6. TÜRKİYE EKMUD BİLİMSEL PLATFORMU
"Antimikrobiyal Direnç ve Akılcı Antimikrobiyal Tedavi"

Yoğun Bakımlarda Antibiyotik Uygulamalarında Farmakokinetik/Farmakodinamik

Uzamış/Sürekli İnfüzyon ve Yüksek Doz Uygulama

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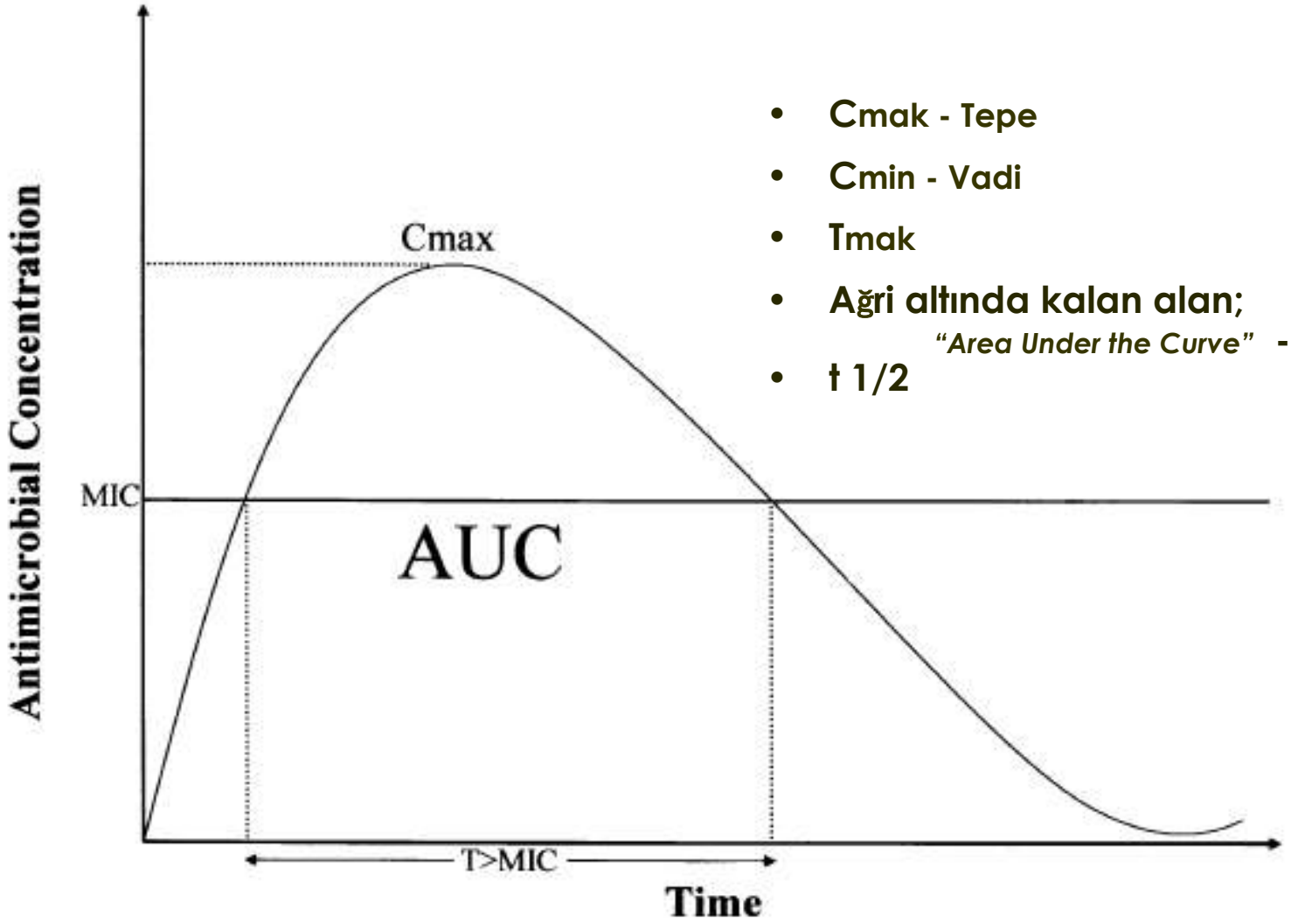
8 Nisan 2017

Yoğun Bakım Hastası...

