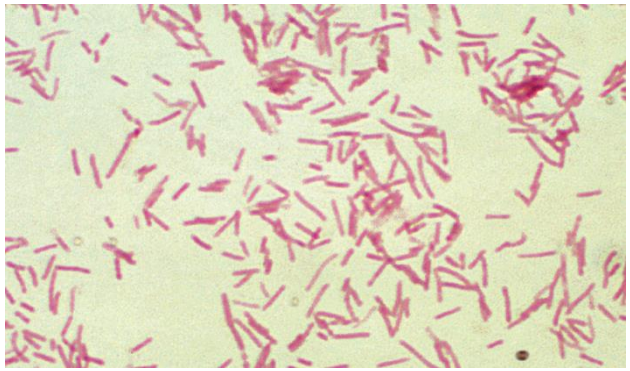
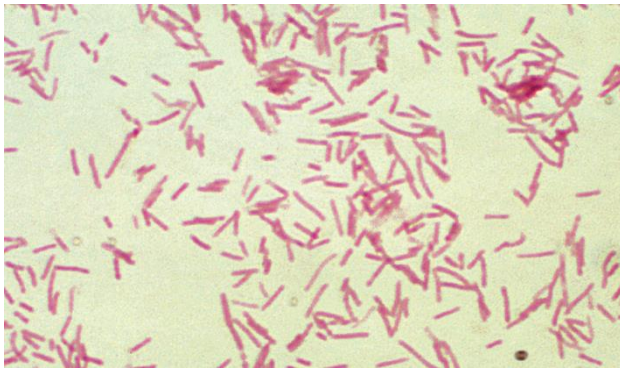
GENİŞLEMİŞ SPEKTRUMLU BETA LAKTAMAZ ÜRETEN ENTERİK BAKTERİ İNFEKSİYONLARININ TEDAVİSİNDE KARBAPENEM GEREKİR

Dr. Bilgül Mete
İ.Ü. Cerrahpaşa İnfeksiyon Hastalıkları ve Klinik Mikrobiyoloji A.D



GSBL



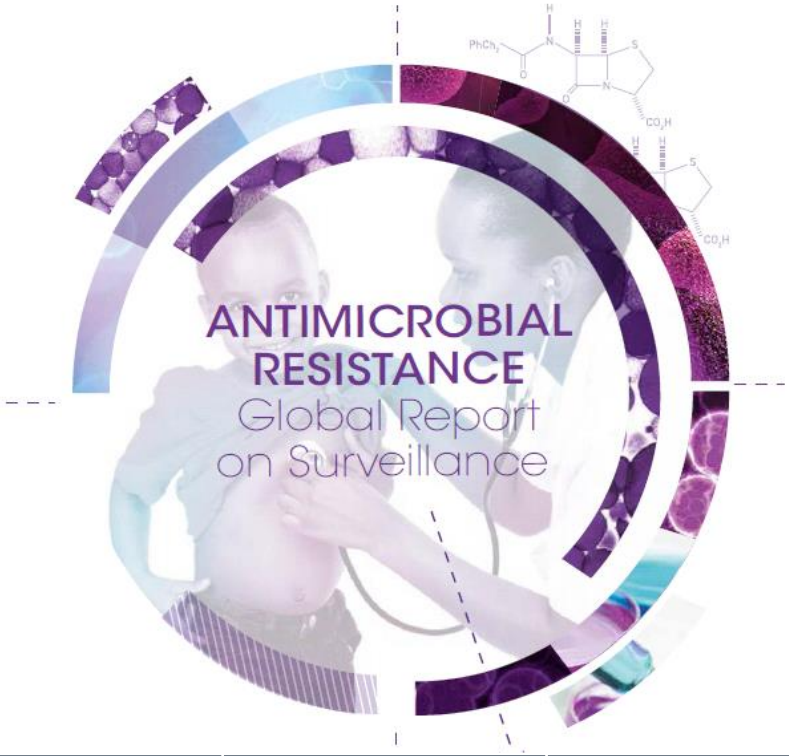
Dirençli

- penisilinler
- sefalosporinler
- aztreonam

Duyarlı

- sefamisin grubu antibiyotikler (sefoksitin, sefotetan, sefmetazol)
- karbapenemler
- klavulanat, sulbaktam ve tazobaktam

EPİDEMİYOLOJİ



	ABD (%)	Avrupa(%)	Güneydoğu Asya (%)
E.coli	0-48	3-82	16-68
K.pneumoniae	4-71	2-82	34-81

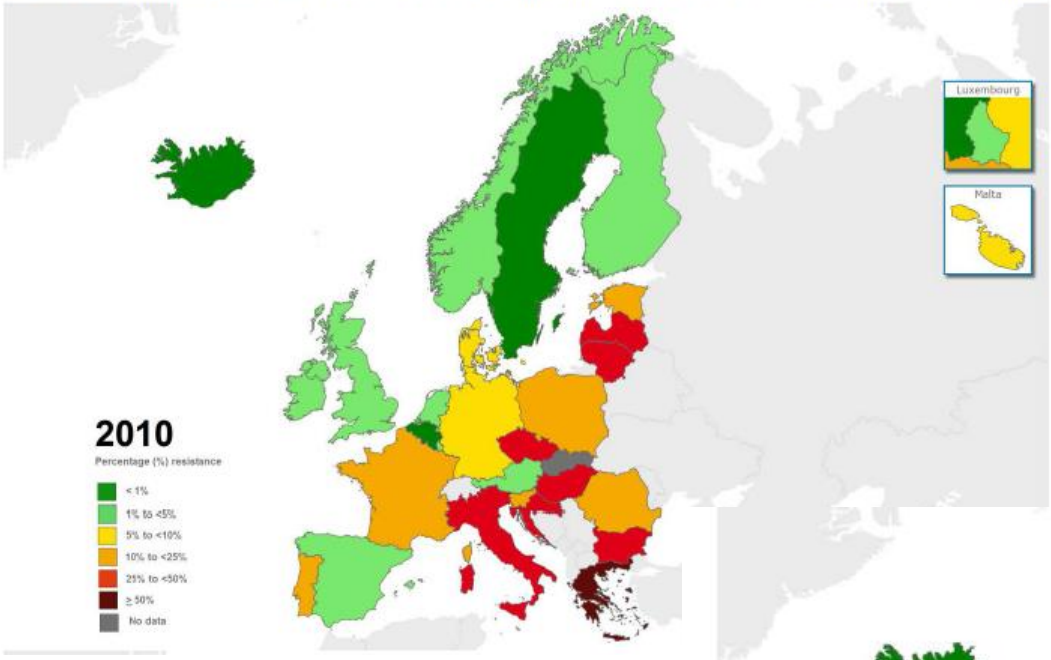
SENTRY Antimikrobiyal Sürveyans Program verileri

	E. coli	*K. pneumoniae*
ABD	%13,7 (4-24)	%23 (11-35)
Avrupa	%16,6	%27,5 ➡ %41,8 ⬆

Sader HS, Farrell DJ, Flamm RK, Jones RN. Antimicrobial susceptibility of Gram-negative organisms isolated from patients hospitalized in intensive care units in United States and European hospitals (2009-2011). Diagn Microbiol Infect Dis. 2014;78(4):443-8.

Denys GA, Callister SM, Dowzicky MJ. Antimicrobial susceptibility among gram-negative isolates collected in the USA between 2005 and 2011 as part of the Tigecycline Evaluation and Surveillance Trial (T.E.S.T.). Ann Clin Microbiol Antimicrob. 2013 Sep 5;12:24.

Figure 1. *Klebsiella pneumoniae*: percentage of invasive isolates with combined resistance to third-generation cephalosporins, fluoroquinolones and aminoglycosides, EU/EEA, 2010 (top), 2013 (bottom)

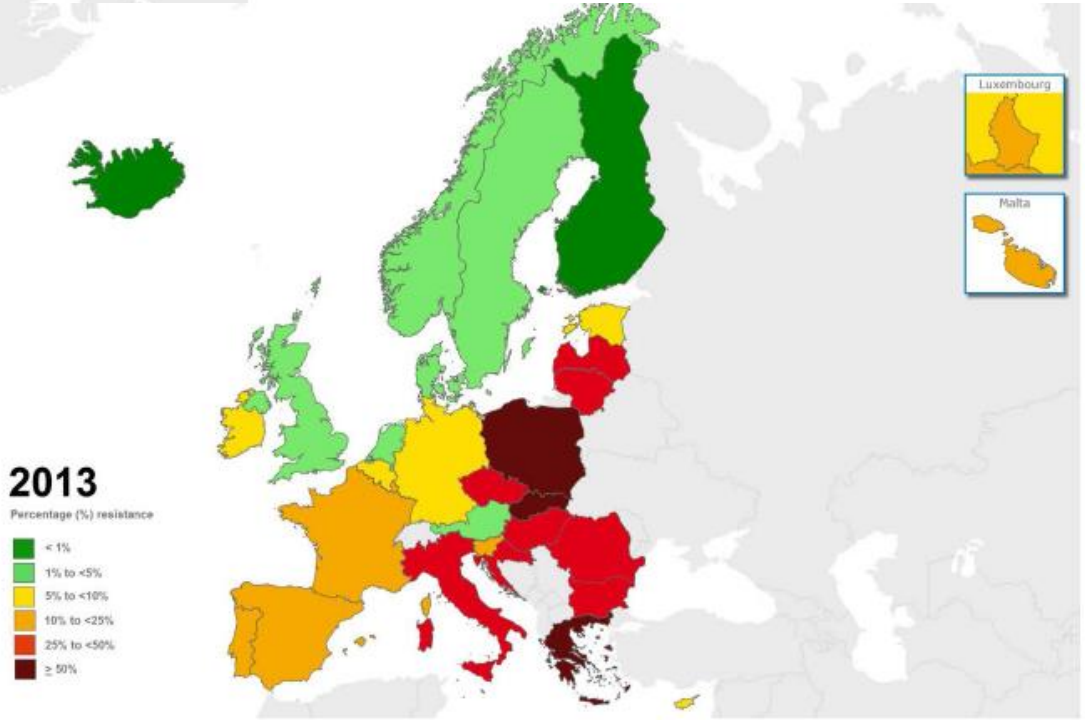


Kinolon, 3. kuşak sefalosporin ve aminoglikozidlere karşı kombine direnç oranı

%10 ➡ %21

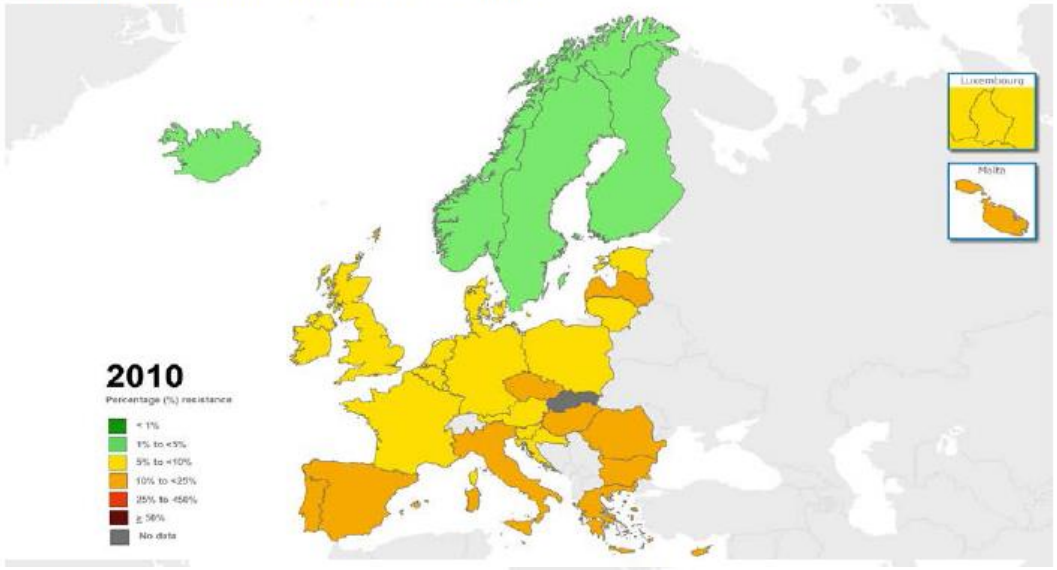
Karbapenem direnci

%4,6 ➡ %8,3



EARS-Net interactive database:
http://www.ecdc.europa.eu/en/healthtopics/antimicrobial-resistance/database

