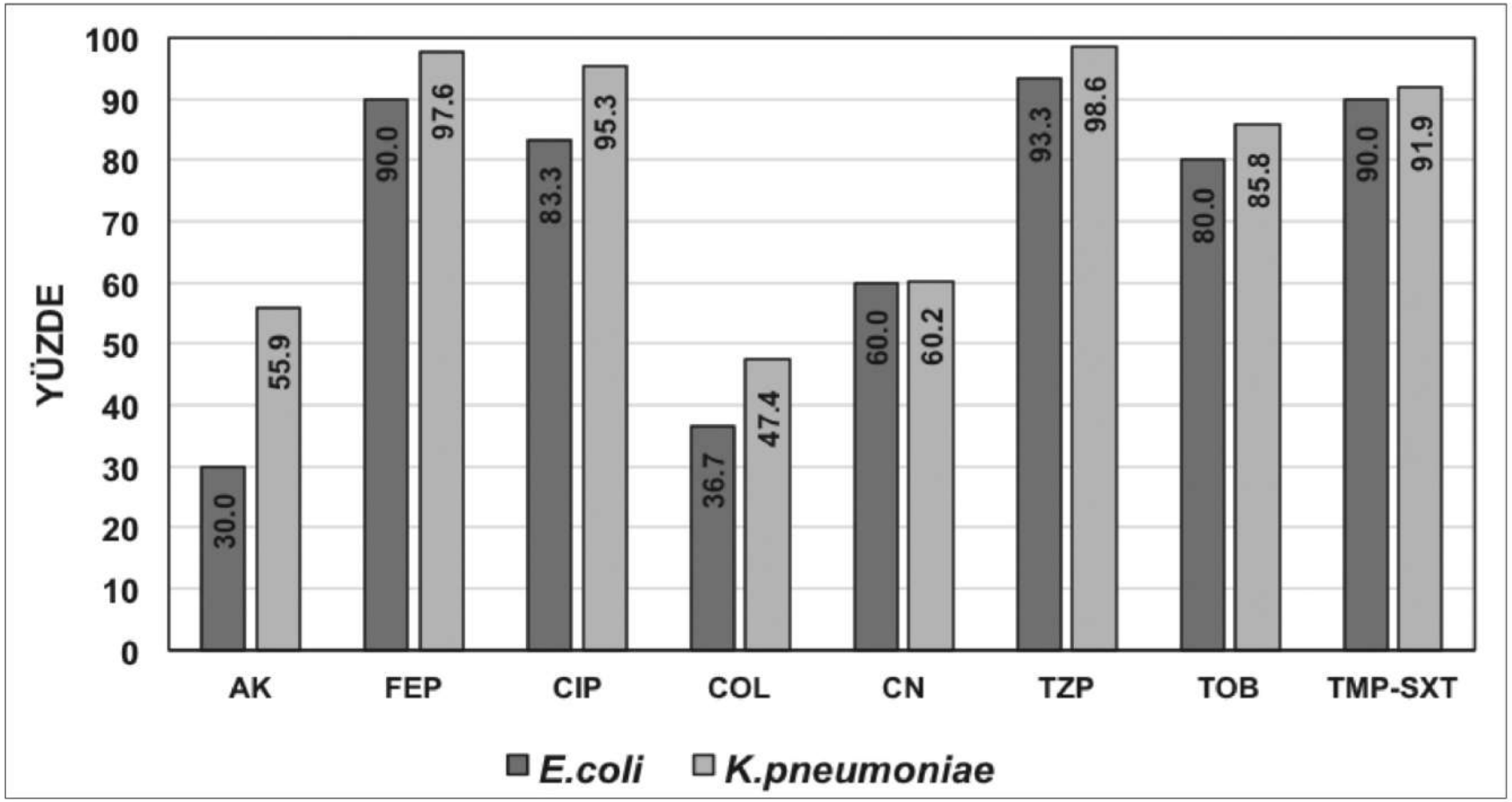
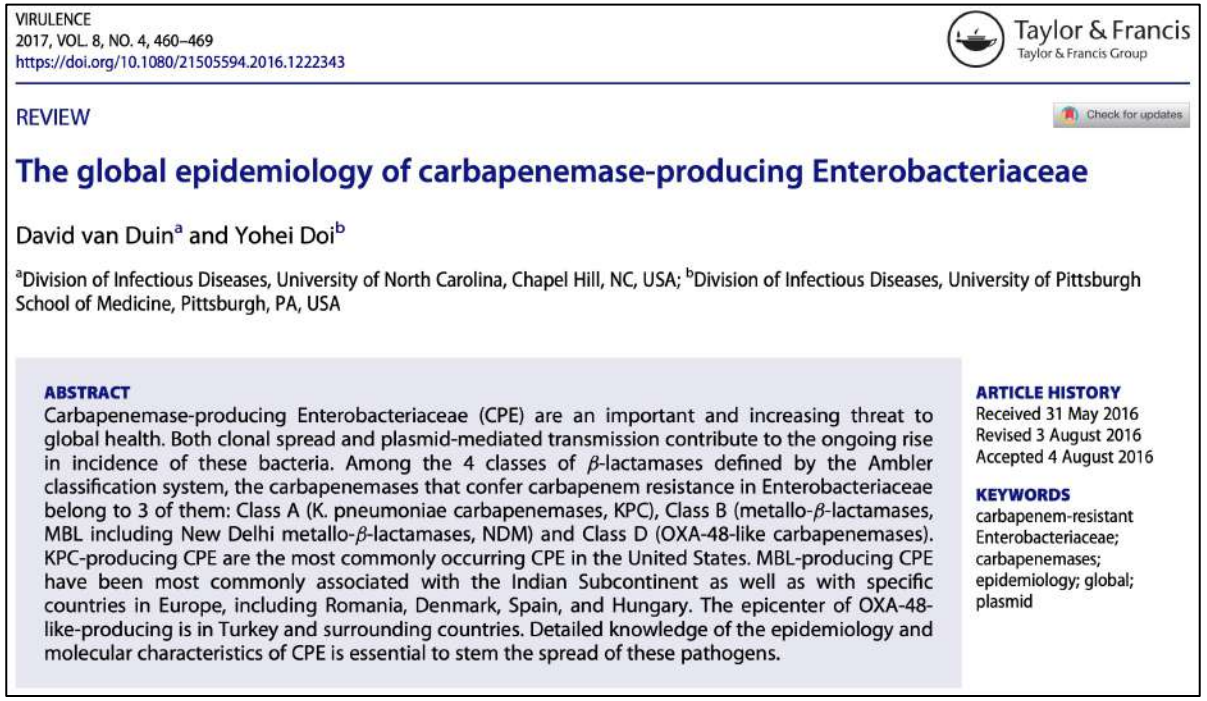
Serap SÜZÜK YILDIZ[1](ID), Hüsniye ŞİMŞEK[1](ID), Zekiye BAKKALOĞLU[1](ID), Yasemin NUMANOĞLU ÇEVİK[1](ID), Can Hüseyin HEKİMOĞLU[1](ID), Selçuk KILIÇ[1](ID), Emine ALP MEŞE[2](ID), Ulusal Karbapenemaz Sürveyans Çalışma Grubu*



Şekil 3. *Karbapenem dirençli izolatların farklı antibiyotiklere karşı direnç yüzdeleri.*



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REVIEW

Check for updates

The global epidemiology of carbapenemase-producing Enterobacteriaceae

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[a]Division of Infectious Diseases, University of North Carolina, Chapel Hill, NC, USA; [b]Division of Infectious Diseases, University of Pittsburgh School of Medicine, Pittsburgh, PA, USA

ABSTRACT

Carbapenemase-producing Enterobacteriaceae (CPE) are an important and increasing threat to global health. Both clonal spread and plasmid-mediated transmission contribute to the ongoing rise in incidence of these bacteria. Among the 4 classes of β-lactamases defined by the Ambler classification system, the carbapenemases that confer carbapenem resistance in Enterobacteriaceae belong to 3 of them: Class A (K. pneumoniae carbapenemases, KPC), Class B (metallo-β-lactamases, MBL including New Delhi metallo-β-lactamases, NDM) and Class D (OXA-48-like carbapenemases). KPC-producing CPE are the most commonly occurring CPE in the United States. MBL-producing CPE have been most commonly associated with the Indian Subcontinent as well as with specific countries in Europe, including Romania, Denmark, Spain, and Hungary. The epicenter of OXA-48-like-producing is in Turkey and surrounding countries. Detailed knowledge of the epidemiology and molecular characteristics of CPE is essential to stem the spread of these pathogens.

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ESBL üreten gram negatif bakteri enfeksiyonlarının tedavisinde uzun yıllar karbapenem kullanılması karbapenem direncini tetikledi

van Duin D, Doi Y. The global epidemiology of carbapenemase-producing *Enterobacteriaceae*. Virulence 2017; 8(4): 460-9.

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85. The Impact of Carbapenem-Sparing Interventions on the Evolution of Resistance in *Pseudomonas aeruginosa* in the USA

Jeffrey Townsend, PhD, Abhishek Pandey, PhD, Amber B Tang, BS, Yiziying Chen, Master's in Biostatistics, Eric M Foster, Dilip Nathwani, MB, Sanjay Merchant, PhD, Eric Sarpong, PhD, Meagan C Fitzpatrick, PhD, Alison Galvani, PhD

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Published: 31 December 2020

Background: Carbapenem resistance (CR) among *Pseudomonas aeruginosa* infections is a pressing public health concern in the United States. Therapeutic alternatives for CR infections are limited. Implementation of a key antimicrobial stewardship intervention such as formulary restriction, which is one of the many stewardship strategies, can minimize selection pressure for resistance. We evaluate the consequent impact of this intervention on bacteremia patients infected with *P. aeruginosa* in the US.

Methods: We developed a population-genetic model of selection for CR. Increases in CR were modeled as a consequence of inappropriate prescription. Inappropriate empiric therapy, i.e. antibiotic, did not cover the organism or appropriate coverage not started within 2-days, was estimated from a published study and future projections were based on historical resistance frequencies and yearly carbapenem consumption associated with *P. aeruginosa* bacteremia. We projected peak *P. aeruginosa* CR frequencies and cumulative CR cases from 2020–2040. We compared scenarios without carbapenem restriction to usage decreased linearly by an amount demonstrated in a previous hospital study (51.7%) over 5 years of implementation starting in 2020 (early implementation) or 2030 (late implementation).

Results: Early and late implementation of carbapenem restriction leads to CR frequencies that ascend as high as 42% and 74% respectively eventually mitigating those frequencies by bringing them down to 23% and 37% respectively. By 2045, early carbapenem restriction could prevent 29,600 CR cases of *P. aeruginosa* bacteremia, compared to 15,200 prevented by late implementation.

Conclusion: We demonstrate that early restriction of carbapenem consumption could markedly reduce future CR in *P. aeruginosa* bacteremia patients. Implementing early carbapenem restriction should be expected to result in a lower ultimate frequency of CR and a lower number of cumulative cases of resistant infections, thereby decreasing the overall burden of CR cases that will be encountered in the future.

Disclosures: Jeffrey Townsend, PhD, Merck (Consultant)Merck (Consultant) Sanjay Merchant, PhD, Merck & Co., Inc. (Employee) Alison Galvani, PhD, Merck (Consultant)

Karbapenem kısıtlamasının uygulanması beklenen direnç oranlarını %74'ten %23'lere kadar düşürebilir.