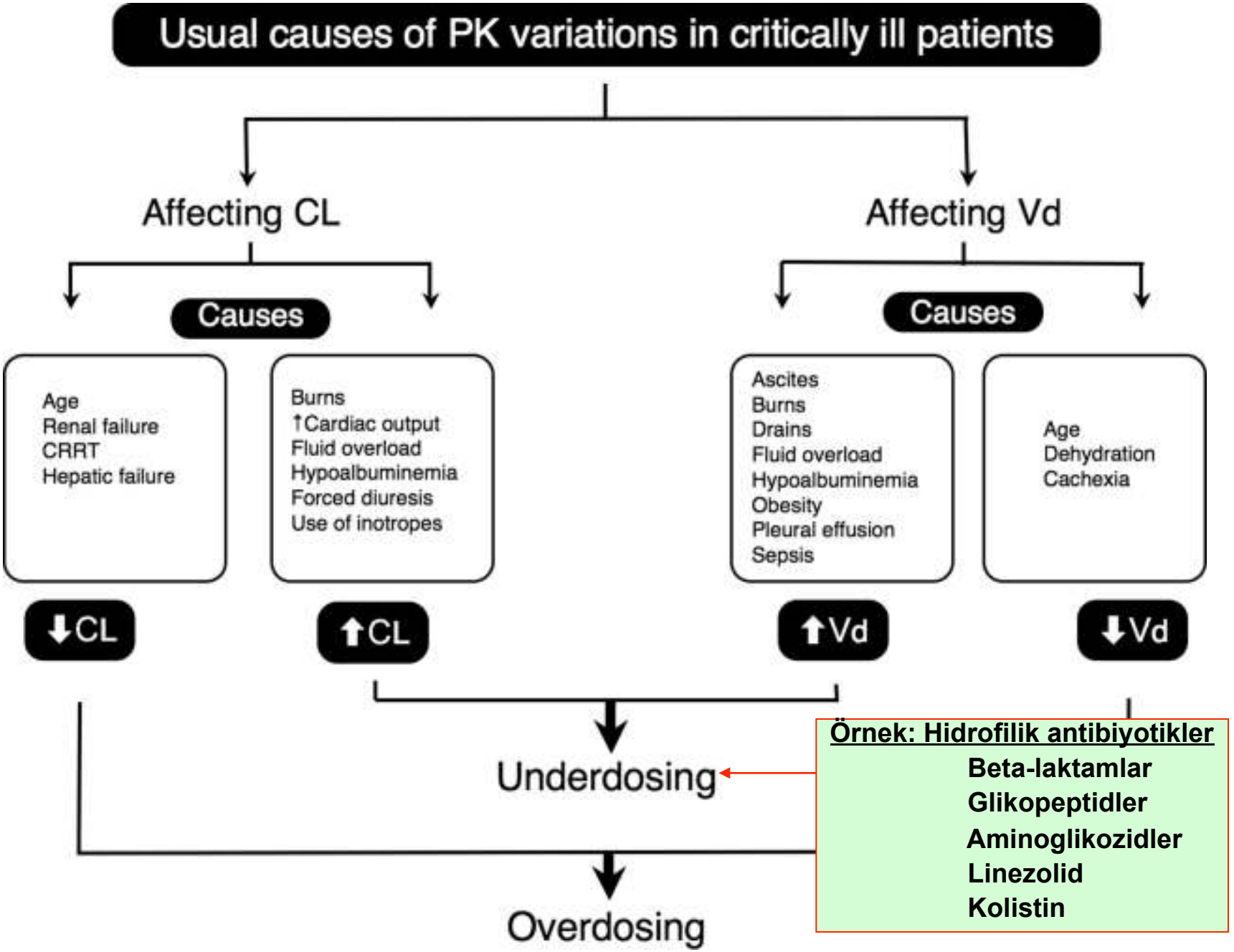
Antibiyotik Tedavi Başarısızlıklarının Başlıca Nedenleri

- ✓ **Yanlış Başarısızlık**
  - **Yanlış tanı**
  - **AB'den etkilenen komorbidite**
  - **AB'in inaktivasyonu**
- ✓ **Hasta ile İlişkili**
  - **Uyum sorunu**
  - **Uygulama yolu hatası**
  - **İmmündüşkün hasta**
- ✓ **Farmakolojik Başarısızlık**
  - **Yetersiz ilaç düzeyi**
  - **Yetersiz drenaj**
- ✓ **Mikrobiyolojik Faktörler**
  - **Direnç gelişimi**
  - **Antimikrobiyal etkinin yetersizliği**

Farmakokinetik Parametreler



- Cmak - Tepe
- Cmin - Vadi
- Tmak
- Ağri altında kalan alan;
  "Area Under the Curve" - AUC
- t 1/2