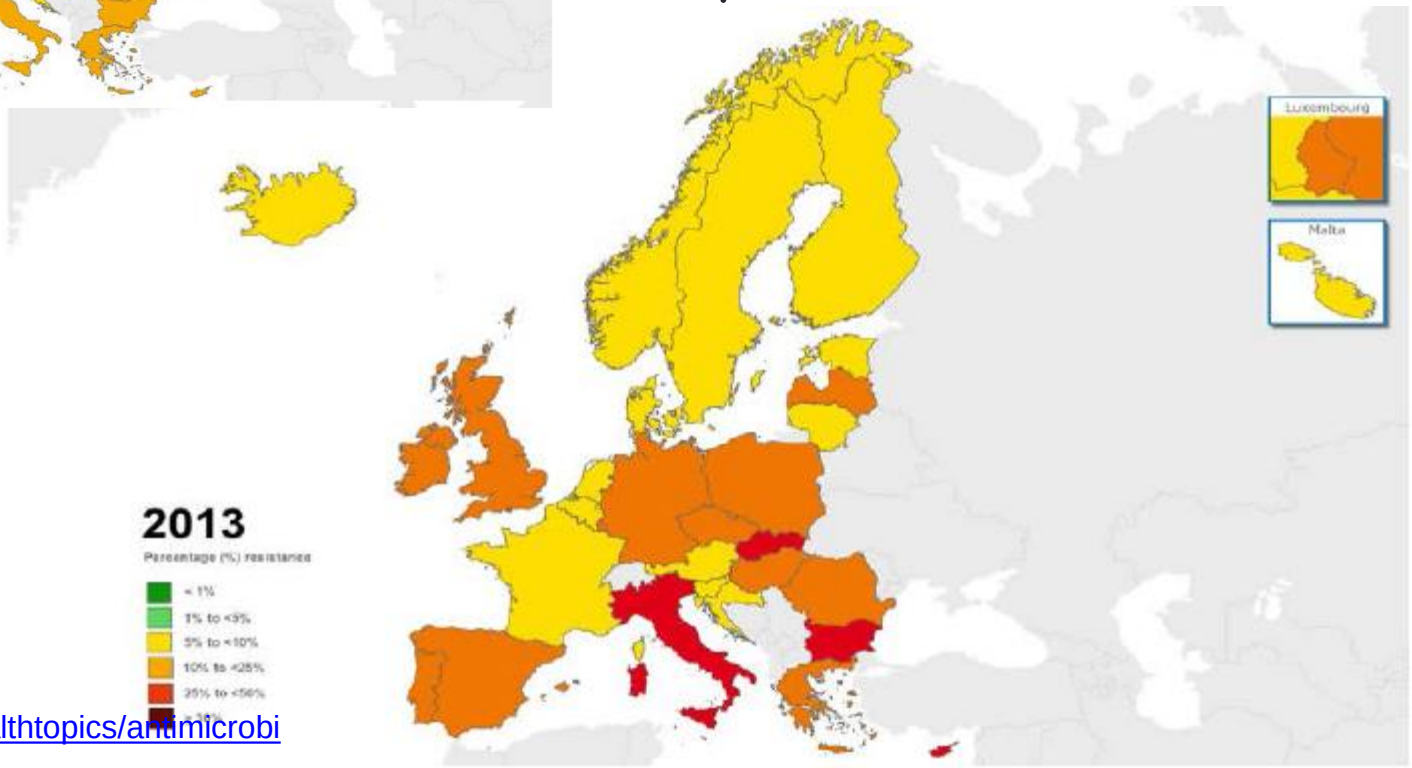
Figure 3. *Escherichia coli*: percentage of invasive isolates with resistance to third-generation cephalosporins, EU/EEA, 2010 (top), 2013 (bottom)



3. kuşak sefalosporine karşı direnç oranı

%9,5 ➡ %12,6

Karbapenem direnci düşük düzeylerde kaldı.



EARS-Net interactive database:
http://www.ecdc.europa.eu/en/healthtopics/antimicrobial-resistance/database

Table A2.4 *Escherichia coli*: Resistance to third-generation cephalosporins[a] European Region

Countries, territories and other areas or groupings	Data source[b,c,d]	Resistance (%)	No. tested isolates	Type of surveillance, population or samples[c]	Period for data collection	Year of publication or report
The former Yugoslav Republic of Macedonia	National data	47.4	19	Invasive isolates		2013
Turkey	National data	43.3	1306	Invasive isolates	2011	2013
Turkmenistan	No information obtained for this report					

Table A2.16 *Klebsiella pneumoniae*: Resistance to third-generation cephalosporins[a] European Region

Countries, territories and other areas or groupings	Data source[b, c, d]	Resistance (%)	No. tested isolates	Type of surveillance, population or samples[c]	Period for data collection	Year of publication or report
Turkey	National data	52.4	794	Invasive isolates	2011	2013
Turkmenistan	No information obtained for this report					
Ukraine	No information obtained for this report[e]					

RİSK FAKTÖRLERİ

Risk faktörleri

E.coli (CTX-M)

- **tekrarlayan üriner sistem** infeksiyonları ve altta yatan renal patoloji
- **öncesinde antibiyotik** (özellikle sefalosporin ve florokinolon) kullanımı
- **hastanede yatış** öyküsü
- bakım evi öyküsü
- ileri yaş
- diabetes mellitus
- altta yatan karaciğer hastalığı
- endemik bölgeye seyahat

K. pneumoniae (SHV,TEM)

- **hastanede veya YBÜ'de** uzun süreli yatış
- **altta yatan hastalığın** ağırlık derecesi
- **entübasyon ve mekanik ventilasyon**
- **üriner veya arteriyel kateterizasyon**
- **öncesinde antibiyotik** (özellikle sefalosporin) kullanımı

MORTALİTE

- GSBL üreten enterik bakterilerin etken olduğu infeksiyonlarda **mortalite oranları yüksek**

- Yüksek mortalitede en önemli etkenlerden biri **etkili tedavide gecikme**

Mortality and delay in effective therapy associated with extended-spectrum β-lactamase production in Enterobacteriaceae bacteraemia: a systematic review and meta-analysis

Mitchell J. Schwaber[1]* and Yehuda Carmeli[1,2]

[1]*Division of Epidemiology, Tel Aviv Sourasky Medical Center, Tel Aviv, Israel;* [2]*Division of Infectious Diseases, Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, MA, USA*

Received 28 February 2007; returned 21 April 2007; revised 22 July 2007; accepted 31 July 2007

Objectives: We performed a systematic review and meta-analysis to examine the impact of extended-spectrum β-lactamase (ESBL) production on mortality and delay in effective therapy in Enterobacteriaceae bacteraemia.

Methods: We searched the PubMed database using the terms 'bacteremia or bloodstream' and 'ESBL or extended-spectrum beta-lactamase'. Included studies contained numbers of and mortality figures for patients with bacteraemia caused by ESBL producers and non-producers. Data extracted included crude relative risk (RR), adjusted odds ratio and 95% confidence intervals (CIs) for mortality and delayed effective therapy. Results were pooled using a random effects model.

Results: Sixteen studies met inclusion criteria. Meta-analysis of crude RRs demonstrated significantly increased mortality in ESBL-associated bacteraemia (pooled RR 1.85, 95% CI 1.39–2.47, $P < 0.001$). However, only one study reported RR controlled for confounding. Ten studies reported comparative data on delay in effective therapy. Meta-analysis of crude RRs demonstrated significantly increased incidence of delay in effective therapy in ESBL-associated bacteraemia (pooled RR 5.56, 95% CI 2.94–10.51, $P < 0.001$).

Conclusions: In Enterobacteriaceae bacteraemia, ESBL production is associated with increased mortality and delay in effective therapy. However, lack of controlled studies limits interpretation regarding causality, and further controlled studies are required.

- GSBL üretiminin kaba mortalite ve etkili tedavi başlanmasında gecikmenin irdelendiği bu meta-analizde **GSBL üretimi** ile **etkili tedavide gecikme** arasında **anlamlı bir ilişki** saptanmıştır.

- GSBL(+) grupta **tedavide gecikmenin >5 kat** olduğu gözlenmiştir.

Journal of Antimicrobial Chemotherapy (2009) **63**, 568–574
doi:10.1093/jac/dkn514
Advance Access publication 6 January 2009

JAC

Analysis of 4758 *Escherichia coli* bacteraemia episodes: predictive factors for isolation of an antibiotic-resistant strain and their impact on the outcome

M. Ortega[1]*, F. Marco[2], A. Soriano[3], M. Almela[2], J. A. Martínez[3], A. Muñoz[3] and J. Mensa[3]

[1]*Emergency Department, Hospital Clínic, IDIBAPS, University of Barcelona, Barcelona, Spain;* [2]*Microbiology Department, Hospital Clínic, IDIBAPS, University of Barcelona, Barcelona, Spain;* [3]*Infectious Diseases Unit, Hospital Clínic, IDIBAPS, University of Barcelona, Barcelona, Spain*

Received 10 October 2008; returned 1 November 2008; revised 16 November 2008; accepted 18 November 2008

GSBL ilişkili bakteremilerde mortaliteyi etkileyen en güçlü bağımsız etmen uygun olmayan empirik tedavi

Table 4. Multivariate analysis of risk factors associated with mortality in *E. coli* bacteraemia

Characteristics	OR	95% CI	*P* value
Shock	10.28	7.80–13.56	<0.001
Inappropriate empirical therapy	4.83	3.48–6.71	<0.001
Pneumonia	4.23	2.52–7.09	<0.001
Liver cirrhosis	2.57	1.82–3.62	<0.001
Intra-abdominal infection	2.41	1.61–3.60	<0.001
Solid-organ cancer	1.83	1.35–2.48	<0.001
Neutropenia	1.75	1.14–2.69	0.01
Chronic renal insufficiency	1.69	1.08–2.66	0.03
Corticosteroids	1.61	1.17–2.22	0.004

Table 5. Proportion of inappropriate empirical therapy according to antibiotic susceptibility pattern

Antibiotic susceptibility pattern	*n*	Inappropriate empirical therapy, *n* (%)[a]	*P* value
FQ-susceptible	3458	146 (4)	<0.001
FQ-resistant	1300	203 (16)	
No ESBL production	4547	239 (5)	<0.001
ESBL-producing strain	211	110 (52)	

TEDAVİ

UPDATE

Recommendation for treatment of severe infections caused by Enterobacteriaceae producing extended-spectrum β-lactamases (ESBLs)

D. L. Paterson

Infectious Disease Section, Instituto per I Trapianti Terapie as Alta Specializzazione, Palermo, Italy and Infectious Disease Division, University of Pittsburgh Medical Center, Pittsburgh, USA

Extended-spectrum β-lactamase (ESBL)-producing organisms are a global problem. No randomized controlled trials have ever been performed to guide optimal treatment. However, in vitro studies and observational studies strongly suggest that carbapenems (imipenem or meropenem) should be regarded as drugs of choice for serious infections due to ESBL-producing organisms. Other β-lactam antibiotics (cefepime, β-lactam/β-lactamase inhibitor combinations) are not suitable as first-line therapy. The increasing frequency of the association between quinolone resistance and ESBL production have greatly limited the role of this class of antibiotic against ESBL producers.

Keywords ESBL, extended-spectrum beta-lactamase, beta-lactamase, carbapenems, cephadosporins, *Klebsiella*

Accepted 17 May 2000

Clin Microbiol Infect 2000: 6: 460–463

Table 1 Treatment recommendations for infections caused by organisms producing extended-spectrum β-lactamases (ESBLs)

Type of infection	First-line therapy	Second-line therapy
Bacteremia	Carbapenem[a] (imipenem or meropenem)	Ciprofloxacin
Nosocomial pneumonia	Carbapenem (imipenem or meropenem)	Ciprofloxacin
Intra-abdominal infection	Carbapenem[a] (imipenem or meropenem)	Ciprofloxacin
Urinary tract infection	Ciprofloxacin	Amoxycillin–clavulanate
Meningitis	Meropenem[a]	Addition of polymyxin B

[a]Removal of central venous lines, drainage of collections and removal of neurosurgical hardware is important for optimal outcome of these infections.

Antibiotic Therapy for *Klebsiella pneumoniae* Bacteremia: Implications of Production of Extended-Spectrum β-Lactamases

David L. Paterson,[1,2] Wen-Chien Ko,[3] Anne Von Gottberg,[4] Sunita Mohapatra,[5] Jose Maria Casellas,[6] Herman Goossens,[7] Lutfiye Mulazimoglu,[8] Gordon Trenholme,[5] Keith P. Klugman,[4] Robert A. Bonomo,[9] Louis B. Rice,[9] Marilyn M. Wagener,[1] Joseph G. McCormack,[2] and Victor L. Yu[1]

[1]Infectious Disease Section, VA Medical Center, Pittsburgh, Pennsylvania; [2]Department of Medicine, University of Queensland, Mater Adults Hospital, Brisbane, Australia; [3]Department of Medicine, National Cheng Kung University Medical College, Tainan, Taiwan; [4]South African Institute of Medical Research, Johannesburg, South Africa; [5]Section of Infectious Diseases, Rush Presbyterian St. Luke's Medical Center, Chicago, Illinois; [6]Departmento de Infectologia y Microbiologia, Sanatorio San Lucas, Buenos Aires, Argentina; [7]Department of Microbiology, University Hospital, Antwerp, Belgium; [8]Department of Microbiology, Marmara University, Istanbul, Turkey; and [9]Infectious Diseases Section, Veterans Affairs Medical Center, Cleveland, Ohio

The prevalence of extended-spectrum β-lactamase (ESBL) production by *Klebsiella pneumonia* approaches 50% in some countries, with particularly high rates in eastern Europe and Latin America. No randomized trials have ever been performed on treatment of bacteremia due to ESBL-producing organisms; existing data comes only from retrospective, single-institution studies. In a prospective study of 455 consecutive episodes of *Klebsiella pneumoniae* bacteremia in 12 hospitals in 7 countries, 85 episodes were due to an ESBL–producing organism. Failure to use an antibiotic active against ESBL-producing *K. pneumoniae* was associated with extremely high mortality. Use of a carbapenem (primarily imipenem) was associated with a significantly lower 14-day mortality than was use of other antibiotics active in vitro. Multivariate analysis including other predictors of mortality showed that use of a carbapenem during the 5-day period after onset of bacteremia due to an ESBL-producing organism was independently associated with lower mortality. Antibiotic choice is particularly important in seriously ill patients with infections due to ESBL-producing *K. pneumoniae*.

Clinical Infectious Diseases 2003; 39:31–7
© 2004 by the Infectious Diseases Society of America. All rights reserved.
1058-4838/2004/3901-0007$15.00

Table 1. Comparison of variables between patients with *Klebsiella pneumoniae* bacteremia treated with carbapenems and those treated with other active antibiotics.