ANTIMICROBIAL AGENTS AND CHEMOTHERAPY, May 2009, p. 1983–1986
0066-4804/09/$08.00+0 doi:10.1128/AAC.01535-08

AMERICAN SOCIETY FOR MICROBIOLOGY | Antimicrobial Agents and Chemotherapy®

Relationship of Carbapenem Restriction in 22 University Teaching Hospitals to Carbapenem Use and Carbapenem-Resistant *Pseudomonas aeruginosa*▽

Amy L. Pakyz,[1] Michael Oinonen,[2] and Ronald E. Polk[1]*

Department of Pharmacy, School of Pharmacy, Virginia Commonwealth University, Medical College of Virginia Campus, Richmond, Virginia,[1] and University HealthSystem Consortium, Oak Brook, Illinois[2]

Karbapenem kısıtlayan 8 hastane diğerleri ile karşılaştırılıyor
Karbapenemleri kısıtlayan hastaneler (n = 8; %36) önemli ölçüde daha az karbapenem kullandı (P = 0.04)
Tüm çalışma yılları için daha düşük karbapenem dirençli P. aeruginosa insidans oranları bildirdi (P = 0.01).

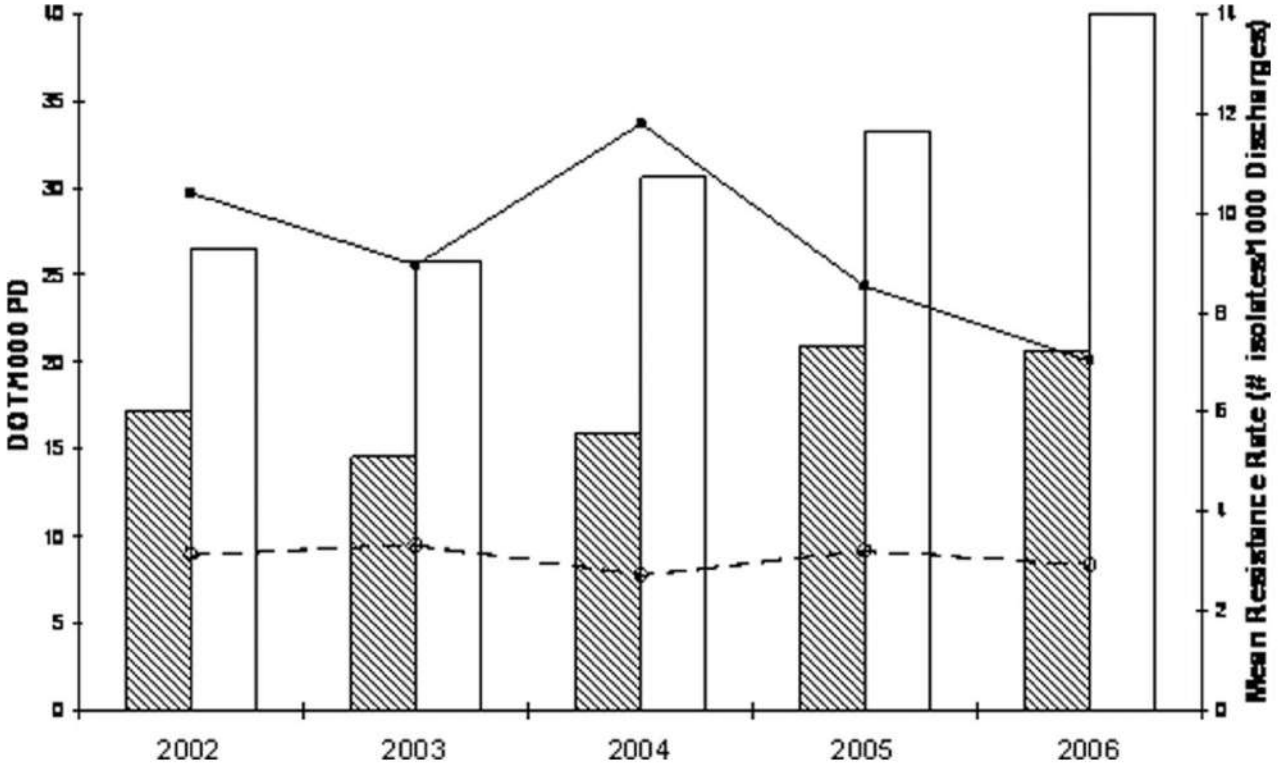
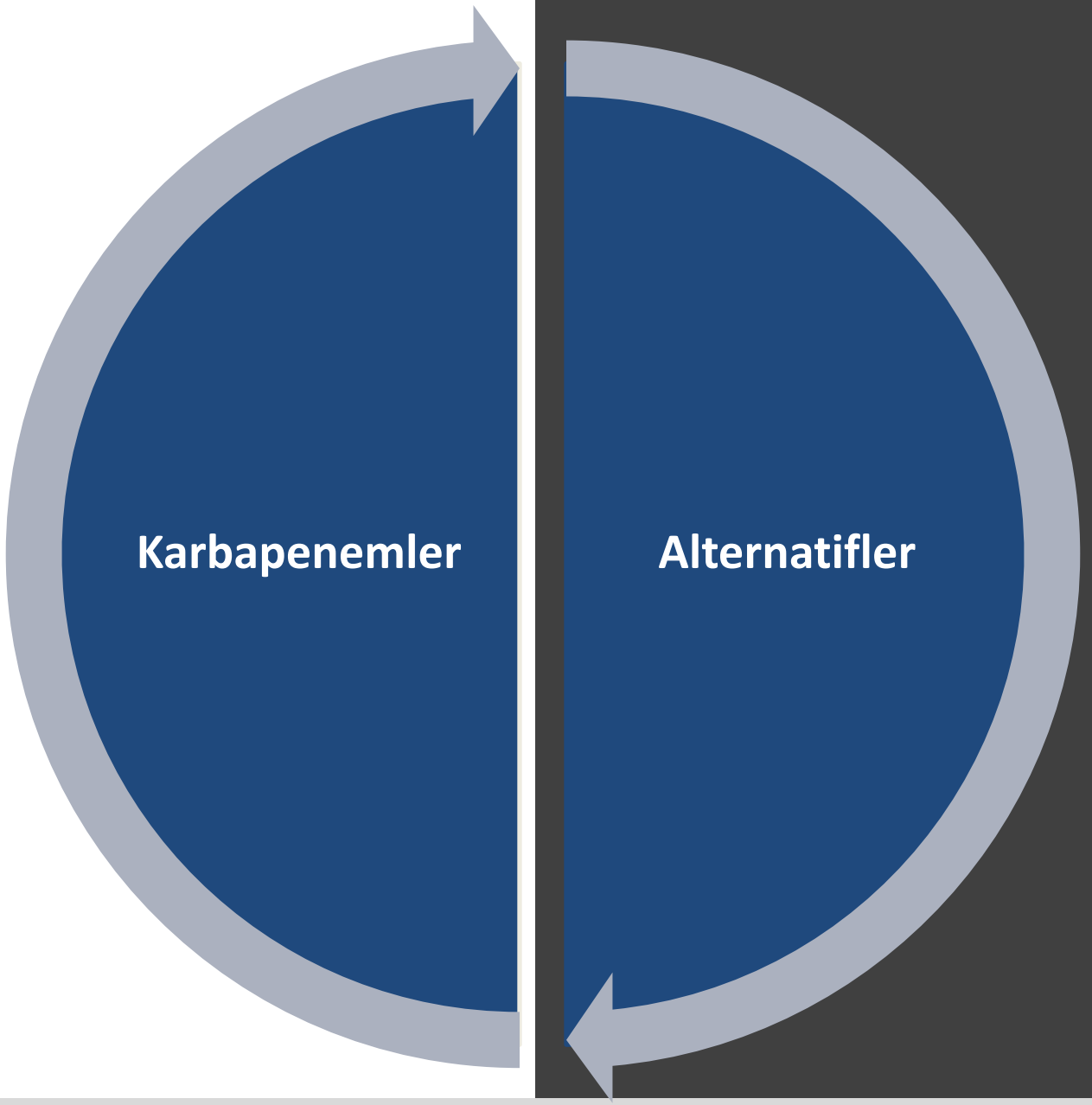


FIG. 1. Mean carbapenem use (DOT/1,000 PD) was significantly lower in hospitals that restricted (shaded bars) versus did not restrict (open bars) carbapenems ($P = 0.04$). Incidence rates of carbapenem-resistant *P. aeruginosa* (number of isolates/1,000 discharges) were lower for hospitals that restricted (dashed line) versus did not restrict (solid line) carbapenems ($P = 0.01$).


Karbapenemler
Alternatifler

Ertapenem

Meropenem

İmipenem

Piperasilin-Tazobaktam

Fosfomisin

Aminoglikozidler

Sefepim

Siprofloksasin

Trimetoprim-Sulfametoksazol

Tigesiklin

Seftazidim-avibactam

Plazomisin

Eravasiklin

Sefiderakol

Olgu 1

- 71 y, erkek hasta COVID-19 pnömonisi ile takip ediliyor
- Yatışının 12. günündeyken ateş şikayeti oluyor.
- Yatışından itibaren internal idrar sondası mevcut.
- KOAH, KKY, KAH ve prostat hipertrofisi tanıları mevcut olan
- FM: Ateşi 38 ^{o}C ve TA: 110/70 mmHg, sağ KVAH hassasiyet mevcut.

- WBC: 11000 (%72 PMNL) /uL, CRP: 56 mg/L, Kr: 1.2 mg/dl.
- İdrar mikroskobisi: 187 lökosit /mm^3 ve ve Gram(-) basiller görüldü.

Tanı: Komplike üriner sistem infeksiyonu
Ampirik Piperasilin-tazobaktam 3x4.5 gr IV tedavisi başlandı

Olgu 1

- Tedavinin 3. gününde genel durum iyi, ateş yanıtı mevcut.
- Kan kültüründen sinyal bildirilmedi.
- İdrar kültürü: ESBL(+) *E.coli* 100.000 cfu/ml.

İdrar kültürü: *E.coli* ESBL(+) 100.000 cfu/ml

Antibiyotik	Yorum	Antibiyotik	Yorum
Ampisilin	R	Amikasin	S
Amoksisilin-klavulonik asit	S	Gentamisin	S
Piperasilin-tazobaktam	S	Siprofloksasin	R
Sefuroksim-aksetil	R	Trimetoprim/ sulfametaksazol	S
Sefiksim	R	Fosfomisin	S
Seftriakson	R	Nitrofurantoin	S
Seftazidim	R		
Ertapenem	S		
İmipenem	S		
Meropenem	S		

Olgu 1

- Kontrol idrar kültürü: Üreme yok
- Kan kültürü: Üreme yok.
- Genel durumu iyi olan hasta **piperasilin-tazobaktam** tedavisinin 5. gününde **trimetoprim-sulfametaksazol** oral ardışık tedavisi ile taburcu edildi.

Olgu 2

- 64 y, bulantı-kusma, ateş, üşüme-titreme şikayetiyle başvuruyor.
- Ekstrapulmoner sarkoidoz ve prostat CA?
- 5 gün önce transüretral prostat rezeksiyonu yapılmış.
- Ateş:38.7 ^{o}C, TA:80/50 mmHg, suprapubik hassasiyet ve sağda KVAH mevcut.