Usual causes of PK variations in critically ill patients
Affecting CL
Affecting Vd
Causes
Causes
Age
Renal failure
CRRT
Hepatic failure
Burns
↑Cardiac output
Fluid overload
Hypoalbuminemia
Forced diuresis
Use of inotropes
Ascites
Burns
Drains
Fluid overload
Hypoalbuminemia
Obesity
Pleural effusion
Sepsis
Age
Dehydration
Cachexia
⬇CL
⬆CL
⬆Vd
⬇Vd
Underdosing
Overdosing
Örnek: Hidrofilik antibiyotikler
Beta-laktamlar
Glikopeptidler
Aminoglikozidler
Linezolid
Kolistin

Farmakokinetik/ Farmakodinamik İndeksler

Zaman- Konsantrasyon / Konsantrasyon-Etki

Zaman - Etki

√AUC / MİK

√AUIC

√Cmak / MİK

√T>MİK

Doz-Süre Etkisine Göre Antibiyotikler

- ✓ Konsantrasyona Bağlı Etki
  - Aminoglikozitler
  - Florokinolonlar
  - Ketolidler
  - Metronidazol
- ✓ Zamana Bağlı Etki
  - Beta-laktamlar
  - Makrolidler
  - Klindamisin
- ✓ Konsantrasyon ve Zamana Bağlı Etki
  - Glikopeptidler
  - Oksazolidinonlar
  - Glisilsiklinler

ANTIMICROBIAL AGENTS AND CHEMOTHERAPY, May 1993, p. 1073–1081 Vol. 37, No. 5
0066-4804/93/051073-09$02.00/0

Pharmacodynamics of Intravenous Ciprofloxacin in Seriously Ill Patients

ALAN FORREST, DAVID E. NIX, CHARLES H. BALLOW, THOMAS F. GOSS, MARY C. BIRMINGHAM, AND JEROME J. SCHENTAG*

Center for Clinical Pharmacy Research, School of Pharmacy, State University of New York at Buffalo, Buffalo, New York 14260, and The Clinical Pharmacokinetics Laboratory, Millard Fillmore Hospital, Buffalo, New York 14209-1194

✓ 74 hasta; 2x200 mg – 3x400 mg i.v.

AUC/MİK	Klinik	Mikr
<125 (n=19)	%42	%26
>125 (n=45)	%80	%82
P	0.005	0.001

Mikrobiyal Eradikasyon

AUC/MİK	Süre
<125	>32 gün
125-250	6.6 gün
>250	1.9 gün

Forrest A, et al. AAC 1993

ELSEVIER

International Journal of Antimicrobial Agents 30 (2007) 162–168

INTERNATIONAL JOURNAL OF Antimicrobial Agents

www.ischemo.org

Pharmacokinetics and pharmacodynamics of levofloxacin in critically ill patients with ventilator-associated pneumonia

Ria Benko[a,*], Maria Matuz[a], Peter Doro[a], Zoltan Peto[b], Anna Molnar[b], Edit Hajdu[c], Erzsebet Nagy[c], Janos Gardi[d], Gyongyver Soos[a]

[a] *Department of Clinical Pharmacy, Faculty of Pharmacy, University of Szeged, H-6725 Szeged, Szikra u. 8, Hungary*
[b] *Department of Anaesthesiology and Intensive Care, Faculty of Medicine, University of Szeged, Szeged, Hungary*
[c] *Department of Clinical Microbiology, Faculty of Medicine, University of Szeged, Szeged, Hungary*
[d] *Endocrine Unit and Research Laboratory, Faculty of Medicine, University of Szeged, Szeged, Hungary*