Variable	Carbapenem group (n = 42)	Noncarbapenem group (n = 29)	P	OR (95% CI)
Male sex	28 (66.7)	14/29 (48.3)	.15	2.1 (0.7–6.4)
Underlying disease				
Neutropenia	3 (7.1)	0 (0)	.27	…
Any immunocompromise	24 (57.1)	7/29 (24.1)	.006	4.19 (1.3–14.0)
Renal failure	11 (27.5)[a]	10 (35.7)[b]	.47	0.68 (0.2–2.2)
Any significant underlying disease	33 (78.6)	21 (72.4)	.55	1.39 (0.4–4.8)
Underlying source of infection				
Pneumonia	9 (21.4)	7 (24.1)	.79	0.86 (0.2–3.0)
Intra-abdominal infection	6 (14.3)	10 (34.5)	.08	0.31 (0.1–1.1)
Urinary tract infection	8 (19.0)	2 (6.9)	.18	3.2 (0.1–15.4)
Wound infection	4 (9.5)	1 (3.4)	.64	2.9 (0.3–25.8)
Other source	7 (16.7)	2 (6.9)	.29	2.7 (0.5–13.5)
Severity-of-illness marker				
Admission to ICU	15 (35.7)	13 (44.8)	.47	0.7 (0.2–2.0)
APACHE III score, mean ± SD	71.7 ± 16	59.2 ± 23	.16	1.03 (0.98–1.08)
Previous LOS, median days	11.5	15.0	.16	0.99 (0.98–1.01)

NOTE. Data are no. of patients/no. for whom data were available (%), unless otherwise indicated. ICU, intensive care unit; LOS, length of stay.

[a] Data are for 40 patients.

[b] Data are for 28 patients.

Table 4. Antibiotic choice and mortality associated with bacteremia due to extended-spectrum β-lactamase–producing *Klebsiella pneumoniae*.

Type of therapy	All-cause 14-day mortality
Carbapenem monotherapy	1/27 (3.7)
Imipenem	1/24
Meropenem	0/3
Quinolone monotherapy (ciprofloxacin)	4/11 (36.3)
Cephalosporin monotherapy	2/5 (40)
Cefepime	1/2
Ceftriaxone	1/2
Cefotaxime	0/1
β-Lactam/β-lactamase inhbitor combination	2/4 (50)
Piperacillin-tazobactam	2/2
Ticarcillin-clavulanate	0/2
Aminoglycoside monotherapy (amikacin)	0/2 (0)
No active antibiotics	7/11 (63.6)

Table 3. Results of multivariate analyses examining risk factors for mortality associated with bacteremia due to extended-spectrum β-lactamase–producing *Klebsiella pneumoniae*.

Mortality risk factor, by time after positive blood culture results	*P*	OR (95% CI)
14-Day mortality		
All cause		
Carbapenem treatment	.017	0.09 (0.01–0.65)
Pitt bacteremia score	.073	1.42 (0.97–2.08)
Admission to ICU	.23	3.46 (0.46–26.26)
Attributed to *K. pneumoniae* bacteremia[a]		
Carbapenem treatment	.013	0.04 (0.002–0.50)
Pitt bacteremia score	.095	1.45 (0.94–2.26)
Admission to ICU	.32	2.89 (0.35–23.90)
28-Day mortality		
All cause		
Admission to ICU	.005	6.90 (1.78–26.69)
LOS before bacteremia	.013	0.97 (0.94–0.99)
Carbapenem treatment	.050	0.28 (0.08–1.00)
Attributed to *K. pneumoniae* bacteremia[a]		
Carbapenem treatment	.001	0.06 (0.01–0.33)
LOS before bacteremia	.019	0.97 (0.94–0.99)
Admission to ICU	.085	4.18 (0.82–21.31)

NOTE. ICU, intensive care unit; LOS, length of hospital stay.

[a] As determined by the treating physicians.

Bulgular

- Prospektif, gözleme dayalı çok merkezli bir çalışma

- **Karbapenem monoterapisi** ile, kinolon ve diğer beta-laktam antibiyotiklerle kıyaslandığında **mortalite anlamlı düzeyde daha düşük.**

J Antimicrob Chemother 2012; **67**: 2793–2803
doi:10.1093/jac/dks301 Advance Access publication 21 August 2012

Journal of Antimicrobial Chemotherapy

Carbapenems versus alternative antibiotics for the treatment of bacteraemia due to Enterobacteriaceae producing extended-spectrum β-lactamases: a systematic review and meta-analysis

Konstantinos Z. Vardakas[1,2], Giannoula S. Tansarli[1], Petros I. Rafailidis[1,2] and Matthew E. Falagas[1–3]*

[1]*Alfa Institute of Biomedical Sciences, 9 Neapoleos St. 151 23 Marousi, Athens, Greece;* [2]*Department of Medicine, Henry Dunant Hospital, 107 Mesogion Avenue, 115 26 Athens, Greece;* [3]*Tufts University School of Medicine, 145 Harrison Avenue, Boston, MA 02111, USA*

*Corresponding author. Tel: +30-694-611-0000; Fax: +30-210-683-9605; E-mail: m.falagas@aibs.gr

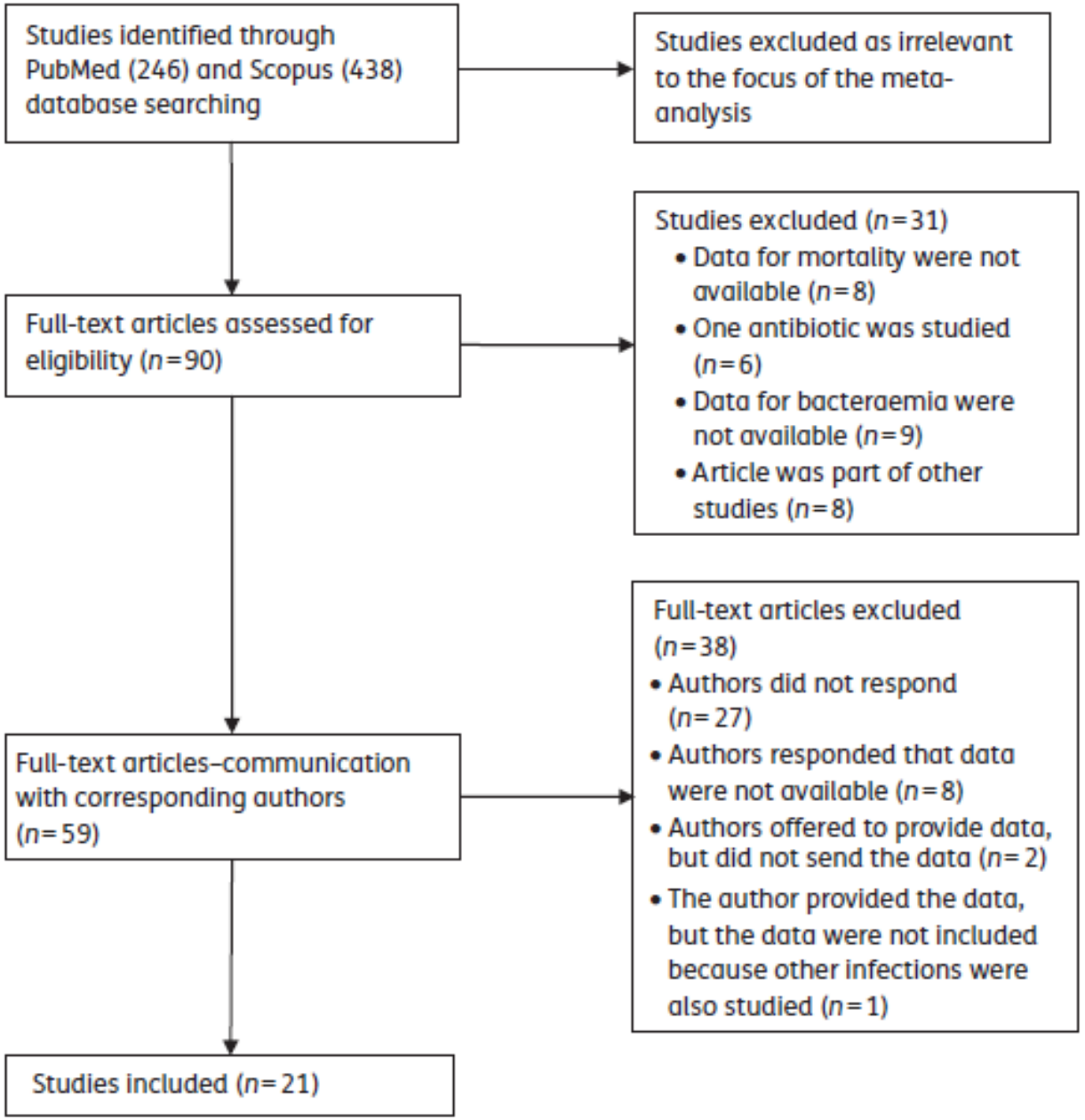
Received 5 April 2012; returned 21 April 2012; revised 28 June 2012; accepted 7 July 2012

Objectives: To study the comparative mortality associated with carbapenems and alternative antibiotics for the treatment of patients with extended-spectrum β-lactamase (ESBL)-positive Enterobacteriaceae bacteraemia.

Methods: We searched systematically PubMed and Scopus databases for studies providing data for mortality among patients treated with carbapenems, β-lactam/β-lactamase inhibitor combinations (BL/BLIs) or non-BL/BLIs (mainly cephalosporins and fluoroquinolones), preferably as monotherapy. Studies focusing on patients of all ages with community- and healthcare-associated bacteraemia were eligible. Data were pooled using the technique of meta-analysis.

Results: Twenty-one articles, studying 1584 patients, were included. *Escherichia coli* and *Klebsiella pneumoniae* were the most commonly studied bacteria. Delay in appropriate treatment up to 6 days was reported. Carbapenems were used mainly as definitive therapy. Carbapenems were associated with lower mortality than non- BL/BLIs for definitive [risk ratio (RR) 0.65, 95% CI 0.47–0.91] and empirical (RR 0.50, 95% CI 0.33–0.77) treatment. No statistically significant differences in mortality were found between carbapenems and BL/BLIs administered as definitive (RR 0.52, 95% 0.23–1.13) or empirical (RR 0.91, 95% CI 0.66–1.25) treatment. BL/BLIs were not associated with lower mortality than non-BL/BLIs administered either definitively (RR 1.59, 95% 0.83–3.06) or empirically (RR 0.82, 95% 0.48–1.41). Data regarding subgroups according to the setting, comorbidity and bacterial species could not be extracted.

Conclusions: Based on data from non-randomized studies, carbapenems may be considered the treatment of choice for empirical treatment of patients with ESBL-producing Enterobacteriaceae bacteraemia. The role of BL/BLIs should be further evaluated for definitive treatment. Further research should focus on faster identification of ESBL-positive pathogens and potential differences in the treatment of each bacterial species.



16 retrospektif , 5 prospektif çalışma

16 çalışma 2000 yılı sonrası

2 çalışma 2000 yılı öncesi

10 çalışma 30 günlük, 2 çalışma 21 günlük, 4 çalışma 14 günlük mortaliteyi irdelemiş

Table 3. Summary of RR estimates on mortality of patients with ESBL-positive Enterobacteriaceae bacteraemia according to antibiotic comparisons

		Definitive treatment		Empirical treatment	
Antibiotic comparisons	No. of studies, D/E	no. of patients, *n*/*N* (%)	RR (95% CI), model used	no. of patients, *n*/*N* (%)	RR (95% CI), model used
Appropriate versus inappropriate	NA/11	NA	NA	89/406 (22) versus 141/370 (38)	**0.64 (0.44–0.88) REM (I^2 44%)**
Carbapenems versus BL/BLIs	11/13	75/398 (19) versus 24/118 (20)	0.52 (0.23–1.13) REM (I^2 71%)	64/317 (20) versus 56/273 (21)	0.91 (0.66–1.25) FEM (I^2 15%)
Carbapenems versus non-BL/BLIs	13/11	69/373 (18) versus 64/274 (23)	**0.65 (0.47–0.91) FEM (I^2 26%)**	30/199 (15) versus 85/304 (28)	**0.50 (0.33–0.77) FEM (I^2 13%)**
Carbapenems versus quinolones	7/8	38/300 (13) versus 13/80 (16)	0.63 (0.34–1.15) FEM (I^2 0%)	21/164 (13) versus 24/65 (37)	**0.34 (0.19–0.62) FEM (I^2 0%)**
Carbapenems versus cephalosporins	10/8	39/285 (14) versus 40/125 (32)	**0.34 (0.22–0.52) FEM (I^2 0%)**	19/100 (19) versus 52/170 (31)	**0.51 (0.32–0.82) FEM (I^2 0%)**
Carbapenems versus all	14/13	89/493 (18) versus 65/308 (21)	0.80 (0.51–1.26) REM (I^2 40%)	64/317 (20) versus 141/577 (24)	0.76 (0.56–1.02) FEM (I^2 18%)
BL/BLI versus non-BLBLIs	10/12	19/64 (30) versus 50/202 (25)	1.59 (0.83–3.06) REM (I^2 48%)	38/193 (20) versus 86/309 (28)	0.82 (0.48–1.41) REM (I^2 53%)

D, definitive treatment; E, empirical treatment; NA, not applicable.
Bold text indicates the outcomes with statistical significance.

Bulgular

- Prospektif ve retrospektif çalışmalar arasında anlamlı bir fark yok.
- **Karbapenemler kesin tedavide**, beta-laktam/beta-laktamaz inhibitörleri **(BL/BLİ) ise empirik tedavide** daha sık tercih ediliyor.
- Mortalite açısından karbapenemler ve BL/BLİ'ler arasında anlamlı bir fark yok.

ancak

BL/BLİ ile empirik tedaviye başlananlarda sonrasında karbapeneme geçildiği dikkati çekiyor.