- WBC: 4000 (%85 PMNL) /uL, PLT:140000 /uL, AST/ALT:49/50 U/L, CRP: 186 mg/L.
- İdrar mikroskobisi: 2120 lökosit /mm^3, Gram(-) basiller mevcut.
- Abd BT Rapor: Sağda renal boyutlar artmış, mesane etrafı çevre mezenter kirli görünümde.

Tanı: Komplike üriner sistem infeksiyonu ve sepsis
Ertapenem 1x1 gr IV ampirik olarak başlandı

Olgu 2

- Tedavinin 2. gününde kan kültüründen Gram(-) basil sinyali bildirildi.
- Tedavinin 3. gününde ateş yanıtı alındı.
  - Kontrol idrar mikroskobisinde: 30 lökosit /mm^3 görüldü, mikroorganizma görülmedi.

  - İdrar kültürü: ***K.pneumoniae*** **ESBL(+)** 100.000 kol/ml
  - Kan kültürü: ***K.pneumoniae*** **ESBL (+)**

Kan ve İdrar kültürü: *K.pneumoniae* ESBL(+)

Antibiyotik	Yorum	Antibiyotik	Yorum
Ampisilin	R	Amikasin	S
Amoksisilin-klavulonik asit	S	Gentamisin	S
Piperasilin-tazobaktam	S	Siprofloksasin	R
Sefuroksim-aksetil	R	Trimetoprim/sulfametaksazol	R
Sefiksim	R	Fosfomisin*	S
Seftriakson	R	Nitrofurantoin*	R
Seftazidim	R		
Ertapenem	S		
İmipenem	S		
Meropenem	S		

* İdrar izolatında

Olgu 2

Kontrol idrar ve kan kültüründe üreme saptanmadı.

Günübirlik ertapenem tedavisi ile taburcu edildi.

Olgu 1

Komplike üriner sistem infeksiyonu
İdrar kültürü: ESBL(+) *E.coli*
Piperasilin-tazobaktam 3x4,5 gr sonrası oral-ardışık
Trimetoprim/Sulfametaksazol ile taburcu edilmiş

Soru
Ampirik Piperasilin-tazobaktam doğru seçenek mi?
Oral ardışık tedavi uygun yaklaşım oldu mu?

Karbapenemler

Olgu 2

Üro-sepsis
Ertapenem 1x1 gr IV ampirik olarak başlandı
Kan ve idrar kültüründe ESBL(+) *K.pneumonia* üremesi var
Ertapenemle tedavisi tamamlanmış

Soru
Karbapenem koruyucu tedavi olarak ampirik
Piperasilin-tazobaktam başlanabilir miydi?
Kültür sonucuna göre karbapenem kesilebilir miydi?

Piperasilin-Tazobaktam

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Narrative review

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

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Unidad Clínica de Enfermedades Infecciosas, Microbiología y Medicina Preventiva, Hospital Universitario Virgen Macarena/Departamento de Medicina, Universidad de Sevilla/Instituto de Biomedicina de Sevilla (IBiS), Sevilla, Spain

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Mortality
Treatment
Urinary tract Infections

ABSTRACT

Background: Extended-spectrum β-lactamase-producing Enterobacteriaceae (ESBL-E) are a frequent cause of invasive infections worldwide. Carbapenems are nowadays the most used drugs to treat these infections. However, due to the increasing rates of resistance to these antimicrobials, carbapenem-sparing alternatives are being investigated.

Objectives and sources: The aim of this narrative literature review is to summarize the published information on the currently available antibiotics for the treatment of ESBL-E infections, providing specific information on three subgroups of patients: Group 1, patients with severe infections or infections from high-risk sources or in severely immunocompromised patients; Group 2, patients with non-severe infections from intermediate-risk source; and Group 3, patients with non-severe urinary tract infection.

Content and implications: For patients in Group 1, the current data would support the use of carbapenems. For milder infections, however, particularly urinary tract infections, other non-carbapenem antibiotics can be considered in selected cases, including beta-lactam/beta-lactam inhibitor combinations, cephamycins, temocillin and aminoglycosides. While specific studies should be performed in these situations, individualized decisions may be taken in order to avoid overuse of carbapenems. **B. Gutiérrez-Gutiérrez, Clin Microbiol Infect 2019;25:932**

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

Ölçüt	Sınıflandırma	Koşullar
İnfeksiyon ciddiyet	Şiddetli	Pitt skoru ≥4, APACHE II skoru>10, yoğun bakım ünitesine kabul ve şiddetli sepsis veya septik şok ile başvuru
	Şiddetli değil	Diğer durumlar
İnfeksiyon Kaynağı	Yüksek risk	Yüksek inokulumlu Enfeksiyonlar, drenaj mümkün olmadığı veya yetersiz yapıldığı enfeksiyonlar (örn. pnömoni, endokardit, yetersiz drenajlı derin yerleşimli enfeksiyonlar)
	Orta risk	Yüksek veya düşük riske dahil değildir (kateterin çıkarıldığı kateter enfeksiyonu, drene safra yolları veya intraabdominal enfeksiyon)
	Düşük risk	Üretral obstruksiyon olan veya olmayan idrar yolu enfeksiyonu
Bağışıklık durumu	Bağışıklığı ağır baskılanmış	Nötropeni (<500/µL), lösemi, lenfoma, <200 CD4/µL ile HIV enfeksiyonu, solit organ veya hematopoietik kök hücre nakli, sitotoksik kemoterapi, steroidler
	Şiddetli değil	Diğer durumlar

Grup 1- İnfeksiyon ciddiyeti şiddetli olan ya da infeksiyon kaynağı yüksek riskli olan ya da bağışıklığı ağır baskılanmış olan

Karbapenemler tercih edilmeli

Grup 2- İnfeksiyon ciddiyeti şiddetli olmayan ve infeksiyon kaynağı orta riskli olanlar

Piperasilin-tazobaktam tercih edilebilir*

Grup 3- İnfeksiyon ciddiyeti şiddetli olmayan ve infeksiyon kaynağı düşük riskli olanlar

Piperasilin-tazobaktam tercih edilebilir*
Aminoglikozit, intravenöz fosfomisin tercih edilebilir

*Uzun infüzyonda 4,5 g/6 saat

B. Gutierrez-Gutierrez, J. Rodríguez-Bano / Clinical Microbiology and Infection 25 (2019) 932 ~ e942

Research

JAMA. 2018;320(10):984-994. doi:10.1001/jama.2018.12163

JAMA | Original Investigation

Effect of Piperacillin-Tazobactam vs Meropenem on 30-Day Mortality for Patients With *E coli* or *Klebsiella pneumoniae* Bloodstream Infection and Ceftriaxone Resistance

A Randomized Clinical Trial

Table 1. Baseline Characteristics of Patients in the Primary Analysis Population[a] (continued)

Characteristic	Pipercillin-Tazobactam (n = 188)	Meropenem (n = 191)
Liver disease[f]	12 (6.4)	18 (9.4)
qSOFA score ≥2[g]	86 (45.7)	77 (40.3)
Weight, mean (SD), kg	67.2 (18.1)	69.3 (19.3)
Empirical antibiotic category		
β-lactam/ β-lactamase inhibitor	38 (20.2)	49 (25.7)
Carbapenem	26 (13.8)	28 (14.7)
Other	124 (66.0)	114 (59.7)
Appropriate empirical antibiotic	126 (67.0)	127 (66.5)
Time to randomization, median (IQR), h	53.6 (44.9-65.6)	52.5 (46.0-63.7)
Time to appropriate antibiotics, median (IQR), h	5.5 (0.4-31.5)	9.6 (0.5-32.1)

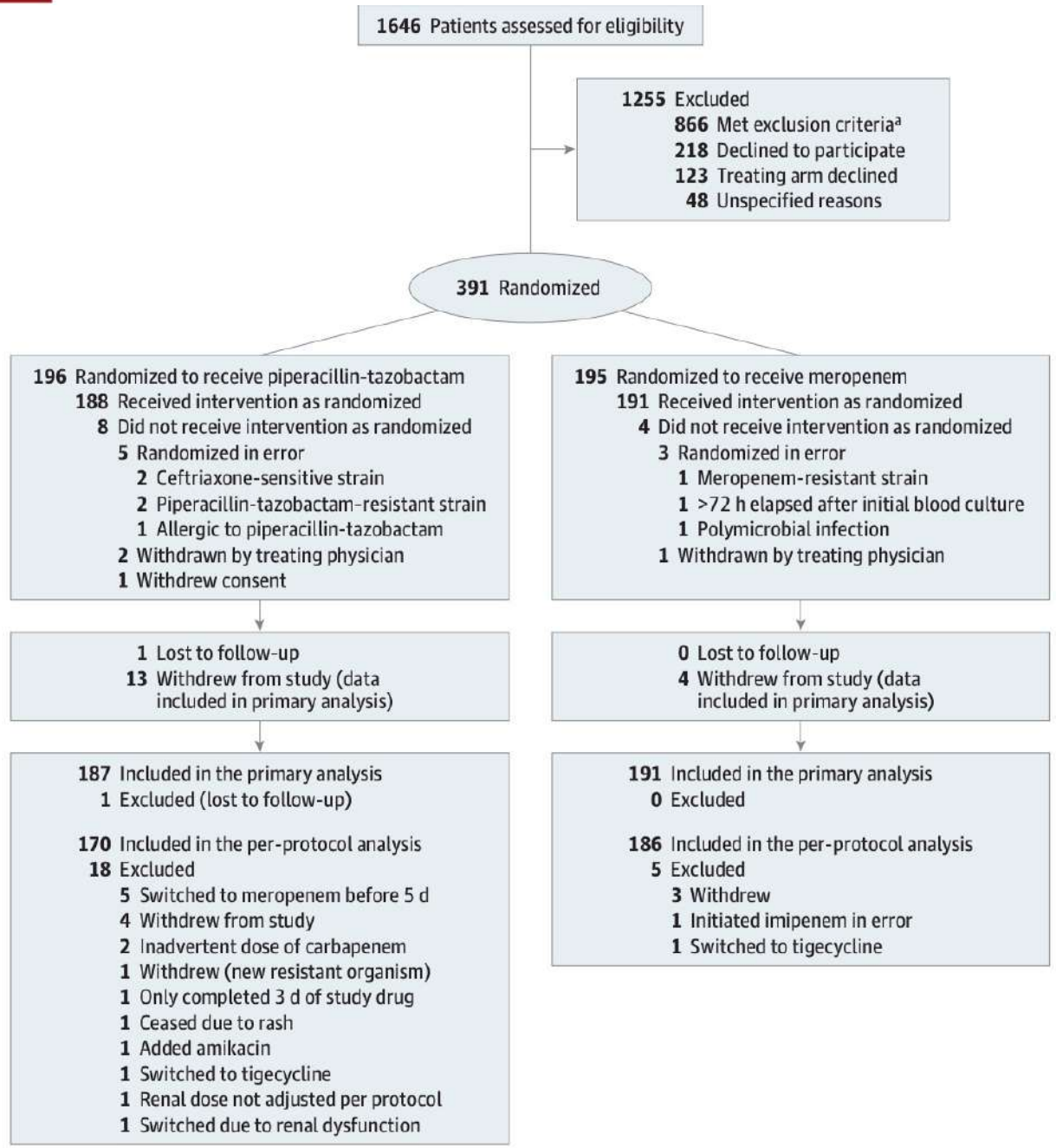
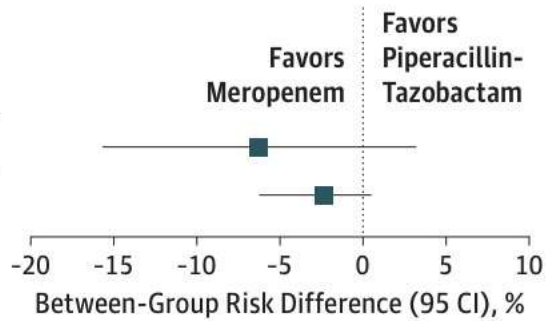