- **Karbapenem ile tedavi** empirik ve kesin tedavi açılarından **sefalosporinlere** kıyasla anlamlı düzeyde daha **düşük mortaliteye** sahip

- BL/BLİ ve diğer antibiyotikler arasında ise mortalite açısından anlamlı bir fark yok.

Sınırlamalar

- Çoğu çalışma kıyaslamaya uygun uyarlanmamış.
- ***E.coli-K. pneumoniae*: mortalite farkları**
- Toplum kökenli, sağlık bakımı ile ilişkili ve hastane kökenli infeksiyonlarda mortalite farkları değerlendirilemiyor.
- **Çoğu çalışma eski**: duyarlı gözüken karbapenem dışı antibiyotikler günümüzde dirençli mi kabul ediliyor?

Clinical Infectious Diseases Advance Access published January 29, 2015

MAJOR ARTICLE

Carbapenem Therapy Is Associated With Improved Survival Compared With Piperacillin-Tazobactam for Patients With Extended-Spectrum β-Lactamase Bacteremia

Pranita D. Tamma,[1] Jennifer H. Han,[2] Clare Rock,[3] Anthony D. Harris,[3] Ebbing Lautenbach,[2] Alice J. Hsu,[4] Edina Avdic,[4] and Sara E. Cosgrove[5]; for the Antibacterial Resistance Leadership Group

[1]Department of Pediatrics, Division of Infectious Diseases, Johns Hopkins University School of Medicine, Baltimore, Maryland; [2]Department of Medicine, Division of Infectious Diseases, University of Pennsylvania School of Medicine, Philadelphia; [3]Department of Epidemiology and Public Health, University of Maryland School of Medicine, [4]Department of Pharmacy, Johns Hopkins Hospital, and [5]Department of Medicine, Division of Infectious Diseases, Johns Hopkins University School of Medicine, Baltimore, Maryland

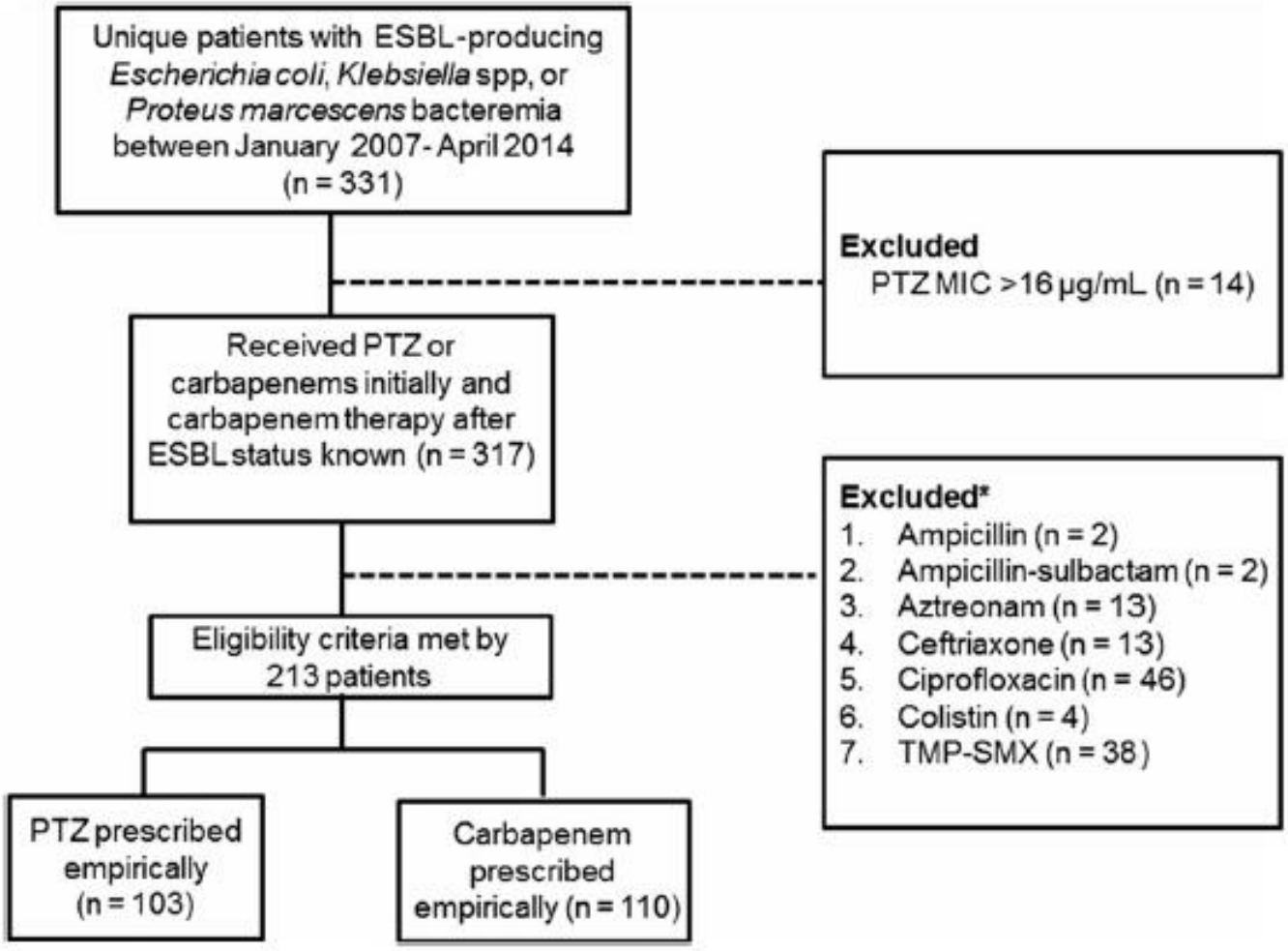
Background. The effectiveness of piperacillin-tazobactam (PTZ) for the treatment of extended-spectrum β-lactamase (ESBL) bacteremia is controversial. We compared 14-day mortality of PTZ vs carbapenems as empiric therapy in a cohort of patients with ESBL bacteremia who all received definitive therapy with a carbapenem.

Methods. Patients hospitalized between January 2007 and April 2014 with monomicrobial ESBL bacteremia were included. A decrease of >3 doubling dilutions in the minimum inhibitory concentration for third-generation cephalosporins tested in combination with 4 μg/mL of clavulanic acid was used to confirm ESBL status. The primary exposure was empiric therapy, defined as antibiotic therapy administered to a patient before ESBL status was known. Patients were excluded if they did not receive a carbapenem after ESBL production was identified. The primary outcome was time to death from the first day of bacteremia. Propensity scores using inverse probability of exposure weighting (IPW) were used to estimate the probability that a patient would receive PTZ vs carbapenems empirically. We calculated overall hazard ratios for mortality censored at 14 days using Cox proportional hazards models on an IPW-adjusted cohort.

Results. A total of 331 unique patients with ESBL bacteremia were identified. One hundred three (48%) patients received PTZ empirically and 110 (52%) received carbapenems empirically. The adjusted risk of death was 1.92 times higher for patients receiving empiric PTZ compared with empiric carbapenem therapy (95% confidence interval, 1.07–3.45).

Conclusions. PTZ appears inferior to carbapenems for the treatment of ESBL bacteremia. For patients at high risk of invasive ESBL infections, early carbapenem therapy should be considered. Our findings should not be extended to β-lactam/β-lactamase inhibitor combinations in development, as limited clinical data are available for these agents.

Keywords. ESBL; piperacillin-tazobactam; carbapenem; gram-negative; resistance.



Kohorta alınan tüm hastalarda GSBL (+)'liği saptandıktan sonra tedavinin karbapeneme değiştirilme koşulu

Table 1. Baseline Characteristics of 213 Patients With Extended-Spectrum β-Lactamase Bacteremia Treated Empirically With Piperacillin-Tazobactam or Carbapenem Therapy, Prior to Culture-Directed Therapy With Carbapenem Therapy[a]

	Complete Cohort (N = 213)			Cohort Adjusted With the Use of Stabilized Inverse Probability of Exposure Weighting		
Characteristic	PTZ/Carbapenem (n = 103 [48%])	Carbapenem (n = 110 [52%])	*P* Value	PTZ/Carbapenem	Carbapenem	*P* Value
Age, mean (SD)	48.1 (22.8)	48.2 (19.0)	.96	48.2	48.0	.89
Male sex, No. (%)	59 (57.3)	72 (60.5)	.63	56.9	57.4	.94
Pitt bacteremia score, mean (SD)	2.3 (1.9)	2.1 (1.3)	.15	2.2	2.1	.79
ICU-level care, day 1	33 (32.0)	39 (35.5)	.70	33	36	.70
ANC ≤100 cells/μL, No. (%)	16 (15.5)	16 (13.4)	.66	14.5	14.4	.99
Likely source of bacteremia, No. (%)						
Central line associated	45 (43.7)	52 (43.7)	1.00	46.3	44.1	.77
Urinary tract	20 (19.4)	24 (20.2)	.89	19.3	18.4	.87
Biliary	7 (6.8)	12 (10.1)	.38	8.3	8.3	.98
Intra-abdominal	20 (19.4)	16 (13.4)	.23	16.3	15.1	.82
Pneumonia	11 (10.7)	9 (7.6)	.43	9.8	11.3	.77
Preexisting medical conditions, No. (%)						
End-stage liver disease	16 (15.5)	14 (11.8)	.42	13.8	13.3	.93
End-stage renal disease	4 (3.9)	7 (5.9)	.49	5.3	7.5	.61
Structural lung disease	13 (12.6)	5 (4.2)	.03	7.7	7.0	.86
Neurologic	11 (10.7)	9 (7.6)	.43	7.5	6.6	.77
Congestive heart failure	8 (7.8)	8 (6.7)	.77	6.4	6.2	.93
Immunocompromised[b], No. (%)	49 (47.6)	76 (69.0)	.04	54.6	57.9	.92

Abbreviations: ANC, absolute neutrophil count; ICU, intensive care unit; PTZ, piperacillin-tazobactam; SD, standard deviation.

[a] All patients had isolates susceptible in vitro to both PTZ and carbapenems (ertapenem, imipenem, meropenem).

[b] Includes corticosteroid therapy equivalent to prednisone ≥2 mg/kg or ≥20 mg daily for at least 14 days, (2) biologic agents in the preceding 30 days, (3) solid organ transplant, (4) hematopoietic stem cell transplant in the preceding 1 year, (5) cancer chemotherapy within 6 months, (6) congenital immunodeficiency, or (7) human immunodeficiency virus with CD4 count ≤200 cells/μL.

Table 2. Fourteen-Day Mortality for 213 Patients With Extended-Spectrum β-Lactamase Bacteremia Treated Empirically With Piperacillin-Tazobactam or Carbapenem Therapy in a Stabilized Inverse Probability–Weighted Cohort[a]

	Univariable Analysis			Multivariable Analysis		
Characteristic	HR	95% CI	*P* Value	Adjusted HR[a]	95% CI	*P* Value
Piperacillin-tazobactam	1.78	1.00–3.13	.05	1.92	1.07–3.45	.03
Age (per 10-y increase)	1.28	1.09–1.50	.11	1.18	0.99–1.41	.07
Pitt bacteremia score	1.55	1.39–1.72	<.001	1.49	1.28–1.72	<.001
Intensive care unit level care, day 1	4.49	2.53–7.98	<.001	4.25	1.86–9.71	<.001
Immunocompromised	1.09	0.62–1.93	.76	. . .	. . .	. . .
Inadequate source control[b]	1.18	0.81–1.72	.39	. . .	. . .	. . .

Abbreviations: CI, confidence interval; HR, hazard ratio.

[a] Inverse probability–weighted sample with additional adjustment for age, Pitt bacteremia score, and intensive care unit–level care.

[b] Inadequate source control refers to central lines not removed in the setting of central line–associated bacteremia or intra-abdominal abscesses not drained when intra-abdominal fluid collections were present.

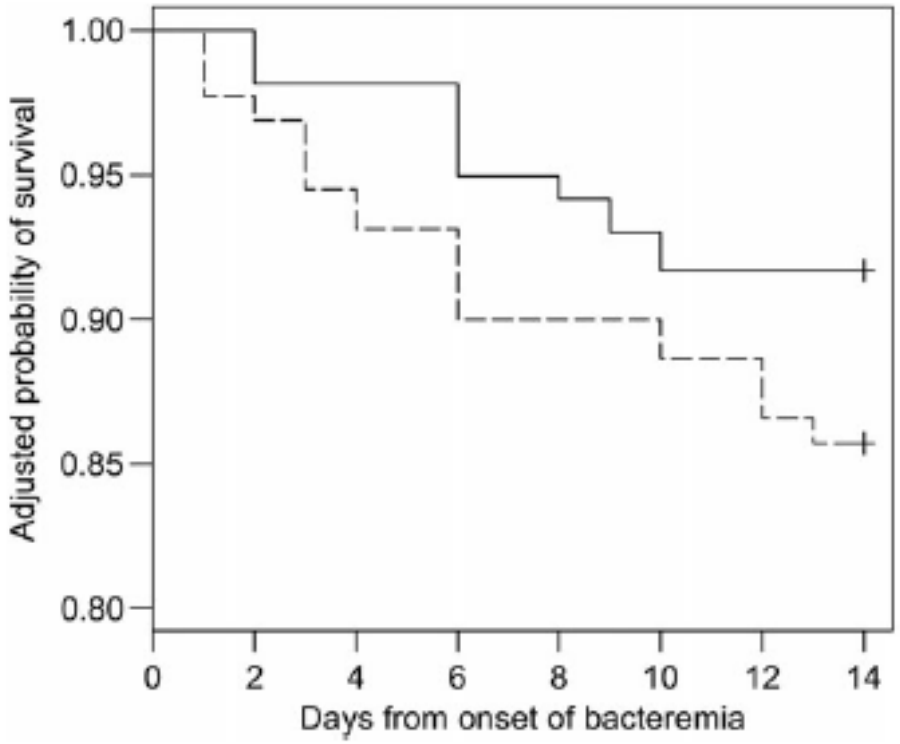


Figure 2. Probability of survival censored at day 14 for patients with extended-spectrum β-lactamase (ESBL)-producing bacteremia in an inverse probability–weighted sample. Solid line represents individuals treated with carbapenems for the entire duration of therapy; dotted line represents individuals treated with piperacillin-tazobactam and converted to carbapenem therapy after ESBL status was known; log-rank test = 0.03.