Table 2. Primary Analysis and Subgroup Analyses

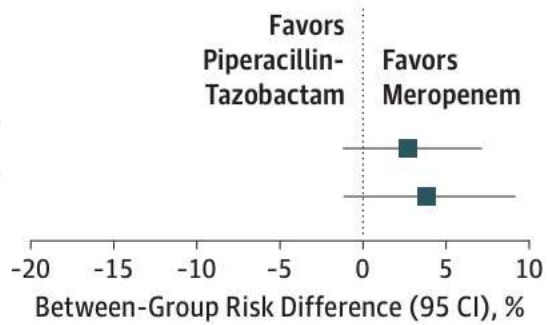
	30-d Mortality, No./Total No. (%)		Risk Difference, % (1-Sided 97.5% CI)[a]	*P* Value for Noninferiority
	Piperacillin-Tazobactam	Meropenem		
Primary analysis	23/187 (12.3)	7/191 (3.7)	8.6 (−∞ to 14.5)	.90
Per-protocol analysis	18/170 (10.6)	7/186 (3.8)	6.8 (−∞ to 12.8)	.76
Subgroup analyses[b]				*P* Value for Interaction
OECD country income				
Middle income	8/37 (21.6)	1/35 (2.9)	18.8 (−∞ to 35.0)	.31
High income	15/150 (10.0)	6/156 (3.9)	6.2 (−∞ to 12.5)	
Pitt score				
≥4	5/18 (27.8)	0/9	27.8 (−∞ to 51.3)	.99
<4	18/169 (10.7)	7/182 (3.9)	6.8 (−∞ to 12.8)	
Infecting species				
E coli	17/161 (10.6)	7/166 (4.2)	6.3 (−∞ to 12.6)	.99
K pneumoniae	6/26 (23.1)	0/25	23.1 (−∞ to 42.3)	
Infection				
HAI	18/107 (16.8)	4/107 (3.7)	13.1 (−∞ to 21.8)	.26
Non-HAI	5/80 (6.3)	3/84 (3.6)	2.7 (−∞ to 10.7)	
Appropriate empirical antibiotic therapy				
Appropriate	18/126 (14.3)	5/127 (3.9)	10.3 (−∞ to 18.0)	.70
Inappropriate	5/61 (8.2)	2/64 (3.1)	5.1 (−∞ to 15.2)	
UT vs non-UT source				
UT	7/102 (6.9)	4/128 (3.1)	3.7 (−∞ to 10.7)	.44
Non-UT	16/85 (18.8)	3/63 (4.8)	14.1 (−∞ to 24.5)	
Immune compromise[c]				
Present	10/51 (19.6)	1/40 (2.5)	17.1 (−∞ to 30.5)	.27
Absent	13/136 (9.6)	6/151 (4.0)	5.6 (−∞ to 12.2)	

Figure 2. Secondary Outcomes

Measure of Success	Patients Meeting End Point, No./Total No. (%)		Between-Group Difference (95% CI)
	Piperacillin-Tazobactam	Meropenem	
Clinical and microbiological success at day 4[a]	121/177 (68.4)	138/185 (74.6)	-6.2 (-15.5 to 3.1)
Microbiological success at day 4	169/174 (97.1)	184/185 (99.5)	-2.3 (-6.1 to 0.4)



Measure of Failure	Patients Meeting End Point, No./Total No. (%)		Between-Group Difference (95% CI)
	Piperacillin-Tazobactam	Meropenem	
Microbiological relapse	9/187 (4.8)	4/191 (2.1)	2.7 (-1.1 to 7.1)
Secondary infection with multiresistant organism or *Clostridium difficile*	15/187 (8.0)[b]	8/191 (4.2)[c]	3.8 (-1.1 to 9.1)



IDSA Guidance on the Treatment of Antimicrobial-Resistant Gram-Negative Infections: Version 1.0

Published by IDSA, 9/8/2020

07.03.2022 Version 1.1

Pranita D. Tamma*, Samuel L. Aitken, Robert A. Bonomo, Amy J. Mathers, David van Duin, Cornel J. Clancy

*Corresponding Author

Rationale: Piperacillin-tazobactam demonstrates *in vitro* activity against a number of ESBL-E [31]. However, a randomized, controlled trial of ESBL-E bloodstream infections indicated inferior results with piperacillin-tazobactam compared to carbapen therapy [28]. The effectiveness of piperacillin-tazobactam in the treatment of invasive ESBL-E infections may be diminished by th
A
[3

Table 2. Recommended antibiotic treatment options for presumed or confirmed extended-spectrum β-lactamase producing Enterobacterales (ESBL-E), assuming *in vitro* susceptibility to agents in table

Source of Infection	Preferred Treatment	Alternative Treatment (first-line options not available or tolerated)
Cystitis	Nitrofurantoin, trimethoprim-sulfamethoxazole	Amoxicillin-clavulanate, single-dose aminoglycosides, fosfomycin (*E. coli* only) Ciprofloxacin, levofloxacin, ertapenem, meropenem, imipenem-cilastatin
Pyelonephritis or cUTI[1]	Ertapenem, meropenem, imipenem-cilastatin, ciprofloxacin, levofloxacin, or trimethoprim-sulfamethoxazole	
Infections outside of the urinary tract	Meropenem, imipenem-cilastatin, ertapenem Oral step-down therapy to ciprofloxacin, levofloxacin, or trimethoprim-sulfamethoxazole can be considered[2].	

Piperasilin-tazobaktam duyarlılığı gösterilse bile, GSBL-E'nin neden olduğu idrar yolu dışındaki enfeksiyonların tedavisinde piperasilin-tazobaktam önerilmez.

İYE'lerle sınırlı olsa bile, GSBL-E enfeksiyonlarının tedavisi için piperasilin-tazobaktam kullanımıyla ilgili endişelerini sürdürüyor ve karbapenem tedavisini öncelikliyor.

AMERICAN SOCIETY FOR MICROBIOLOGY | Antimicrobial Agents and Chemotherapy

A Multinational, Preregistered Cohort Study of β-Lactam/β-Lactamase Inhibitor Combinations for Treatment of Bloodstream Infections Due to Extended-Spectrum-β-Lactamase-Producing *Enterobacteriaceae*

Belén Gutiérrez-Gutiérrez,[a] Salvador Pérez-Galera,[a] Elena Salamanca,[a] Marina de Cueto,[a] Esther Calbo,[b] Benito Almirante,[c] Pierluigi Viale,[d] Antonio Oliver,[e] Vicente Pintado,[f] Oriol Gasch,[g] Luis Martínez-Martínez,[h] Johann Pitout,[i] Murat Akova,[j] Carmen Peña,[k] José Molina,[a] Alicia Hernández,[l] Mario Venditti,[m] Nuria Prim,[n] Julia Origüen,[o] German Bou,[p] Evelina Tacconelli,[q] Mario Tumbarello,[r] Axel Hamprecht,[s] Helen Giamarellou,[t] Manel Almela,[u] Federico Pérez,[v] Mitchell J. Schwaber,[w] Joaquín Bermejo,[x] Warren Lowman,[y] Po-Ren Hsueh,[z] Marta Mora-Rillo,[aa] Clara Natera,[bb] Maria Souli,[cc] Robert A. Bonomo,[v,dd] Yehuda Carmeli,[w] David L. Paterson,[ee] Alvaro Pascual,[a,ff] Jesús Rodríguez-Baño,[a,gg] the REIPI/ESGBIS/INCREMENT Group

Çok merkezli retrospektif bir kohort

Amaç: Farklı odaklardan kaynaklanan çeşitli ESBL-E'ye bağlı KDİ tedavisi için BLBLI'lerin karbapenemler kadar etkili olup olmadığını değerlendirmekti.

ESBL-E'ye bağlı KDİ olan hastalar incelendi;
ampirik tedavi kohortunda 365 hasta
Hedefe yönelik tedavi kohortunda 601 hasta

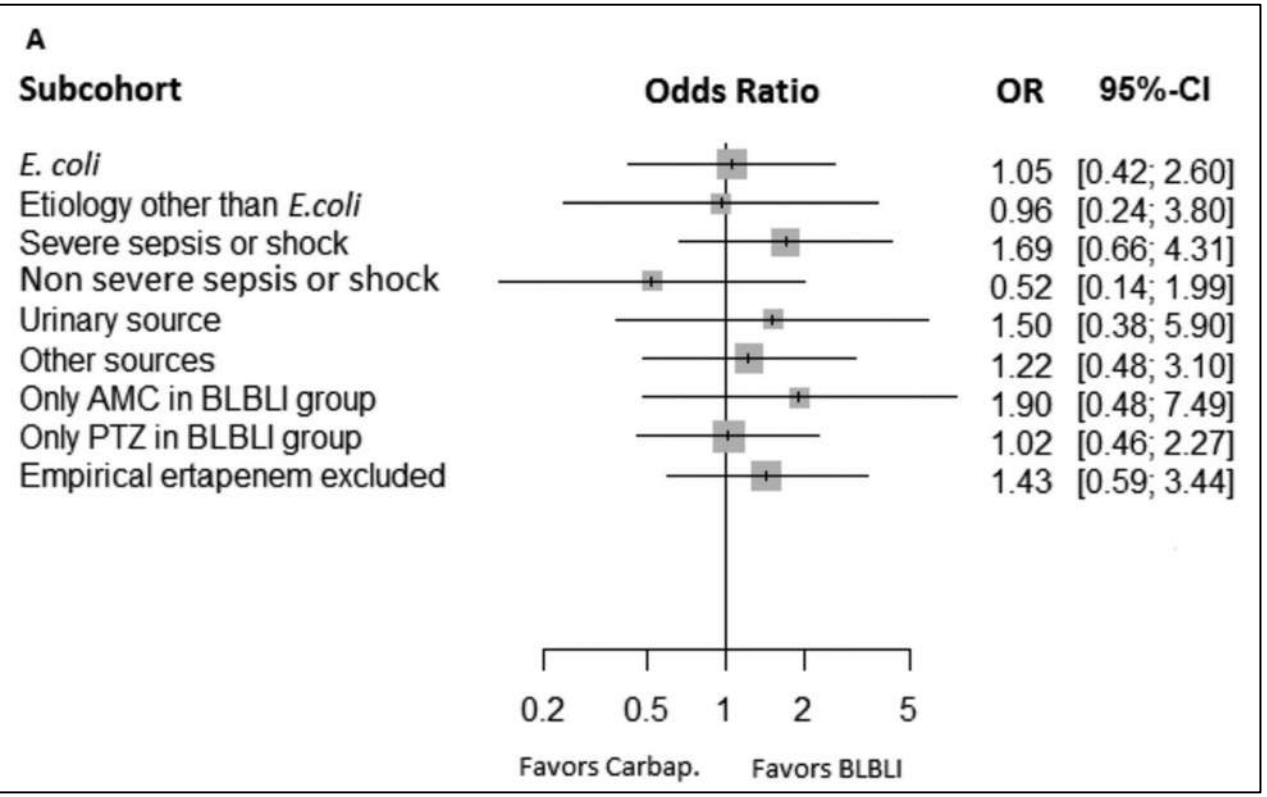
TABLE 1 Characteristics of patients with bloodstream infections caused by extended-spectrum-β-lactamase-producing *Enterobacteriaceae* in the empirical- and targeted-therapy cohorts

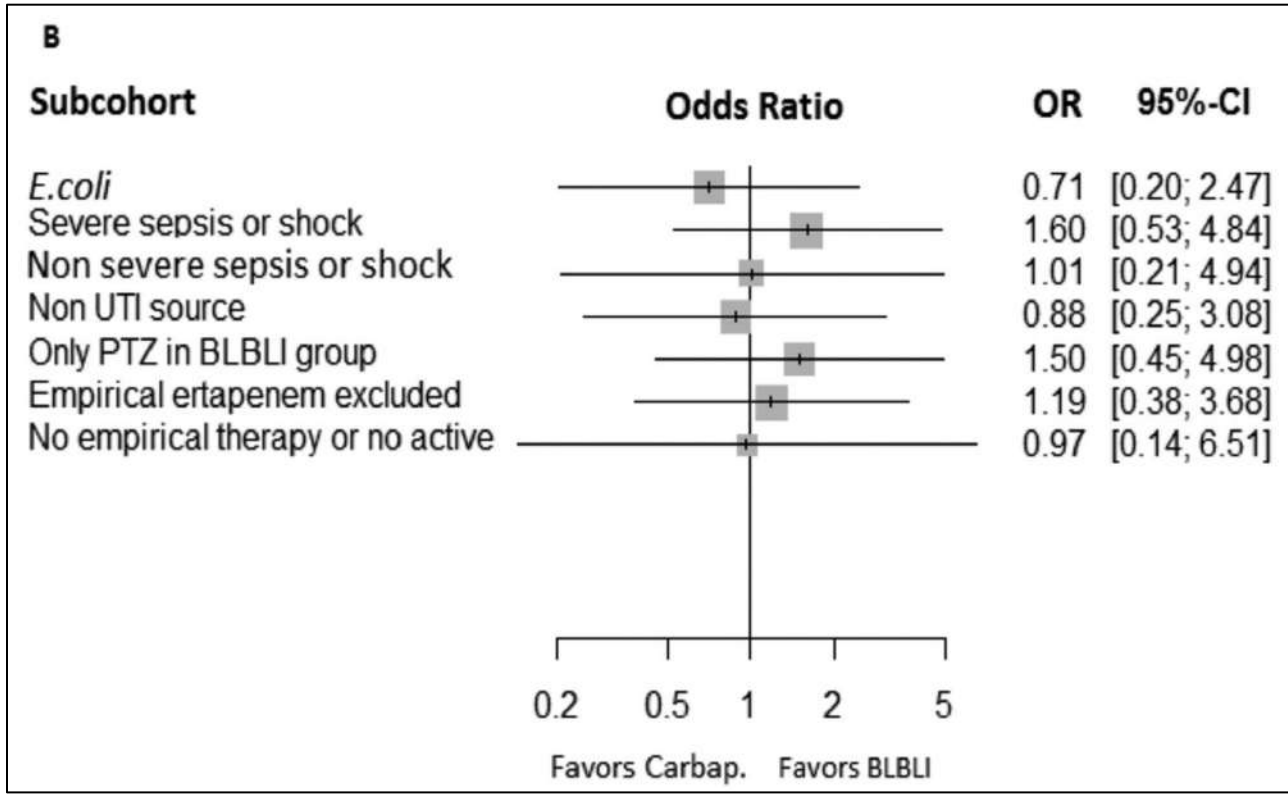
Characteristic	No. (%) of patients (unless otherwise specified) in indicated group					
	Empirical-therapy cohort			Targeted-therapy cohort		
	BLBLI (n = 170)	Carbapenem (n = 195)	P value[a]	BLBLI (n = 92)	Carbapenem (n = 509)	P value[a]
Age [median (IQR[b])]	71.5 (59–79)	66 (54.5–76)	0.005[c]	70.5 (56–80)	68 (56–78)	0.22[c]
Male sex	95 (55.9)	117 (60.0)	0.42	55 (59.8)	295 (58.0)	0.74
Enterobacteriaceae species						
E. coli	130 (76.3)	136 (69.7)	0.15	71 (77.2)	368 (72.3)	0.33
K. pneumoniae	29 (17.1)	45 (23.1)	0.15	13 (14.1)	101 (19.8)	0.20
Other	11 (6.5)	14 (7.2)	0.79	8 (8.7)	40 (7.9)	0.78
Nosocomial acquisition	75 (44.1)	91 (46.7)	0.63	38 (41.3)	247 (48.5)	0.2
Source						
Urinary tract	77 (45.3)	91 (46.7)	0.79	39 (42.4)	233 (45.8)	0.55
Biliary tract	25 (14.7)	24 (12.3)	0.5	9 (9.8)	62 (12.2)	0.51
Other (high-risk source)	68[d] (40.0)	80[e] (41.0)	0.84	44[f] (47.8)	214[g] (42.0)	0.30
ICU[h] admission	13 (7.6)	26 (13.3)	0.071	4 (4.3)	62 (12.2)	0.02
McCabe classification, nonfatal	81 (47.6)	95 (48.7)	0.84	47 (51.1)	263 (51.7)	0.92
Cancer	50 (29.4)	74 (37.9)	0.068	38 (41.3)	208 (40.9)	0.86
Pitt score [median (IQR)]	1 (0–3)	1 (0–3)	0.30[c]	1 (0–2)	1 (0–2)	0.19[c]
Severe sepsis or shock	67 (39.4)	72 (36.9)	0.86	31 (33.7)	164 (32.2)	0.94
Targeted therapy with:						
Carbapenem	80 (47.1)	169 (86.7)	<0.0001			
BLBLI	65 (38.2)	8 (4.1)	<0.0001			
Other drug	25 (14.7)	18 (9.2)	0.11			
Empirical therapy with:						
Carbapenem				4 (4.3)	141 (27.7)	<0.0001
BLBLI				56 (60.9)	140 (27.5)	<0.0001
Other drug				32 (34.8)	228 (44.8)	0.07
Active empirical therapy				65 (70.7)	304 (59.7)	0.047
Cure/improvement	136 (80.0)	154 (79.0)	0.81	83 (90.2)	435 (85.5)	0.22
30-day mortality	30 (17.6)	39 (20.0)	0.60	9 (9.8)	71 (13.9)	0.28

[a] P values were calculated by χ^2 test, except where otherwise specified.
[b] IQR, interquartile range.
[c] Mann-Whitney U test.
[d] Other sources included unknown, 21; intra-abdominal, 20; pneumonia, 12; skin, 7; vascular, 7; other, 1.
[e] Other sources included unknown, 27; vascular, 19; intra-abdominal, 16; pneumonia, 10; skin, 5; other, 3.
[f] Intra-abdominal, 17; unknown, 13; vascular, 6; skin, 3.
[g] Unknown, 74; intra-abdominal, 51; vascular, 33; pneumonia, 26; skin, 15; other, 15.
[h] ICU, intensive care unit.

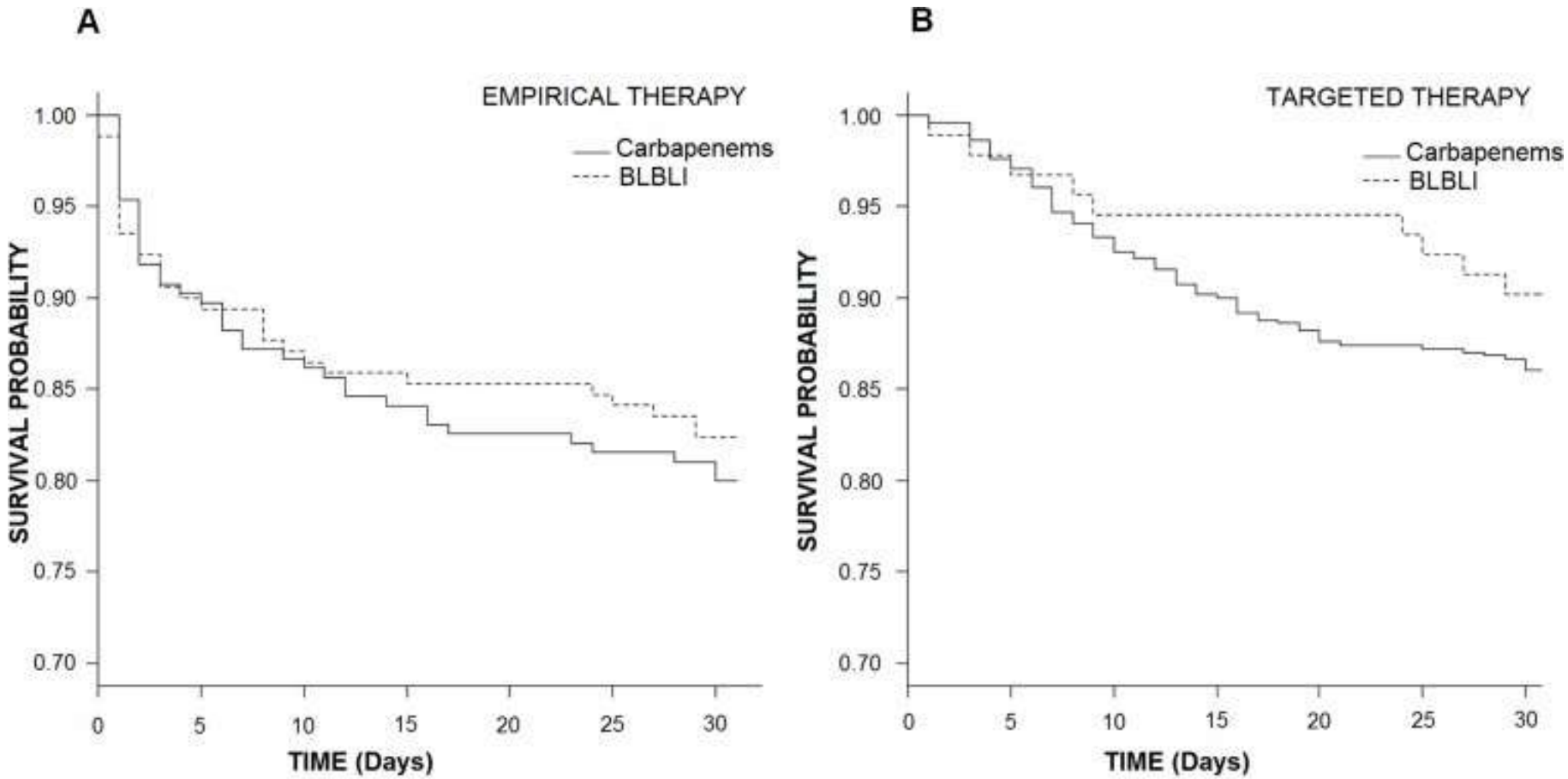
Ampirik tedavi

Hedefe yönelik tedavi





Spesifik alt popülasyonlardaki duyarlılık analizi, BLBLI'ler ile tedavinin etkilerinin etiyoloji, şiddetli sepsis veya şok, kaynak veya kullanılan spesifik antibiyotiklerden bağımsız olarak benzer olduğunu göstermiştir.