Bulgular

- **Düzeltilmiş mortalite riski** (yaş, Pitt bakteremi skoru, YBÜ bakımı) empirik olarak piperasilin/tazobaktam **(PTZ) alan grupta 1,92 kat daha yüksek**

- Risk faktörleri olan olası GSBL bakteremilerinde empirik tedavide **karbapenem** tercihi

Sınırlamalar

- Tek merkez
- Sadece PTZ, diğer BL/BLİ'ler değil
- GSBL enzim tipi?

β-Lactam/β-Lactam Inhibitor Combinations for the Treatment of Bacteremia Due to Extended-Spectrum β-Lactamase–Producing *Escherichia coli*: A Post Hoc Analysis of Prospective Cohorts

Jesús Rodríguez-Baño,[1,2] María Dolores Navarro,[1] Pilar Retamar,[1] Encarnación Picón,[1] Álvaro Pascual,[1,3] and the Extended-Spectrum Beta-Lactamases–Red Española de Investigación en Patología Infecciosa/Grupo de Estudio de Infección Hospitalaria Group[a]

[1]Unidad Clínica de Enfermedades Infecciosas y Microbiología, Hospital Universitario Virgen Macarena, and [2]Departamentos de Medicina and [3]Microbiología, Universidad de Sevilla, Spain

(See the Editorial Commentary by Perez and Bonomo, on pages 175–7.)

Background. Extended-spectrum ß-lactamase–producing *Escherichia coli* (ESBL-EC) is an important cause of invasive infections. Alternatives to carbapenems—considered the drugs of choice—are needed because of the emergence of carbapenemase-producing enterobacteria. The efficacy of ß-lactam/ß-lactam inhibitors (BLBLI) in such infections is controversial.

Methods. The authors performed a post hoc analysis of patients with bloodstream infections due to ESBL-EC from 6 published prospective cohorts. Mortality and length of hospital stay in patients treated with an active BLBLI (amoxicillin-clavulanic acid [AMC] and piperacillin-tazobactam [PTZ]) or carbapenem were compared in 2 cohorts: the empirical therapy cohort (ETC) and the definitive therapy cohort (DTC). Confounding was controlled by multivariate analysis; for patients in the ETC, a propensity score for receiving carbapenem was also used.

Results. The ETC included 103 patients (BLBLI, 72; carbapenem, 31), and the DTC included 174 (BLBLI, 54; carbapenem, 120). Mortality rates at day 30 for those treated with BLBLI versus carbapenems were 9.7% versus 19.4% for the ETC and 9.3% versus 16.7% for the DTC, respectively ($P > .2$, log-rank test). After adjustment for confounders, no association was found between either empirical therapy with BLBLI (adjusted hazard ratio [HR], 1.14; 95% confidence interval [CI], .29–4.40; $P = .84$) or definitive therapy (adjusted HR, 0.76; 95% CI, .28–2.07; $P = .5$) and increased mortality. Furthermore, BLBLI therapy, with respect to carbapenem, was not found to influence length of hospital stay.

Conclusions. These results suggest that AMC and PTZ are suitable alternatives to carbapenems for treating patients with bloodstream infections due to ESBL-EC if active in vitro and would be particularly useful as definitive therapy.

Clinical Infectious Diseases 2012;54(2):167–74
© The Author 2011. Published by Oxford University Press on behalf of the Infectious Diseases Society of America. All rights reserved. For Permissions, please e-mail: journals.permissions@oup.com.
DOI: 10.1093/cid/cir790

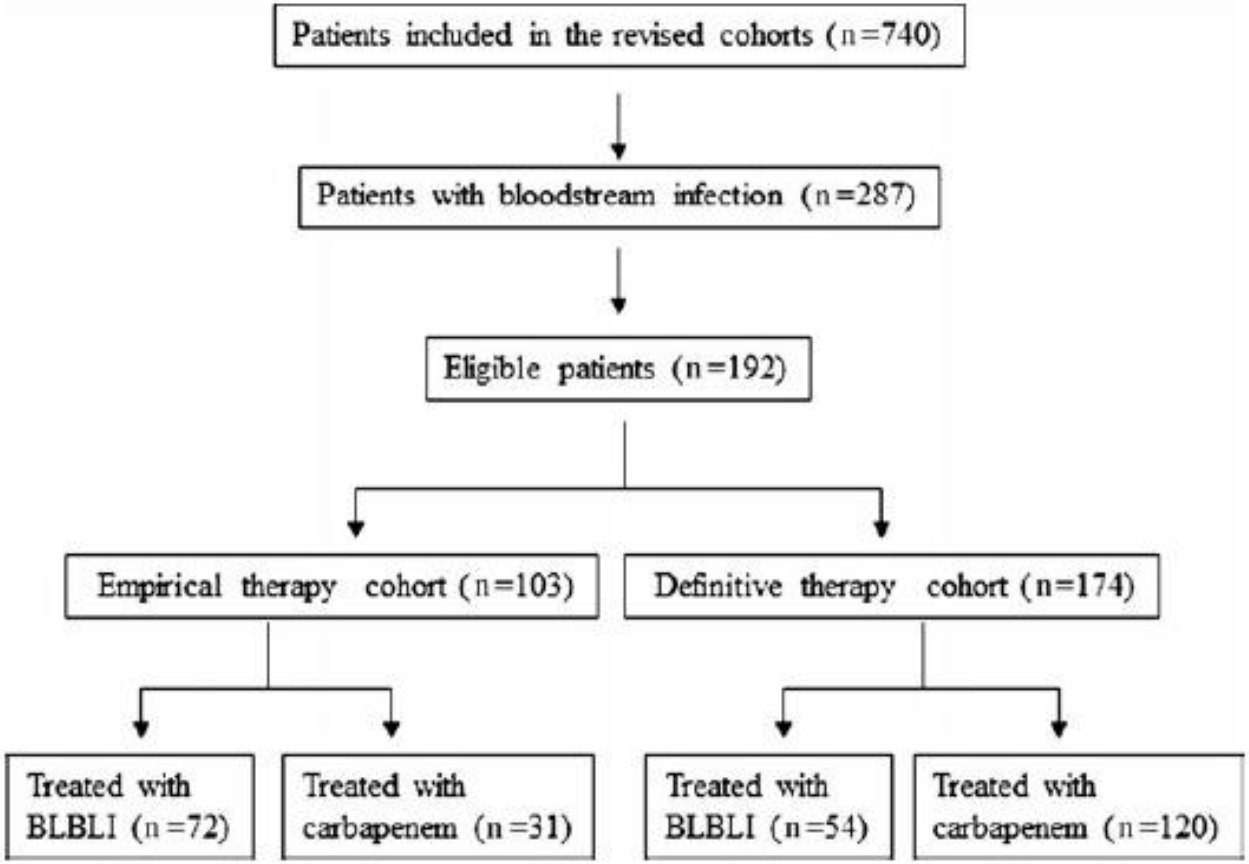


Figure 1. Flow chart of patients included in the study. BLBLI, β-lactam/β-lactamase inhibitor.

Table 2. Characteristics of Patients With Bloodstream Infections (BSIs) Caused by Extended-Spectrum β-Lactamase–Producing *Escherichia coli*, According to Therapy[a]

Characteristic	Empirical Therapy Cohort			Definitive Therapy Cohort		
	BLBLI (n = 72)	Carbapenem (n = 31)	*P*	BLBLI (n = 54)	Carbapenem (n = 120)	*P*
Mortality, no. of deaths						
Day 7	2 (2.8)	3 (9.7)	.1[c]	1 (1.9)	5 (4.2)	.6[c]
Day 14	7 (9.7)	5 (16.1)	.3	3 (5.6)	14 (11.7)	.2
Day 30	7 (9.7)	6 (19.4)	.1	5 (9.3)	20 (16.7)	.1
Hospital stay after BSI , median (IQR), d	12 (8–28)	13 (9–25)	.7[b]	13 (8–22)	13 (10–25)	.04[b]

Table 3. Mortality at 30 Days in Patients Who Received Empirical Therapy With an Active β-Lactam/β-Lactam Inhibitor, According to Minimum Inhibitory Concentration of the Antimicrobial Used[a]

	Minimum Inhibitory Concentration, mg/L				
Antimicrobial	≤1	2	4	8	16
Piperacillin-tazobactam	0/10	0/8	1/4	2/6	1/7
Amoxicillin-clavulanate	…	…	1/12	2/25	…

[a] Data are expressed as No. of patients who died/No. of patients treated.

30 günlük mortalite

MİK ≤ 4 µg/ml olan olgularda %4,5

MİK ≥8 µg/ml olan olgularda %23

Bulgular

- Bu çalışmada amoksisilin klavulanat (AMC) ve PTZ karbapenem ile kıyaslandığında mortalite açısından **anlamlı bir fark gösterilememiştir**.

Sınırlamalar

- Hastaların %70'inde bakteremi **üriner veya biliyer sistem** kaynaklı
- Kökenlerin büyük bir bölümü CTX-M tipi enzim üretmektedir (PTZ duyarlılığı).
- Öte yandan hastaların >%90'ına **PTZ 4x4,5 g** gibi yüksek bir dozda verilmiştir.

Monte-Carlo benzetim sistemiyle oluşturulan **farmakodinamik/farmakokinetik** çalışma sonuçlarına göre:

- **4X3,375 g PTZ** ile yüksek MİK düzeylerinde (8-16 mg/L) %50 fT> MİK sağlanamayabilir.
- Ancak **MİK ≤8mg/L** olan olgularda farmakodinamik hedefe ulaşılabilir.

Ambrose PG, Bhavnani SM, Jones RN. Pharmacokineticspharmacodynamics of cefepime and piperacillin-tazobactam against Escherichia coli and Klebsiella pneumoniae strains producing extended-spectrum b-lactamases: report from the ARREST program. Antimicrob Agents Chemother 2003; 47: 1643–6.
Reese AM, Frei CR, Burgess DS. Pharmacodynamics of intermittent and continuous infusion piperacillin/tazobactam and cefepime against extended-spectrum b-lactamase-producing organisms. Int J Antimicrob Agents 2005; 26: 114–9.

- **16mg/L MİK** düzeyinde hedefe ulaşabilmek için en az **6X3,375 g PTZ** dozu gerekebilir.
- Bu dozda bile kritik hastalarda MİK ≤8mg/L olan olgularda farmakodinamik hedefe ulaşılabilir.

- Uzamış infüzyon bir çözüm?

Lodise TP Jr, Lomaestro B, Drusano GL. Piperacillin-tazobactam for Pseudomonas aeruginosa infection: clinical implications of an extended-infusion dosing strategy. Clin Infect Dis 2007; 44: 357–63.

Test/Report Group	Antimicrobial Agent	Disk Content	Zone Diameter Interpretive Criteria (nearest whole mm)				MIC Interpretive Criteria (µg/mL)			
			S	SDD	I	R	S	SDD	I	R
β-LACTAM/β-LACTAMASE INHIBITOR COMBINATIONS										
B	Amoxicillin-clavulanate	20/10 µg	≥18		14–17	≤13	≤8/4		16/8	≥32/16
B	Ampicillin-sulbactam	10/10 µg	≥15		12–14	≤11	≤8/4		16/8	≥32/16
B	Piperacillin-tazobactam	100/10 µg	≥21		18–20	≤17	≤16/4		32/4–64/4	≥128/4
B	Ticarcillin-clavulanate	75/10 µg	≥20		15–19	≤14	≤16/2		32/2–64/2	≥128/2

CLSI,2014

Penicillins[1]	MIC breakpoint (mg/L)		Disk content (µg)	Zone diameter breakpoint (mm)	
	S ≤	R >		S ≥	R <
Piperacillin-tazobactam	8[4]	16[4]	30-6	20	17

EUCAST, 2015

AAC
Journals.ASM.org

Impact of the MIC of Piperacillin-Tazobactam on the Outcome of Patients with Bacteremia Due to Extended-Spectrum-β-Lactamase-Producing *Escherichia coli*

Pilar Retamar,[a] Lorena López-Cerero,[a] Miguel Angel Muniain,[a,b] Álvaro Pascual,[a,c] Jesús Rodríguez-Baño,[a,b] the ESBL-REIPI/GEIH Group

Unidad Clínica de Enfermedades Infecciosas y Microbiología, Hospital Universitario Virgen Macarena, Sevilla, Spain[a]; Departamento de Medicina[b] and Departamento de Microbiología,[c] Universidad de Sevilla, Sevilla, Spain

We investigated the impact of the piperacillin-tazobactam MIC in the outcome of 39 bloodstream infections due to extended-spectrum-β-lactamase-producing *Escherichia coli*. All 11 patients with urinary tract infections survived, irrespective of the MIC. For other sources, 30-day mortality was lower for isolates with a MIC of ≤2 mg/liter than for isolates with a higher MIC (0% versus 41.1%; $P = 0.02$).