A
EMPIRICAL THERAPY
Carbapenems
BLBLI
SURVIVAL PROBABILITY
1.00
0.95
0.90
0.85
0.80
0.75
0.70
0
5
10
15
20
25
30
TIME (Days)
B
TARGETED THERAPY
Carbapenems
BLBLI
SURVIVAL PROBABILITY
1.00
0.95
0.90
0.85
0.80
0.75
0.70
0
5
10
15
20
25
30
TIME (Days)

Open Forum Infectious Diseases

MAJOR ARTICLE

Efficacy of Noncarbapenem β-Lactams Compared to Carbapenems for Extended-Spectrum β-Lactamase–Producing Enterobacterales Urinary Tract Infections

Daniel T. Anderson,[1,a] Benjamin Albrecht,[1] K. Ashley Jones,[1] Jesse T. Jacob,[2,3] Mary Elizabeth Sexton,[2] Zanthia Wiley,[2] William C. Dube,[2] Benjamin Lee,[3] and Sujit Suchindran[2]

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Background. Extended-spectrum β-lactamase (ESBL)–producing Enterobacterales are frequent causes of urinary tract infections (UTIs). Severe infections caused by ESBL Enterobacterales are often treated with carbapenems, but optimal treatment for less severe infections such as UTIs is unclear.

Methods. This retrospective cohort study included patients admitted to 4 hospitals in an academic healthcare system with an ESBL UTI treated with either a noncarbapenem β-lactam (NCBL) or a carbapenem for at least 48 hours from 1 April 2014 to 30 April 2018. Those who received an NCBL were compared to those receiving a carbapenem, with a primary outcome of hospital length of stay (LOS) and secondary outcomes of clinical and microbiological response, days until transition to oral therapy, rate of relapsed infection, and rate of secondary infections with a multidrug-resistant organism.

Results. Characteristics were similar among patients who received carbapenems (n = 321) and NCBLs (n = 171). There was no difference in LOS for the NCBL group compared to the carbapenem group (13 days vs 15 days, $P = .66$). The NCBL group had higher rates of microbiologic eradication (98% vs 92%, $P = .002$), shorter time to transition to oral therapy (5 days vs 9 days, $P < .001$), shorter overall durations of therapy (7 days vs 10 days, $P < .001$), and lower rates of relapsed infections (5% vs 42%, $P = .0003$).

Conclusions. Patients treated with NCBLs had similar LOS, higher rates of culture clearance, and shorter durations of antibiotic therapy compared to patients treated with carbapenems, suggesting that treatment for ESBL UTIs should not be selected solely based on phenotypic resistance.

Keywords. antimicrobial resistance; antimicrobial stewardship; ESBL; extended-spectrum β-lactamase; urinary tract infection.

Open Forum Infectious Diseases, Volume 9, Issue 3, March 2022, ofac034,

https://doi.org/10.1093/ofid/ofac034

- 1 Nisan 2014 ile 30 Nisan 2018 tarihleri arasında 4 farklı hastaneye başvuran ve İYE tanısı ile yatarak tedavi alan hastalar değerlendiriliyor.
  - 18 yaşından büyük,
  - İdrar kültürüne GSBL üreten bir organizma üreyen
  - En az 48 saat boyunca bir karbapenem veya karbapenem dışı beta-laktam ile tedavi edilen hastalar alındı.
- 492 hasta çalışmaya dahil edildi.
- Karbapenem kolunda 321, NCBL kolunda 171 hasta

- **Birincil sonuç;** hastanede kalış süresi.
- **İkincil sonuçlar;**
  - Klinik yanıt
  - Mikrobiyolojik eradikasyon
  - Hastane içi mortalite
  - Oral tedaviye geçiş için günleri
  - Toplam tedavi günleri
  - İdrar dışındaki bir bölgede çoklu ilaca dirençli organizma (MDRO) ile yeni enfeksiyon oranı

Table 2. Characteristics of Patients With a Complicated Urinary Tract Infection Treated With a Carbapenem Compared to Those Treated With a Noncarbapenem β-Lactam

Hospitalization Outcome	Carbapenem (n = 244)	NCBL (n = 118)	*P* Value
Hospital LOS, d, median (IQR)	18.3 (6–14)	13.9 (4–12)	.59
Positive clinical response[a]	232 (95)	114 (97)	.46
In-hospital mortality	12 (5)	6 (5)	.97
Rates of CDI	18 (8)	6 (5)	.31
Secondary MDR within 30 d	27 (11)	6 (5)	.07
Secondary CRE within 30 d	1 (0.8)	0 (0)	1
Microbiologic eradication[b]	222 (91)	115 (98)	.005
Days to transition to oral therapy, mean (SD)	10 (4)	5 (3)	<.0001
Days of therapy, mean (SD)	10 (4)	8 (3)	<.0001
Relapsed infection within 30 d	37 (15)	4 (3)	.0009

https://doi.org/10.1093/ofid/ofac034

CMI CLINICAL MICROBIOLOGY AND INFECTION

ESCMID EUROPEAN SOCIETY OF CLINICAL MICROBIOLOGY AND INFECTIOUS DISEASES

European Society of Clinical Microbiology and Infectious Diseases (ESCMID) guidelines for the treatment of infections caused by multidrug-resistant Gram-negative bacilli (endorsed by European society of intensive care medicine)

Mical Paul [§] • Elena Carrara [§] • Pilar Retamar • ... Johan W. Mouton [†] • Evelina Tacconelli [§] •

Jesús Rodríguez-Baño [§] • Show all authors • Show footnotes

Published: December 15, 2021 • DOI: https://doi.org/10.1016/j.cmi.2021.11.025

ESBL-E'de Tedavi Seçenekleri

Öneri	Öneri Gücü	Kanıt düzeyi
Düşük riskli, şiddetli olmayan enfeksiyonlarda piperasilin-tazobaktam veya amoksisilin/klavulanik asit başlanabilir. Şiddetli olmayan cUTI için TMP-SMX düşünülebilir.	İyi klinik uygulama	Orta / uzman önerisi
Tüm hastalar için karbapenem tedavisini takiben stabil olan bir hasta için eski BL-BLI'ler, kinolonlar, TMP-SMX veya duyarlılık paternine göre diğer antibiyotiklerle tedaviye devam edilebilir.	İyi klinik uygulama	Uzman önerisi

ESCMID guidelines for the treatment of infections caused by MDR-GNB. Clin Microbiol Infect; 2021.

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

Piperacillin/tazobactam as an alternative antibiotic therapy to carbapenems in the treatment of urinary tract infections due to extended-spectrum β-lactamase-producing Enterobacteriaceae: an in silico pharmacokinetic study

Hélène Guet-Revillet [a,b,1], Elise Tomini [b,1], Aurélie Emirian [c,d], Olivier Join-Lambert [a,b], Hervé Lécuyer [a,b], Jean-Ralph Zahar [e,f,2,*], Vincent Jullien [g,h]

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[d] Université Paris-Est, Créteil, France
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Table 1
Susceptibility of extended-spectrum β-lactamase-producing *Escherichia coli* (ESBL-Ec) and *Klebsiella pneumoniae* (ESBL-Kp) strains to piperacillin/tazobactam.

	ESBL-Ec (n = 144)	ESBL-Kp (n = 111)
Inhibition zone diameter ≥21 mm	133 (92.4%)	74 (66.7%)
MIC ≤8 mg/L	128 (88.9%)	51 (45.9%)
MIC_{50}	2	8
Minimum MIC (mg/L)	0.5	0.19
Maximum MIC (mg/L)	16	64

MIC, minimum inhibitory concentration; MIC_{50}, MIC for 50% of the isolates.

Serbest piperasilin plazma konsantrasyonlarını MİK'in üzerinde tutma olasılığı, iki farklı popülasyon farmakokinetik modeliyle 120 mL/dk'lık bir kreatinin klirensi (CLCr) ile simüle edilerek belirlendi.

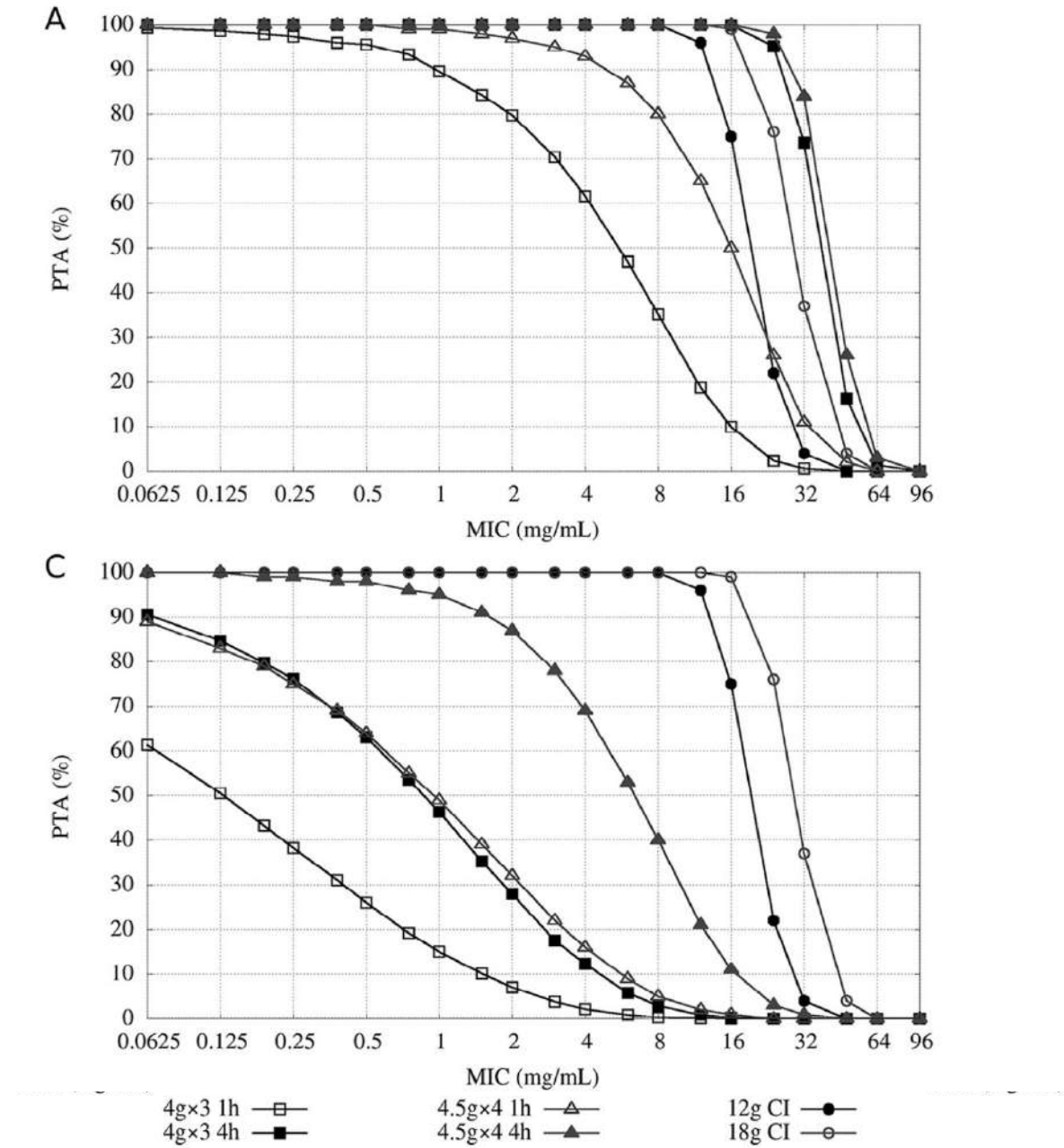

Fig. 1. Probability of target attainment (PTA) according to the pharmacokinetic/pharmacodynamic target, the minimum inhibitory concentration (MIC) and the model used: (a) PTA for 50%$fT_{>MIC}$ and Model A; (b) PTA for 50%$fT_{>MIC}$ and Model B; (c) PTA for 100%$fT_{>MIC}$ and Model A; and (d) PTA for 100%$fT_{>MIC}$ and Model B. %$fT_{>MIC}$, percentage of the dosing interval that the free drug concentration exceeds the MIC of the micro-organism; CI, continuous infusion.

BMJ Open

Piperacillin–tazobactam versus meropenem for treatment of bloodstream infections caused by third-generation cephalosporin-resistant Enterobacteriaceae: a study protocol for a non-inferiority open-label randomised controlled trial (PeterPen)

Roni Bitterman ,[1,2] Fidi Koppel,[1] Cristina Mussini,[3] Yuval Geffen,[4] Michal Chowers,[5,6] Galia Rahav,[7,8] Lior Nesher,[9,10] Ronen Ben-Ami,[6,11] Adi Turjeman,[6,12] Maayan Huberman Samuel,[12] Matthew P Cheng,[13] Todd C Lee,[13] Leonard Leibovici,[6,12] Dafna Yahav,[6,14] Mical Paul[1,2]

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ABSTRACT

Introduction The optimal treatment for extended-spectrum β-lactamase (ESBL)-producing Enterobacteriaceae bloodstream infections has yet to be defined. Retrospective studies have shown conflicting results, with most data suggesting the non-inferiority of beta-lactam–beta-lactamase inhibitor combinations compared with carbapenems. However, the recently published MERINO trial failed to demonstrate the non-inferiority of piperacillin–tazobactam to meropenem. The potential implications of the MERINO trial are profound, as widespread adoption of carbapenem treatment will have detrimental effects on antimicrobial stewardship in areas endemic for ESBL and carbapenem-resistant bacteria. Therefore, we believe that it is justified to re-examine the comparison in a second randomised controlled trial prior to changing clinical practice.

Methods and analysis PeterPen is a multicentre, investigator-initiated, open-label, randomised controlled non-inferiority trial, comparing piperacillin–tazobactam with meropenem for third-generation cephalosporin-resistant *Escherichia coli* and *Klebsiella* bloodstream infections. The study is currently being conducted in six centres in Israel and one in Canada with other centres from Israel, Italy and Canada

Trial registration numbers ClinicalTrials.gov Registry (NCT03671967); Israeli Ministry of Health Trials Registry (MOH_2018-12-25_004857).

Strengths and limitations of this study

- The study addresses a question of critical importance to antibiotic stewardship.
- Assuming the sample size estimates are correct, this pragmatic randomised controlled trial will provide a more definitive answer.
- Susceptibilities determined by automated methods may underestimate piperacillin–tazobactam resistance, and resistance genes will not be available in real time. Hence, there will be a risk of misclassified patients.
- Antibiotic levels will not be tested to direct dosing; however, extended infusion regimens have been chosen to match expected target attainment for most patients.
- The study will reflect current standard of care provided to patients.

Olgu 1

Komplike üriner sistem enfeksiyonu
Ampirik Piperasilin-tazobaktam başlanmış
İdrar kültürü: ESBL(+) *E.coli* 100.000 cfu/ml
5 gün 3x4,5 gr Piperasilin-tazobaktam sonrası oral-ardışık
Trimetoprim/Sulfametaksazol ile taburcu edilmiş

Soru: Ampirik Piperasilin-tazobaktam doğru seçenek mi?
Oral ardışık tedavi uygun yaklaşım oldu mu?

Olgu 2

Komplike üriner sistem enfeksiyonu
Hipotansif, Genel durumu kötü
Ertapenem 1x1 gr IV ampirik olarak başlandı
Kan ve idrar kültüründe ESBL(+) *K.pneumonia* üremesi var
Ertapenemle tedavisi tamamlanmış.

Soru: Ampirik Piperasilin-tazobaktam başlanabilir miydi?
Kültür sonucuna göre karbapenem kesilebilir miydi?

Olgu 3

- 60 y, erkek hasta ateş, üşüme-titreme, bulantı ve idrar yapmada zorlanma şikayeti ile başvurdu.
- Hipertansiyon ve KAH öyküsü mevcut ve COVID-19 pnömonisi nedeniyle takip edildiği YBÜ den 10 gün önce taburcu edilmiş.
  - Hastanın 5 gün önce dış merkezdeki idrar kültüründe ESBL(+) *K.pneumoniae* 100.000 kol/ml üremesi mevcut olup yalnızca fosfomisin ve imipenem duyarlı olarak rapor edilmiş.
- Ateş: 38.8^{o}C, TA:110/70 mmHg, sağda KVAH pozitif.
- WBC: 12810 (%92 PMNL) PLT: 114000 /uL, CRP: 100 mg/dl, AST/ALT: 94/149 U/L.
- İdrar mikroskobik inceleme: 260 lökosit/mm^3 ve Gram(-) basil mevcut.

Tanı: Komplike üriner sistem infeksiyonu
Fosfomisin 3X4 gr IV ampirik olarak başlandı

Olgu 3

- Tedavinin 2. gününde ateş dışında diğer vital bulguları stabil olan hastanın kan kültüründe Gram (-) basil sinyali bildirilmesi üzerine fosfomisin kesilerek imipenem 4x500 mg IV tedavisine geçildi.

- İmipenem tedavisinin 24. saatinde ateş yanıtı alındı.
- İmipenem tedavisinin 48. saatinde (yatışının 4. gününde) hastanın genel durumu iyi, ateş olmadı.
  - idrar kültürü: ***K.pneumoniae*** **ESBL(+)** 100.000 kol/ml
  - kan kültürü: ***K.pneumoniae*** **ESBL (+)**

Kan ve İdrar kültürü: *K.pneumoniae* ESBL (+)

Antibiyotik	Yorum	Antibiyotik	Yorum
Ampisilin	R	Siprofloksain	R
Amoksisilin-klavulonik asit	S	Amikasin	S
Piperasilin-tazobaktam	S	Trimetoprim-sulfametaksazol	S
Seftazidim	R	Fosfomisin*	S
Seftriakson	R	Nitrofurantoin*	S
Sefepim	R		
Ertapenem	S		
İmipenem	S		
Meropenem	S		

* İdrar izolatında

Olgu 3

- Hastanın idrar ve kan kültürü raporuna istinaden imipenem tedavisi kesilerek tekrar fosfomisin 3x4 gr IV başlandı
- Kontrol kan ve idrar kültüründe üreme olmadı.
- **Fosfomisin** tedavisi tamamlanarak taburcu edildi.

- GSBL-E infeksiyonlarında fosfomisin karbapenem koruyucu seçenek olarak kullanılabilir mi?
- Bakteremili hastalarda fosfomisin monoterapisi kullanılabilir mi?

Clinical Infectious Diseases
MAJOR ARTICLE

Fosfomycin for Injection (ZTI-01) Versus Piperacillin-tazobactam for the Treatment of Complicated Urinary Tract Infection Including Acute Pyelonephritis: ZEUS, A Phase 2/3 Randomized Trial

Keith S. Kaye,[1] Louis B. Rice,[2] Aaron L. Dane,[3] Viktor Stus,[4] Olexiy Sagan,[5] Elena Fedosiuk,[5] Anita F. Das,[7] David Skarinsky,[8,a] Paul B. Eckburg,[8,a] and Evelyn J. Ellis-Grosse[8,a]

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233'ü fosfomisin ve 231'i piperasilin-tazobaktam alan 465 hasta

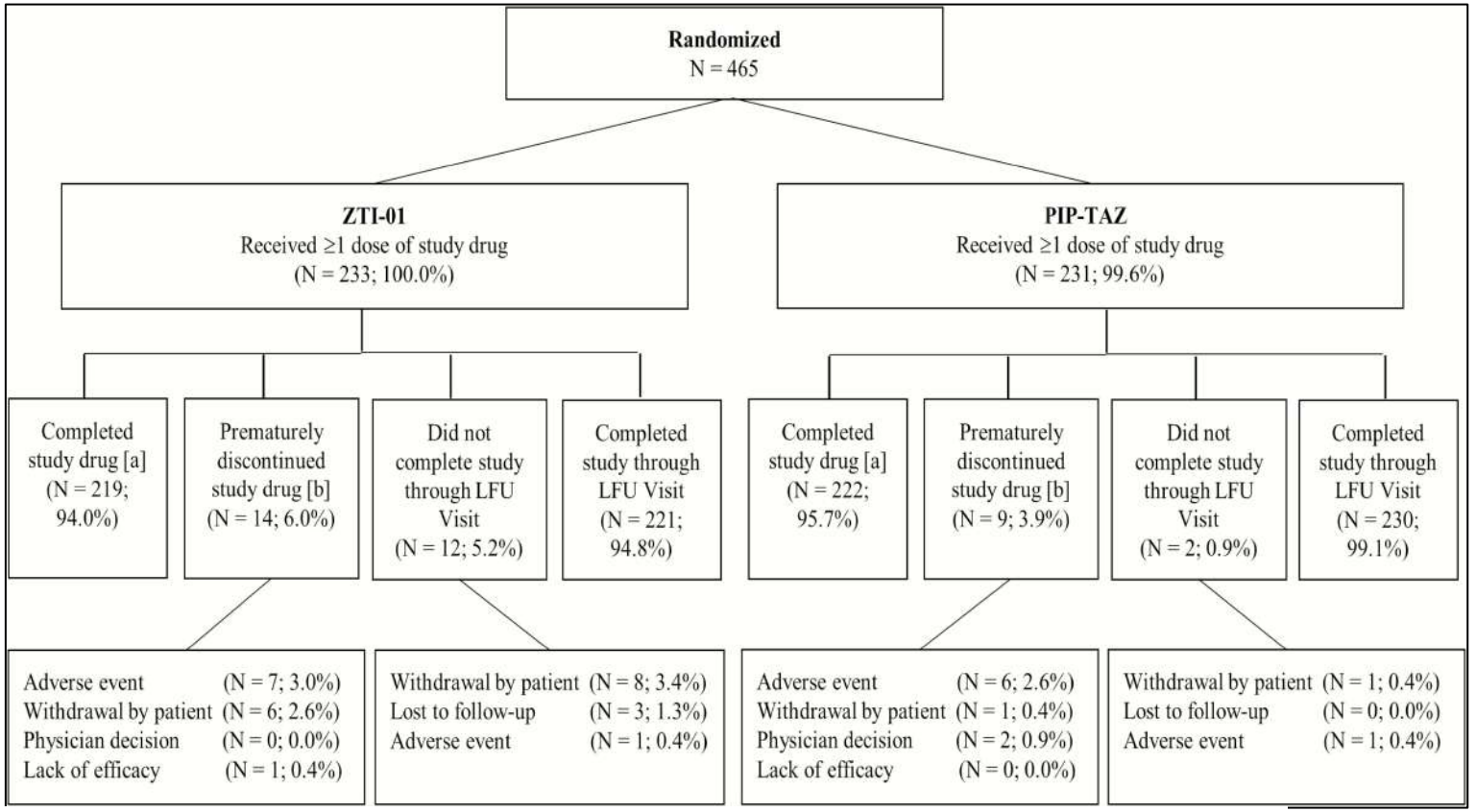

Table 4. Clinical and Microbiologic Outcomes Among Patients With Baseline Pathogens Demonstrating Phenotypic Resistance Characteristics (Test of Cure, Microbiologic Modified Intent-to-Treat) [9]