Clinical Infectious Diseases 2013;56(4):488–95
© The Author 2012. Published by Oxford University Press on behalf of the Infectious Diseases Society of America. All rights reserved. For Permissions, please e-mail: journals.permissions@oup.com.
DOI: 10.1093/cid/cis916

Cefepime Therapy for Monomicrobial Bacteremia Caused by Cefepime-Susceptible Extended-Spectrum Beta-Lactamase–Producing *Enterobacteriaceae*: MIC Matters

Nan-Yao Lee,[1,2] Ching-Chi Lee,[1,2] Wei-Han Huang,[4] Ko-Chung Tsui,[5,8] Po-Ren Hsueh,[6,7,a] and Wen-Chien Ko[1,2,3,a]

[1]Department of Internal Medicine, [2]Center for Infection Control, National Cheng Kung University Hospital and Medical College, and [3]Department of Medicine, National Cheng Kung University Medical College, Tainan; [4]Department of Clinical Pathology, Buddhist Tzu-Chi General Hospital, Hualien; [5]Department of Clinical Pathology Cathay General Hospital, and Departments of [6]Laboratory Medicine and [7]Internal Medicine, National Taiwan University Hospital, National Taiwan University College of Medicine, Taipei; and [8]Fu-Jen Catholic University School of Medicine, New Taipei City, Taiwan

Background. Extended-spectrum ß-lactamase (ESBL)–producing *Enterobacteriaceae* isolates are important clinical pathogens. In addition, the efficacy of cefepime for such infections is controversial.

Methods. We performed a retrospective study of monomicrobial bacteremia caused by ESBL producers at 2 medical centers between May 2002 and August 2007. The patients definitively treated with in vitro active cefepime (cases) were compared with those treated with a carbapenem (controls) in a propensity score–matched analysis to assess therapeutic effectiveness. The 30-day crude mortality is the primary endpoint.

Results. A total of 178 patients were eligible for the study. Patients who received cefepime (n = 17) as definitive therapy were more likely to have a clinical failure (odds ratio [OR] 6.2; 95% confidence interval [CI], 1.7–22.5; $P = .002$), microbiological failure (OR 5.5; 95% CI, 1.3–25.6; $P = .04$), and 30-day mortality (OR 7.1; 95% CI, 2.5–20.3; $P < .001$) than those who received carbapenem therapy (n = 161). Multivariate regression revealed that a critical illness with a Pitt bacteremia score ≥4 points (OR 5.4; 95% CI, 1.4–20.9; $P = .016$), a rapidly fatal underlying disease (OR 4.4; 95% CI, 1.5–12.6; $P = .006$), and definitive cefepime therapy (OR 9.9; 95% CI, 2.8–31.9; $P < .001$) were independently associated with 30-day crude mortality. There were 17 case-control pairs in the propensity scores matched analysis. The survival analysis consistently found that individuals who received cefepime therapy had a lower survival rate (log-rank test, $P = .016$).

Conclusions. Based on the current Clinical and Laboratory Standards Institute susceptible breakpoint of cefepime (minimum inhibitory concentration ≤8 μg/mL), cefepime definitive therapy is inferior to carbapenem therapy in treating patients with so-called cefepime-susceptible ESBL-producer bacteremia.

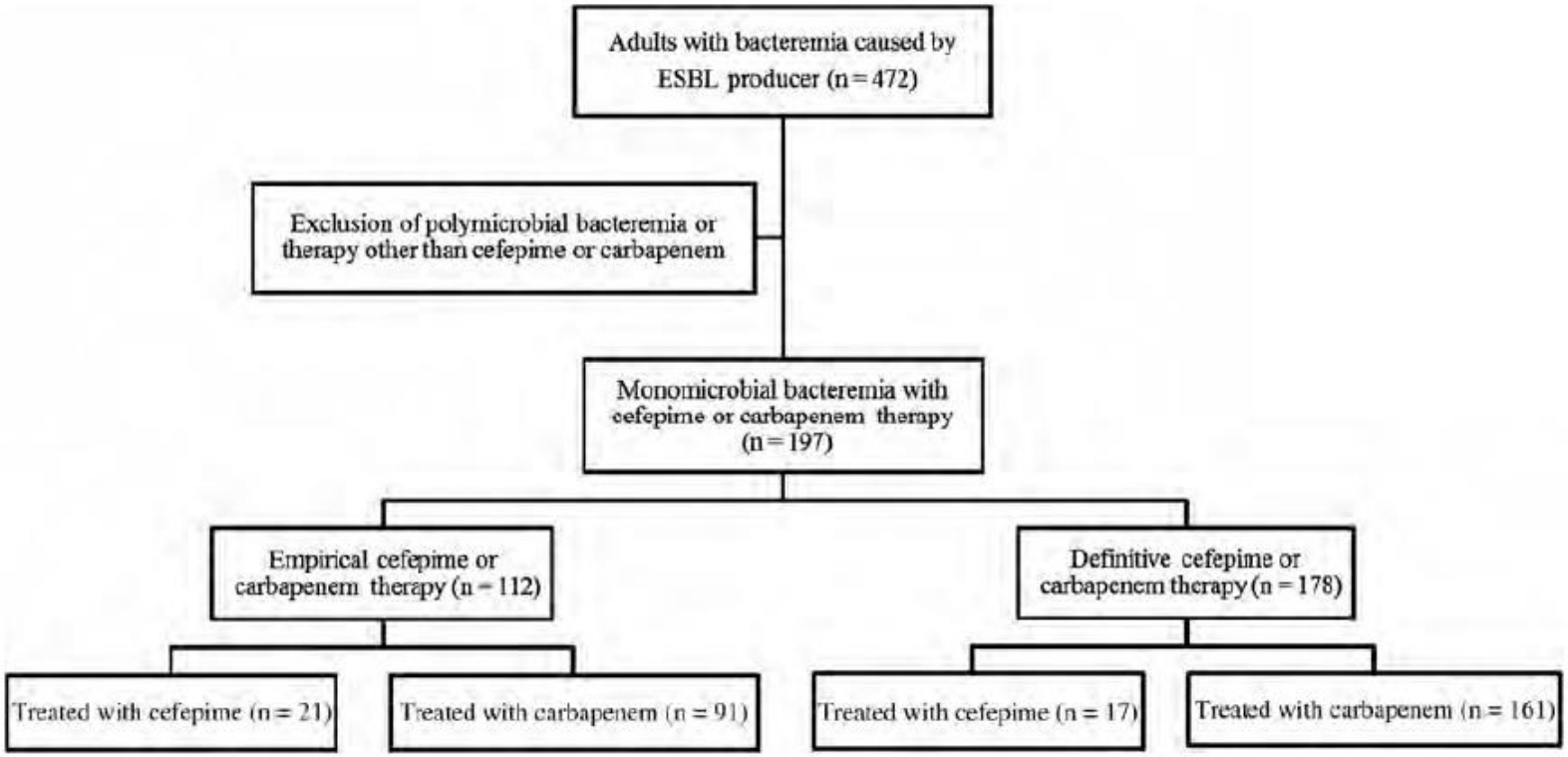


Figure 2. Study inclusion and exclusion criteria applied for patient identification. Abbreviation: ESBL, extended-spectrum ß-lactamase.

Table 2. Multivariate Logistic Regression Analysis of Associations Between Different Variables and 30-Day Mortality in the Definitive Therapy Cohort

			Univariate Analysis		Multivariate Analysis	
Variable	Survivors (n = 141)	Nonsurvivors (n = 37)	OR (95% CI)	*P* Value	OR (95% CI)	*P* Value
Age, years (mean ± SD)	65.1 ± 17.1	69.7 ± 16.9	…	.15	…	…
Male	78 (55.1)	21 (56.8)	1.06 (.51–2.2)	1.0	…	…
Hospital-onset bacteremia	96 (68.1)	31 (83.8)	2.42 (.94–6.22)	.07	1.46 (.47–4.48)	.51
Urosepsis	38 (27.0)	1 (2.7)	0.08 (.01–.57)	.001	0.18 (.02–1.43)	.1
Pitt bacteremia score ≥4 points	85 (60.3)	34 (91.9)	7.47 (2.19–25.49)	<.001	5.36 (1.37–20.91)	.016
Rapidly fatal underlying disease	9 (6.4)	11 (29.7)	6.21 (2.34–16.47)	<.001	4.42 (1.54–12.64)	.006
Definitive therapy with cefepime	7 (5.0)	10 (27.0)	7.09 (2.48–20.27)	<.001	9.93 (2.77–31.91)	<.001

Data are given as number (percentage) unless otherwise specified. Ellipses indicate not available.
Abbreviations: CI, confidence interval; OR, odds ratio; SD, standard deviation.

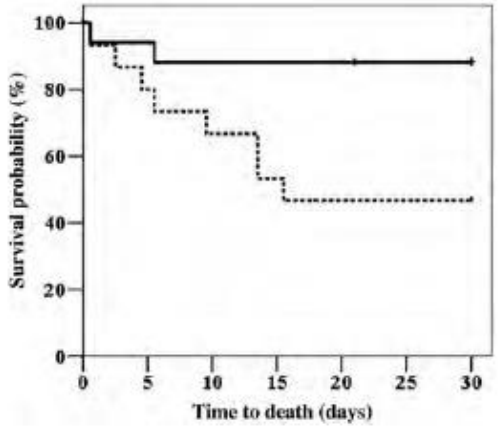


Figure 3. Kaplan-Meier survival analysis curves for patients with bacteremia caused by extended-spectrum ß-lactamase–producing organisms; bacteremia treated using a carbapenem (solid line) vs cefepime (broken line; log-rank test, $P = .016$).

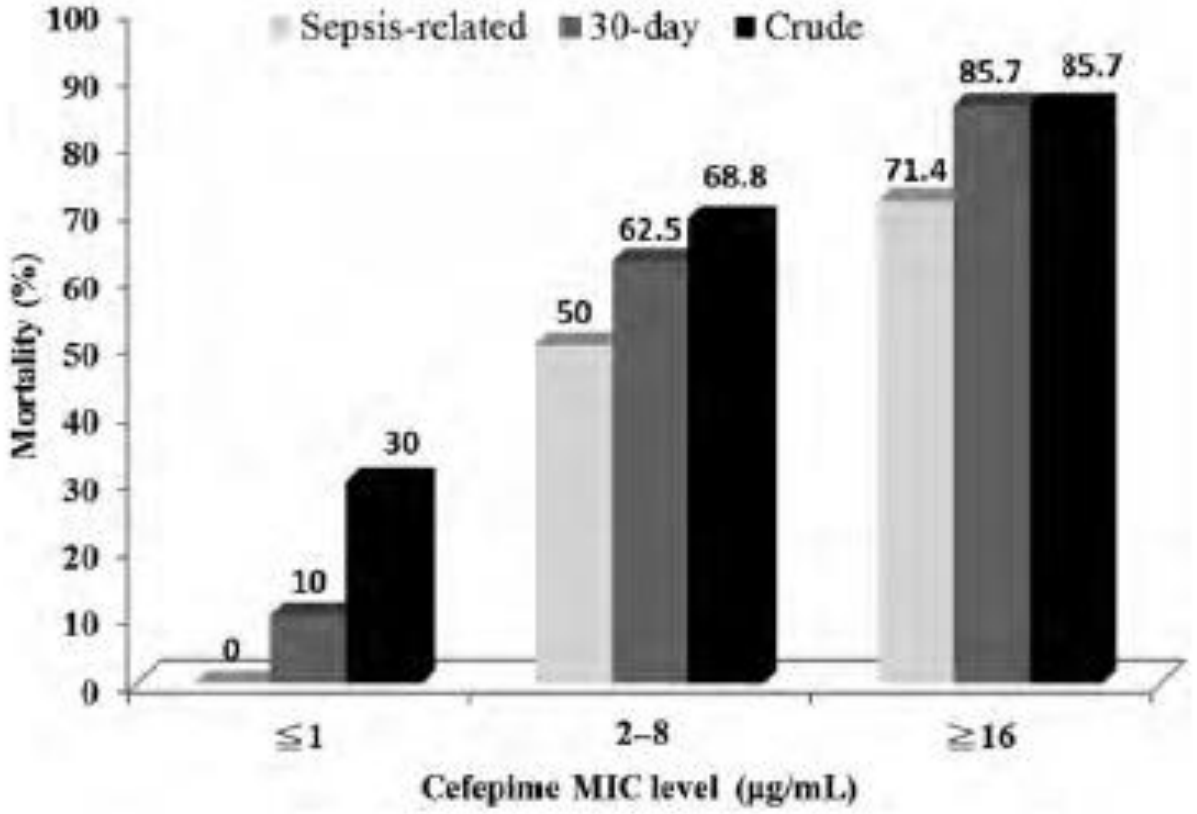


Figure 1. Mortality rates of 3 subgroups of patients who received cefepime therapy (n = 33) stratified by the cefepime minimum inhibitory concentration. Abbreviation: MIC, minimum inhibitory concentration.

Bulgular

- Sefepim ve karbapenem ile ilişkili 30 günlük kaba mortalitenin karşılaştırıldığı bir çalışma

- Multivariat analiz sonuçlarına göre **nihai sefepim tedavisi 30 günlük mortalite ile ilişkili** bağımsız bir etken

- Sefepim (3X1-2 g) tedavisi alan olgular detaylı incelendiğinde **MİK düzeyleri ≤ 1µg/ml olan kökenlerde** sepsis ilişkili, 30 günlük **kaba mortalite anlamlı olarak daha düşük**

ANTIMICROBIAL AGENTS AND CHEMOTHERAPY, Nov. 2003, p. 3442–3447 Vol. 47, No. 11
0066-4804/03/$08.00+0 DOI: 10.1128/AAC.47.11.3442–3447.2003
Copyright © 2003, American Society for Microbiology. All Rights Reserved.

Cefepime versus Imipenem-Cilastatin for Treatment of Nosocomial Pneumonia in Intensive Care Unit Patients: a Multicenter, Evaluator-Blind, Prospective, Randomized Study

G. Zanetti,[1]* F. Bally,[1] G. Greub,[1] J. Garbino,[2] T. Kinge,[2] D. Lew,[2] J.-A. Romand,[2] J. Bille,[1] D. Aymon,[1] L. Stratchounski,[3] L. Krawczyk,[4] E. Rubinstein,[5] M.-D. Schaller,[1] R. Chiolero,[1] M.-P. Glauser,[1] A. Cometta,[1] and the Cefepime Study Group†

Division of Infectious Diseases, Department of Microbiology, and Intensive Care Unit, Centre Hospitalier Universitaire Vaudois, Lausanne, ... rsitaire, Geneva,[2] Switzerland; Smole... iczy, Sosnowiec, Poland[4]; and Ch... homer, Israel[5]

Sefepim grubunda başarısızlık

Received 23 June 2003/Returned for modification 30 June 2003/Accepted 22 July 2003

In a randomized, evaluator-blind, multicenter trial, we compared cefepime (2 g three times a day) with imipenem-cilastatin (500 mg four times a day) for the treatment of nosocomial pneumonia in 281 intensive care unit patients from 13 centers in six European countries. Of 209 patients eligible for per-protocol

30 günlük mortalite sefepim alan grupta anlamlı oranda yüksek (p=0,25)

noninferiority of −15%. In addition, therapy of pneumonia caused by an organism producing an extended-spectrum β-lactamase (ESBL) failed in 4 of 13 patients in the cefepime group but in none of 10 patients in the imipenem group. However, the clinical efficacies of both treatments appeared to be similar in a secondary intent-to-treat analysis (95% CI for difference, −9 to 14%) and a multivariate analysis (95% CI for odds ratio, 0.47 to 1.75). Furthermore, the all-cause 30-day mortality rates were 28 of 108 (26%)

Sefepim 3x2 g gibi yüksek bir dozda uygulanıyor
Sefepimin etkisiz kaldığı olgularda MİK düzeyi 2-4 µg/ml

inferior to imipenem, some secondary analyses showed that the two regimens had comparable clinical and microbiological efficacies. Cefepime appeared to be less active against organisms producing an ESBL, but primary and secondary resistance to imipenem was more common for *P. aeruginosa*. Selection of a single agent for therapy of nosocomial pneumonia should be guided by local resistance patterns.

GSBL (+) *E. coli* ve *K. pneumoniae* ile ilgili **farmakodinamik/farmakokinetik** çalışma sonuçlarına göre:

- **MİK düzeyi ≤ 4µg/ml olduğunda sefepimin 2X2 g** ya da 3X1 g dozunda kullanımıyla çoğu olguda farmakodinamik hedefe ulaşılacağı düşünülmektedir (1, 2).

- Chopra ve ark'larının çalışmasında ise sefepim **MİK düzeyi ≤ 2µg/ml olan olgularda mortalite oranı %38 (5/13)** gibi yüksek bir oran göstermektedir (3).

[1]Ambrose PG, Bhavnani SM, Jones RN. Pharmacokineticspharmacodynamics of cefepime and piperacillin-tazobactam against Escherichia coli and Klebsiella pneumoniae strains producing extended-spectrum b-lactamases: report from the ARREST program. Antimicrob Agents Chemother 2003; 47: 1643–6.
[2]Reese AM, Frei CR, Burgess DS. Pharmacodynamics of intermittent and continuous infusion piperacillin/tazobactam and cefepime against extended-spectrum b-lactamase-producing organisms. Int J Antimicrob Agents 2005; 26: 114–9.
[3]Chopra T, Marchaim D, Veltman J et al. Impact of cefepime therapy on mortality among patients with bloodstream infections caused by extended-spectrum-b-lactamase-producing Klebsiella pneumoniae and Escherichia coli. Antimicrob Agents Chemother 2012; 56: 3936–42.

Test/Report Group	Antimicrobial Agent	Disk Content	Zone Diameter Interpretive Criteria (nearest whole mm)				MIC Interpretive Criteria (µg/mL)			
			S	SDD	I	R	S	SDD	I	R
B	Cefepime	30 µg	≥25	19–24	–	≤18	≤2	4–8	–	≥16

CLSI,2014

Cephalosporins[1]	MIC breakpoint (mg/L)		Disk content (µg)	Zone diameter breakpoint (mm)	
	S ≤	R >		S ≥	R <
Cefepime	1	4	30	24	21

EUCAST, 2015

Bacteremia Due to *Klebsiella pneumoniae* Isolates Producing the TEM-52 Extended-Spectrum β-Lactamase: Treatment Outcome of Patients Receiving Imipenem or Ciprofloxacin

Andrea Endimiani,[1] Francesco Luzzaro,[1] Mariagrazia Perilli,[2] Gianluigi Lombardi,[1] Alessandra Colì,[1] Antonio Tamborini,[1] Gianfranco Amicosante,[2] and Antonio Toniolo[1]

[1]Laboratorio di Microbiologia, Ospedale di Circolo and Università dell'Insubria, Varese, and [2]Dipartimento di Scienze e Tecnologie Biomediche, Università di L'Aquila, L'Aquila, Italy

The treatment outcome of 35 cases of bacteremia due to *Klebsiella pneumoniae* isolates producing TEM-52 extended-spectrum β-lactamase was studied. Twenty-eight cases, classified as "nonfatal disease" using the McCabe and Jackson classification, were investigated with regard to ciprofloxacin and imipenem response. Because ciprofloxacin was active in vitro against 21 of 28 isolates, only the treatment outcome of the ciprofloxacin-susceptible subgroup was evaluated. Eight of 10 cases occurred in patients who experienced a complete response to imipenem; 2 of 10 failed to respond. In contrast, only 2 of 7 cases had a partial response to ciprofloxacin, and, in 5 of 7 cases, the treatment failed. Statistical analysis revealed a significant difference in the treatment outcome of the 2 groups ($P = .03$). Because the isolates had minimum inhibitory concentrations of ciprofloxacin close to the susceptibility breakpoint, treatment failure could be ascribed to the inability of the drug to reach therapeutic concentrations at infected sites.

Clinical Infectious Diseases 2004; 38:243–51
© 2004 by the Infectious Diseases Society of America. All rights reserved.
1058-4838/2004/3802-0009$15.00

Bulgular

- 35 GSBL (+) *K. pneumoniae* olgusunda **imipenem-silastatin ve siprofloksasin** tedavisinin değerlendirildiği bir çalışma

- Tedavi sonuçlarının **imipenem tedavisi ile anlamlı düzeyde daha iyi olduğu** gözlendi.

- Bu çalışmanın önemli noktalarından biri değerlendirilen etkenlerin ilgili antibiyotiklere **duyarlı MİK düzeylerine** sahip olmalarıydı.

Karbapenem dışı antibiyotikler

- GSBL (+) kökenler aynı zamanda başta **florokinolon, aminoglikozid, trimetoprim/sulfametoksazol ve tetrasiklinler** olmak üzere farklı antibiyotiklere karşı dirençleri de birlikte barındırabilir.

- BL/BLİ'lerinin etkinliği **GSBL tipine** olduğu kadar **inhibitör tipine** göre de değişkenlik gösterir:

bazı CTX-M tipi GSBL'lerde tazobaktam, klavulanik asite üstünlük gösterirken her iki inhibitör TEM ve SHV tipi GSBL'de daha etkilidir.

Falagas ME, Karageorgopoulos DE. Extended-spectrum beta-lactamase-producing organisms. J Hosp Infect. 2009 Dec;73(4):345-54.

- Tazobaktam GSBL'leri genellikle inhibe edebilse de çoğu mikroorganizma aynı anda **birden fazla GSBL üreterek** tazobaktamın etkinliğini azaltabilir.

- Ayrıca **eş zamanlı diğer direnç mekanizmaların** (AmpC beta-laktamaz gibi) varlığı da tazobaktamın etkinliği sınırlandırabilir.

.

Tamma PD, Han JH, Rock C, et al. Carbapenem Therapy Is Associated With Improved Survival Compared With Piperacillin-Tazobactam for Patients with Extended-Spectrum β-Lactamase Bacteremia. Clin Infect Dis. 2015.

- **Sefalosporin ve BL/BLİ** ile tedavide sonuçların karbapenemlere kıyasla daha olumsuz olmasının altta yatan etmenlerinden birinin **inokulum etkisiyle** açıklanabileceği düşünülmektedir.

- **BL** antibiyotiklerle ilgili bir diğer sorun **farmakodinamik hedefe ulaşamama** olabilir

Paterson DL, Ko WC, Von Gottberg A, et al. Antibiotic therapy for Klebsiella pneumoniae bacteremia: implications of production of extended- spectrum beta-lactamases. 39:31–7.

- **Kinolon**larda da **inokulum** etkisiyle MİK düzeyinin arttığı gösterilmiştir.

- Tedavi başarısızlığı, kinolonların bakterinin yoğun olduğu dokularda **yeterli konsantrasyona** ulaşamamasından kaynaklanabilir (1,2).

[1]Paterson DL, Ko WC, Von Gottberg A, et al. Antibiotic therapy for Klebsiella pneumoniae bacteremia: implications of production of extended- spectrum beta-lactamases. 39:31–7.
[2]Endimiani A, Luzzaro F, Perilli M, et al.Bacteremia Due to *Klebsiella pneumoniae* Isolates Producing the TEM-52 Extended-Spectrum b-Lactamase: Treatment Outcome of Patients Receiving Imipenem or Ciprofloxacin. Clin Infect Dis 2004;38:243-51.

JPPT

REVIEW ARTICLE

Beyond Susceptible and Resistant, Part II: Treatment of Infections Due to Gram-Negative Organisms Producing Extended-Spectrum β-Lactamases

Jennifer Curello, PharmD[1] and Conan MacDougall, PharmD, MAS[2]

[1]Department of Pharmaceutical Services, University of California Los Angeles Medical Center, Los Angeles, California,
[2]Department of Clinical Pharmacy, University of California, San Francisco School of Pharmacy, San Francisco, California

J Pediatr Pharmacol Ther 2014;19(3):156–164

Hasta özellikleri	İnfeksiyon	İlk seçenek tedavi	Alternatif tedavi
Hastaneye yatırılmış	Herhangi	**Karbapenem**	Florokinolon (ciddi beta-laktam allerji)
Septik şok veya immunsupressif	Pnömoni, odak kontrolü sağlanamayan karın içi infeksiyon, piyelonefrit, damar içi infeksiyon	**Karbapenem**	PTZ (MİK<16 mg/L), florokinolon
Klinik olarak stabil, immünkompetan	Odak kontrolü sağlanmış karın içi infeksiyon, kateterin çıkarıldığı kateter ilişkili infeksiyon, drenaj sağlanan deri/yumuşak doku infeksiyonu, alt üriner sistem infeksiyonu	PTZ (MİK<16 mg/L), karbapenem, florokinolon	Sefepim (MİK<8 mg/L), aminoglikozid (alt üriner sistem infeksiyonu)
Ayaktan hasta	Alt üriner sistem infeksiyonu	Florokinolon, TMP/SMX, nitrofurantoin, fosfomisin	AMC (yüksek klavulanik asit miktarı içeren formül)

(7) Following evaluation of PK-PD properties, limited clinical data, and MIC distributions, revised interpretive criteria for cephalosporins (cefazolin, cefotaxime, ceftazidime, ceftizoxime, and ceftriaxone) and aztreonam were first published in January 2010 (M100-S20) and are listed in this table. Cefuroxime (parenteral) was also evaluated; however, no change in interpretive criteria was required for the dosage indicated below. When using the current interpretive criteria, routine ESBL testing is no longer necessary before reporting results (ie, it is no longer necessary to edit results for cephalosporins, aztreonam, or penicillins from susceptible to resistant). However, ESBL testing may still be useful for epidemiological or infection control purposes. For laboratories that have not implemented the current interpretive criteria, ESBL testing should be performed as described in Table **3A**.

CLSI,2014

GSBL enzim tipine göre direnç

Enzim tipi	PTZ duyarlılığı
CTX-M-15	%67,2
CTX-M-14	%92,9
CMY	%81,5
SHV	%45,8

- Lokal antibiyotik direnç paternleri, enzim tiplerini belirleyecek moleküler epidemiyoloji verileri yol gösterici

Castanheira M, Farrell SE, Krause KM, et al. Contemporary diversity of β-lactamases among Enterobacteriaceae in the nine US census regions and ceftazidime-avibactam activity tested against isolates producing the most prevalent β-lactamase groups. *Antimicrob Agents Chemother* 2014; **58:** 833–38.

Table 1. Worldwide antimicrobial susceptibilities of ESBL-EC and ESBL-K before the 2009/10 era

	Percentage of susceptible ESBL-producing isolates											
	USA						Europe + worldwide		Europe		Europe	
	SENTRY[25] 1998–2004 (all sources)		MYSTIC[26] 2000–04 (all sources)		SMART[27] 2007–08 (intra-abdominal)		SENTRY[25] 1998–2004 (all sources)		MYSTIC[26] 2000–04 (all sources)		SMART[28] 2008 (intra-abdominal)	
Antibiotic	120 *E. coli*	322 *Klebsiella*	2134 *E. coli*	1442 *Klebsiella*	21 *E. coli*	32 *Klebsiella*	603 *E. coli*	1313 *Klebsiella*	4582 *E. coli*	3655 *Klebsiella*	173 *E. coli*	57 *Klebsiella*
Imipenem	100	99	100	100	100	94	100	99	99	99	100	90
Ertapenem	—	—	—	—	100	78	—	—	—	—	99	84
Cefepime	63	89	73	90	48	47	42	51	42	70	9	9
Piperacillin/ tazobactam	73	53	75	62	62	28	69	45	72	52	65	26
Ampicillin/ sulbactam	—	—	—	—	24	3	—	—	—	—	7	5

SENTRY (worldwide) includes Europe, Asia and Latin America. SENTRY, MYSTIC and SMART 2008 (USA) used susceptibility criteria from CLSI 2006, CLSI 2005 and CLSI 2009, respectively. The susceptible breakpoints during these periods were: imipenem MIC ≤4 mg/L, ertapenem MIC ≤2 mg/L, cefepime MIC ≤8 mg/L, piperacillin/tazobactam MIC ≤16/4 mg/L and ampicillin/sulbactam MIC ≤8/4 mg/L. SMART 2008 (Europe) used pre-2010 EUCAST criteria. The susceptible breakpoints were: imipenem MIC ≤2 mg/L, ertapenem MIC ≤0.5 mg/L, cefepime MIC ≤1 mg/L and piperacillin/tazobactam MIC ≤8 mg/L. Exception: ampicillin/sulbactam (EUCAST) had only a resistant breakpoint listed; MIC >8 mg/L (resistant).