Phenotype	Clinical cure[a]		Microbiologic eradication[b]	
	Fosfomycin *n/N* (%)	Piperacillin-tazobactam *n/N* (%)	Fosfomycin *n/N* (%)	Piperacillin-tazobactam *n/N* (%)
ESBL	52/56 (93%)	51/55 (93%)	32/58 (55%)	27/57 (47%)
Aminoglycoside-resistant	29/30 (97%)	29/31 (94%)	20/30 (67%)	12/32 (38%)
CRE	9/9 (100%)	11/13 (85%)	5/9 (56%)	4/13 (31%)
MDR	34/37 (92%)	28/31 (90%)	20/37 (54%)	12/33 (36%)

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Original Investigation | Infectious Diseases

Effectiveness of Fosfomycin for the Treatment of Multidrug-Resistant *Escherichia coli* Bacteremic Urinary Tract Infections

A Randomized Clinical Trial

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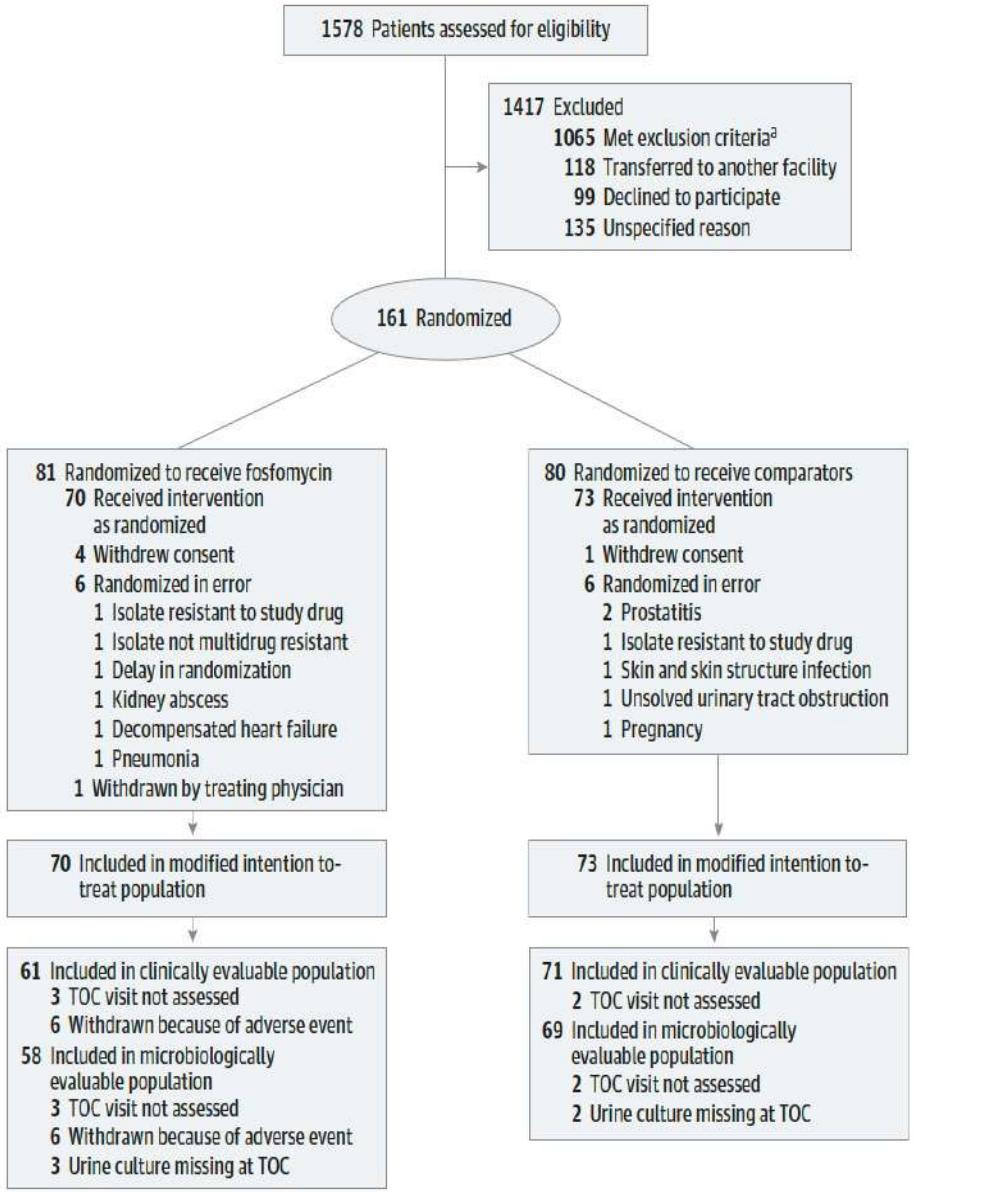
Amaç: E coli'ye bağlı bakteriyemik idrar yolu enfeksiyonlarının hedeflenen tedavisinde fosfomisinin, seftriakson veya meropenemle karşılaştırılması

Dahil edilme kriterleri; Fosfomisin ve seftriakson veya meropenem duyarlılığı olan *E.coli'nin* etken olduğu bakterreminin eşlik ettiği üriner sistem enfeksiyonu olan ve hastanede yatan yetişkin hastalar, en az 4 gün IV tedavi alacaklar
Hariç tutma kriterleri; septik şok, prostatit, böbrek nakli, polikistik böbrek hastalığı, palyatif bakım, Sınıf III veya IV kalp yetmezliği, karaciğer sirozu ve hemodiyaliz hastaları ve randomizasyondan önce 72 saatten fazla aktif ampirik tedavi alma

Birincil sonuç, tedavinin tamamlanmasından 5 ila 7 gün sonra klinik ve mikrobiyolojik kür idi; eşitsizlik marjı %7 kabul edildi.

Fosfomisin disodyum (4 g her 6 saatte bir, 60 dakikalık infüzyon)
Seftriakson (1 g/gün, 2-4 dk)
Meropenem (her 8 saatte bir 1 g, 15-30 dakika içinde intravenöz olarak).
4 günlük intravenöz tedaviden sonra aktif bir oral ilaca geçişe izin verildi.

Figure. Patient Recruitment and Flow Through Study



JAMA Network Open. 2022;5(1):e2137277. doi:10.1001/jamanetworkopen.2021.37277

Table 2. Patients Reaching CMC and Reasons for Not Reaching It

	Patients, No./total No. (%)			
	Receiving fosfomycin	Receiving comparator	Risk difference (1-sided 95% CI)[a]	*P* value, 1-sided
CMC at TOC among MITT (measures of success)				
All patients	48/70 (68.6)	57/73 (78.0)	−9.4 (−21.5 to ∞)	.10
Patients with ceftriaxone-susceptible isolates[b]	25/31 (80.6)	27/31 (87.0)	−6.4 (−21.7 to ∞)	.24
Patients with ceftriaxone-resistant isolates[b]	23/39 (59.0)	30/42 (71.4)	−12.4 (−29.8 to ∞)	.12

Reasons for not reaching CMC at TOC among MITT (measures of failure)				
Clinical or microbiological failure				
All patients	10/70 (14.3)	14/73 (19.7)	−5.4 (−∞ to 4.9)	.19
Patients with ceftriaxone-susceptible isolates[b]	3/31 (9.7)	4/31 (12.9)	−3.2 (−∞ to 10.0)	.34
Patients with ceftriaxone-resistant isolates[b]	7/39 (17.9)	10/42 (23.8)	−8.9 (−∞ to 6.9)	.25
Other reasons				
Withdrawn because of adverse events	6/70 (8.5)[c]	0/73 (0)	8.5 (−∞ to 13.9)	.006
Missed assessment at TOC	3/70 (4.2)	2/73 (2.7)	1.5 (−∞ to 6.5)	.31
TOC assessed but urine culture at TOC not available	3/70 (4.2)	0/73 (0)[d]	4.2 (−∞ to 8.1)	.03

Fosfomisin, MDR *E.coli'nin* neden olduğu bakteremili üriner sistem enfeksiyonlarında meropenem veya seftriaksona karşı non-inferior değildi.

Bununla birlikte, veriler ilacın etkili olduğunu ve özellikle önceden kalp hastalığı olmayan ve sodyum aşırı yüklenmesi ile ilgili sorunları düşük riski olan seçilmiş hastalar arasında kullanılabileceğini düşündürmektedir.

Son olarak, araştırmacılar seftriakson veya meropenem ile karşılaştırıldığında fosfomisine maruz kalmanın neden olduğu ikincil hasarın boyutunu araştırmaya çalıştılar.

Kayıt sırasında ve çalışma süresi boyunca periyodik olarak 38 hastadan alınan rektal sürveyans swabları, tedavinin sonunda, fosfomisin alan hiçbir hastanın seftriakson dirençli veya meropenem dirençli gram-negatif organizmalarla yeni kolonize olmadığını ortaya koydu (*P* = .01).

Bununla birlikte, seftriakson ile tedavi edilen 2 hasta ve meropenem ile tedavi edilen 2 hasta, sırasıyla GSBL üreten organizmalar ve OXA-48 üreten organizmalar ile kolonize olmuştu.

Genel olarak elde edilen bu veriler, fosfomisinin seftriakson ve meropenemden daha az ekolojik hasara neden olabileceği fikrini desteklemektedir

- GSBL-E infeksiyonlarında fosfomisin karbapenem koruyucu seçenek olarak kullanılabilir mi?
- Bakteremili hastalarda fosfomisin monoterapisi kullanılabilir mi?

Sonuç olarak

Karbapenem koruyucu tedaviler, uygulanması zorunlu olan ve daha fazla çalışma ile şiddetli hasta gruplarında etkinliğinin belirlenmesi gereken bir stratejidir.

Bu alanda, kombine antibiyoterapileri, karbapenem koruyucu seçenekler arasında değerlendiren çalışmalara ihtiyaç vardır.

Etken mikroorganizmanın tanımlama ve direnç paterninin belirleme süresi hızlı ise koruyucu stratejinin daha kolay uygulanabilir.

Seftazidim-avibaktam gibi yeni BL-BLI alternatifler, karbapenem dirençli organizmalar için ayrılmalıdır .

Karbapenem Tedavisinden Vazgeçelim mi?
Nasıl Vazgeçelim?

Katılımınız için teşekkürler

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