Nguyen HM, Shier KL, Graber CJ.Determining a clinical framework for use of cefepime and b-lactam/b-lactamase inhibitors in the treatment of infections caused by extended-spectrum-b-lactamase-producing Enterobacteriaceae. J Antimicrob Chemother 2014; 69: 871–880.

Original Article

Gram-negative bacilli causing infections in an intensive care unit of a tertiary care hospital in Istanbul, Turkey

Seniha Senbayrak Akcay[1], Asuman Inan[1], Simin Cevan[2], Ayse Nilufer Ozaydin[3], Naz Cobanoglu[2], Seyfi Celik Ozyurek[1], Sebahat Aksaray[2]

[1] *Department of Infectious Diseases and Clinical Microbiology, Haydarpasa Numune Education and Research Hospital, Uskudar, Istanbul, Turkey*
[2] *Department of Microbiology and Clinical Microbiology, Haydarpasa Numune Education and Research Hospital, Uskudar, Istanbul, Turkey*
[3] *Department of Public Health, Marmara University, Faculty of Medicine, Uskudar, Istanbul, Turkey*

Abstract

Introduction: This study aimed to demonstrate the changing epidemiology of infecting microorganisms and their long-term resistance profiles and to describe the microbiological point of view in anti-infective management of intensive care unit (ICU) patients.

Methodology: A total of 5,690 isolates of Gram-negative bacilli were included in this study. Antibiotic susceptibility was tested using the disk diffusion method and Vitek 2 system. Chi-square tests were used for hypothesis testing.

Results: The most frequently isolated organisms were *A. baumannii* (37.3%), *P. aeruginosa* (30.3%), *Enterobacter* spp. (10.4%), *E. coli* (10.4%), and *Klebsiella* spp. (8.9%). *A. baumannii* was the most frequently isolated organism from the respiratory tract (43.4%); the susceptibility rates for imipenem and meropenem decreased to 7% and 6% ($p < 0.0001$), respectively. The percentage of multidrug-resistant (MDR) *A. baumannii* isolates continuously increased from 18.7% in 2004 to 69% in 2011 ($p < 0.0001$), whereas MDR *P. aeruginosa* isolates increased from 1.5% to 22% ($p < 0.0001$). Carbapenem-resistant *Klebsiella* isolates emerged in 2010 and increased to 20% in the next year. The rates of ESBL-producing *Enterobacteriaceae* in the ICU was very high in 2011 – 50% for *E. coli* and 80% for *Klebsiella* strains.

Conclusion: The most common isolated Gram-negative bacillus in our study was *A. baumannii* and that the prevalence of MDR isolates has increased markedly over. Accordingly, the comparison of antibiotic resistance of other pathogens in 2004 and 2011 displayed an increasing trend. These data imply the urgent need for new and effective strategies in our hospital and in the region.

Key words: Gram-negative bacilli; Antibiotic resistance; ICU; MDR

J Infect Dev Ctries 2014; 8(5):597-604. doi:10.3855/jidc.4277

Table 3. Trends in antibiotic resistance among various GNB between 2004 and 2011

Pathogen	Antibiotic	Resistance rates (%) 2004	2005	2006	2007	2008	2009	2010	2011	p	Trend
Klebsiella spp.	Imipenem	0	0	0	0	0	0	5.0	20.0	-	*
	Meropenem	0	0	0	0	0	0	7.0	19.0	-	*
	Piperacilin-tazobactam	18.8	20.8	18.2	21.2	64.3	63.6	79.3	75.8	< 0.0001	↑
	Gentamicin	18.8	20.8	15.2	21.2	11.9	18.2	30.4	44.3	< 0.0001[b]	↑
	Amikacin	12.5	16.7	15.2	15.2	33.3	14.3	24.4	28.9	0.043[b]	↑
	Ceftazidime	81.3	83.3	90.9	93.9	76.2	88.3	90.4	80.5	0.305[b]	-
	Ceftriaxone	93.8	91.7	90.9	97.0	78.6	88.3	92.6	89.9	0.854[c]	-
	Cefepime	50.0	58.3	69.7	90.9	76.2	31.2	90.4	79.9	0.035[d]	↑
	Cefoperazone-sulbactam	31.3	25.0	21.2	24.2	50.0	44.2	60.0	59.1	< 0.0001	↑
	Ciprofloxacin	37.5	79.2	63.6	66.7	54.8	22.1	26.7	63.8	0.132	-
	Levofloxacin	31.3	70.8	57.6	72.7	81.0	18.2	16.3	77.2	0.838	-
Enterobacter spp.	Imipenem	0	0	0	0	0	0	0	0	-	-
	Meropenem	0	0	0	0	0	0	0	0	-	-
	Piperacilin-tazobactam	38.2	31.3	25.6	57.1	55.4	48.8	63.9	41.4	< 0.0001	↑
	Gentamicin	16.2	13.4	18.3	22.6	18.1	33.8	19.4	36.2	0.002	↑
	Amikacin	10.4	7.5	12.2	11.9	21.7	7.5	19.4	10.3	0.252	-
	Ceftazidime	50.0	62.7	53.7	44.0	71.1	67.5	77.4	62.1	0.002	↑
	Ceftriaxone	54.4	65.7	52.4	65.5	91.6	72.5	77.8	70.7	< 0.0001	↑
	Cefepime	54.4	58.2	46.3	46.4	57.8	42.5	73.6	58.6	0.161	-
	Cefoperazone-sulbactam	14.7	28.4	22.0	23.8	44.6	43.8	47.2	29.3	< 0.0001	↑
	Ciprofloxacin	20.6	25.4	35.4	53.6	48.2	45.0	15.3	29.3	0.618	-
	Levofloxacin	22.1	32.8	28.8	46.4	55.4	42.5	13.9	29.3	0.767	-
E. coli	Imipenem	0	0	0	0	0	0	0	0	-	-
	Meropenem	0	0	0	0	0	0	0	0	-	-
	Piperacilin-tazobactam	20.0	24.3	41.8	22.4	9.9	31.2	32.0	25.8	0.478	-
	Gentamicin	20.0	15.7	50.9	36.5	32.1	44.0	26.7	27.4	0.173	-
	Amikacin	7.3	1.4	10.9	5.9	9.9	3.7	4.0	6.5	-	*
	Ceftazidime	76.4	70.0	70.9	57.6	82.7	74.3	61.3	51.6	0.040	↑
	Ceftriaxone	78.2	71.4	78.2	60.0	82.7	75.2	62.7	53.2	0.016	↑
	Cefepime	61.8	68.6	70.9	56.5	75.3	73.4	58.7	50.0	0.262	-
	Cefoperazone-sulbactam	3.6	7.1	10.9	14.1	14.8	20.2	22.7	21.0	< 0.0001	↑
	Ciprofloxacin	58.2	61.4	69.1	49.4	74.1	67.0	54.7	51.6	0.577	-
	Levofloxacin	54.5	41.4	76.4	69.4	75.3	62.4	54.7	50.0	0.914	-

Table 6 ***Klebsiella pneumoniae*: Resistance to carbapenems[a] (summary of reported or published proportions of resistance, by WHO region)**

Data sources based on at least 30 tested isolates[b]	Overall reported range of resistant proportion (%)	Reported range of resistant proportion (%) in invasive isolates[c] (no. of reports)
African Region – National data (n=4 countries) – Publications (n=0)	 0–4	
Region of the Americas – National data or report to ReLAVRA (n=17 countries) – Publications (n=2) from 2 additional countries	 0–11 0–2	
Eastern Mediterranean Region – National data (n=4 countries) – Surveillance network[d] (n=1) in 1 additional country – Publications (n=9) from 5 additional countries	 0–54 6 0–21	 54 (n=1) 0 (n=1)
European Region – National data or report to EARS-Net (n=31 countries) – Publications (n=3) from 2 additional countries	 0–68 2–7	 0–68 (n=30) 2 (n=1)
South-East Asia Region – National data (n=4 countries) – Publications (n=15) from 2 additional countries	 0–8 0–55	 0–52 (n=3)
Western Pacific Region – National data (n=9 countries) – Institute surveillance (data from 2 hospitals in 1 country) – Publications (n=2) from 2 additional countries	 0–8 0–1 0–11	

EARS-Net, European Antimicrobial Resistance Surveillance Network; PAHO, Pan American Health Organization; ReLAVRA, Latin American Antimicrobial Resistance Surveillance Network.

a. Based on antibacterial susceptibility testing with doripenem, ertapenem, imipenem or meropenem
b. Reported proportions may vary between compound used for testing and some countries report data for several compounds, or data from more than one surveillance system.
c. Invasive isolates are deep infections, mostly bloodstream infections and meningitis.
d. US Naval Medical Research Unit No 3, Global Disease Detection Program, Egypt.

Yeni antimikrobiyaller

- Sefepim-sulbaktam
- Seftriakson-sulbaktam
- Seftazidim-avibaktam (komplike karın içi ve üriner sistem infeksiyonları)
- Seftolozan-tazobaktam (komplike karın içi ve üriner sistem infeksiyonları)
- Seftarolin-avibaktam
- Tigesiklin (komplike karın içi ve deri ve yumuşak doku infeksiyonları)

β-lactam and β-lactamase inhibitor combinations in the treatment of extended-spectrum β-lactamase producing Enterobacteriaceae: time for a reappraisal in the era of few antibiotic options?

Patrick N A Harris, Paul A Tambyah, David L Paterson

The spread of extended-spectrum β-lactamase (ESBL) genes in Enterobacteriaceae such as *Escherichia coli* or *Klebsiella* spp is a major challenge to modern medical practice. Carbapenems are the treatment of choice for serious infections caused by ESBL producers; however, carbapenem resistance has increased globally. ESBL producers might be susceptible to β-lactam-β-lactamase inhibitor (BLBLI) combination antibiotics such piperacillin–tazobactam or amoxicillin–clavulanate. These drugs are frequently avoided in serious infections caused by ESBL producers because of the inoculum effect in-vitro (especially for piperacillin–tazobactam), animal data suggesting inferior efficacy when compared with carbapenems, concerns about pharmacokinetic–pharmacodynamic drug target attainment with standard doses, and poor outcomes shown in some observational studies. Prospective cohort data and a meta-analysis suggest that BLBLIs are non-inferior to carbapenems in the treatment of bloodstream infections caused by ESBL producers. We examine why BLBLIs are perceived as inferior in the treatment of infection with ESBL producers, and discuss data that suggest these concerns might not be strongly supported by clinical evidence.

Lancet Infect Dis 2015

Published Online
February 23, 2015
http://dx.doi.org/10.1016/S1473-3099(14)70950-8

University of Queensland Centre for Clinical Research, Brisbane, QLD, Australia (Prof P N A Harris MBBS, Prof D L Paterson PhD); **Department of Infectious Diseases, National University Hospital, Singapore**

SONUÇLAR

- GSBL üreten *Enterobacteriaceae* bakteremilerinin tedavisini belirlemeye yönelik **randomize kontrollü çalışma bulunmamaktadır**.

- GSBL (+) bakteremiler **yüksek mortalite** ile seyretmekte ve bu duruma neden olan en önemli etmenlerden biri ise **uygun antibiyoterapide gecikmedir**.

- GSBL (+) enterik bakteri infeksiyonlarında günümüzde en seçkin tedavi hala karbapenemler olsa da artan karbapenem kullanımı **karbapenem direncini** de gündeme getirmektedir.

- İn-vitro veriler ve retrospektif klinik çalışmalar **karbapenem ile tedavi** edilen olguların diğer antibiyotiklerle tedavi edilen olgulara kıyasla daha **düşük mortalite** ile seyrettiği yönünde

olsa da

- Gözlemsel çalışmalar **BL/BLİ'ye** in-vitro duyarlı kökenlerle gelişen infeksiyonlarda, **MİK düzeyi düşük ise BL/BLİ'lerle tedavi sonuçlarının karbapenemlerle benzer** olduğunu gösteriyor.

- GSBL risk faktörlerini taşıyan hastalar
- ağır sepsis veya septik şok
- bakteremi
- pnömoni
- odak kontrolü sağlanamayan karın içi infeksiyonlar

empirik tedavide ilk seçenekte hala karbapenemler önerilmektedir.

- Empirik tedaviyi belirlerken epidemiyolojik direnç verileri ve enzim tiplerinin bilinmesi yol gösterici.

- Hızlı moleküler testlere ihtiyaç var.

- klinik durumu düzelen
- odak kontrolü sağlanan
- mortalitesi daha düşük olan üriner ya da biliyer sistem kaynaklı infeksiyonlar
- MİK düzeyleri duyarlı sınırda olan hastalar

sefalosporinler ya da BL/BLİ ile de-eskalasyona gidilebilir.

- Ancak **duyarlı ama yüksek MİK düzeylerinde veya bazı GSBL tipi enzimlerin** sık görüldüğü bölgelerde klinik başarısızlık olabileceği akılda tutulmalıdır.

Teşekkür ederim...