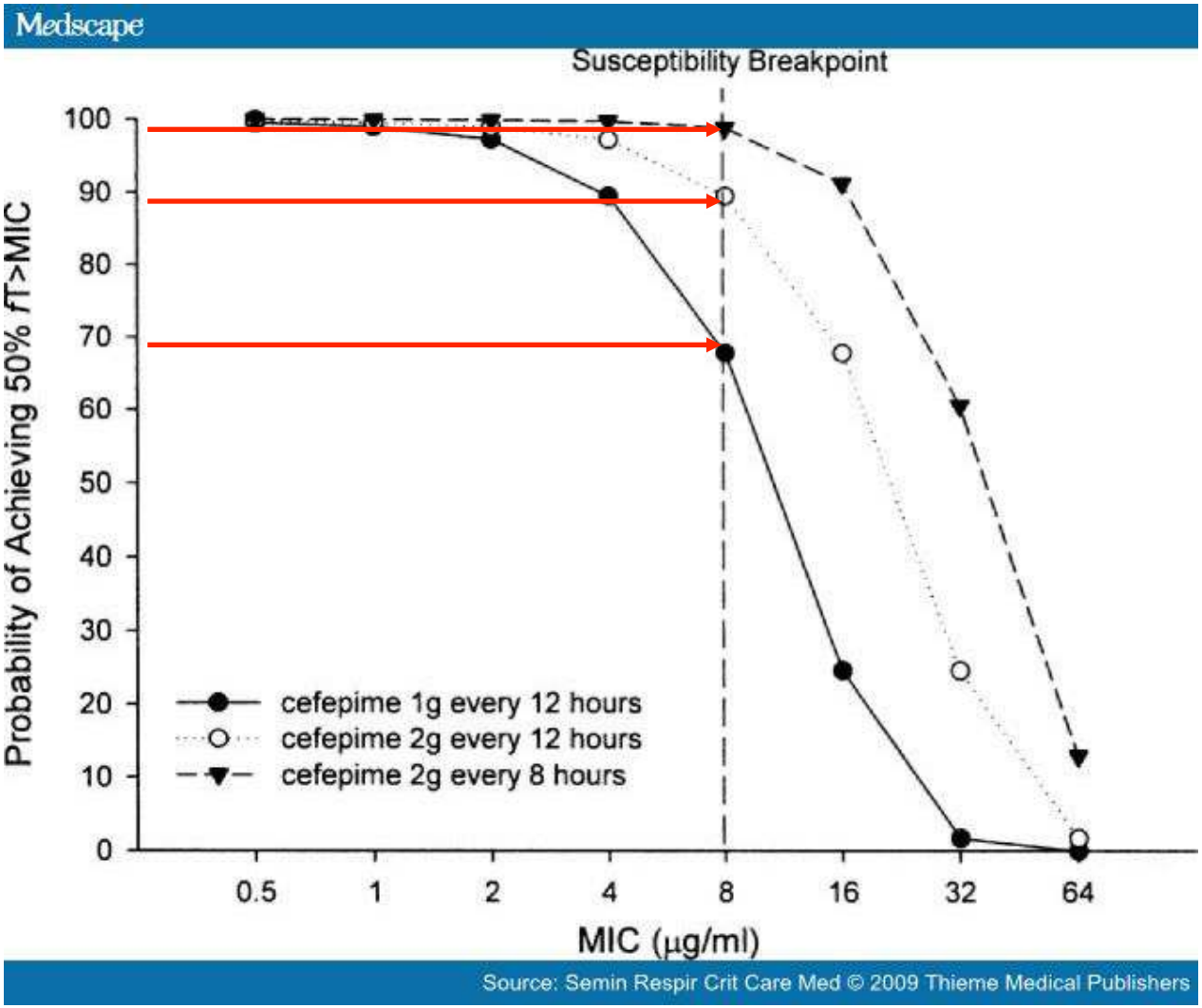
Target PK/PD parameters	Study MIC[b] 0.31 mg/L	Dedicated MIC values			
		0.25 mg/L	0.5 mg/L	1 mg/L	2 mg/L[c]
C_{max}/MIC					
10	12	12	12	8	0
12	12	12	12	5	0
AUC/MIC					
30	12	12	12	12	7
50	12	12	12	11	1
100	12	12	11	1	0
125	12	12	7	0	0
250	4	7	0	0	0

Kinolonlar

- ✓ Standart dozlarda bir çok patojen için AUC/MİK>125 oranını sağlayamazlar
- ✓ Duyarlılık sınır değerleri FD bakış açısıyla Sipro 0.25, Levo: 0.5 (?) olmalı
- ✓ Nozokomiyal pnömoni için siprofloksasinin 8 saatte bir 400 mg, levofloksasinin 750 mg/gün kullanımı önerilmekte

Deryke CA. Pharmacotherapy 2007

Sefepim – doz seçimi



Deryke CA. Diagn Microbiol Infect Dis 2007

Intensive Care Med (2006) 32:775–778
DOI 10.1007/s00134-006-0136-3

BRIEF REPORT

Olivier Mimoz
Delphine Rolland
Michèle Adenis
Sandrine Marchand
Dominique Breilh
Ivan Brumpt
Bertrand Debaene
William Coutt

Steady-state trough serum and epithelial lining fluid concentrations of teicoplanin 12 mg/kg per day in patients with ventilator-associated pneumonia

- ✓ 12mg/kg; ilk iki gün 12 st, sonra 24 st ara ile
- ✓ 4-6.gün örnekleme
- ✓ Serum düzeyleri beklenenden düşük; ELF düzeyi beklenenden yüksek
- ✓ **VİP dozu en az 12mg/kg olmalı**

Vankomisin

- ✓ AUC/MIK en iyi gösterge: >400
- ✓ Standart dozlarda (2x1g) S. aureus MİK>1 mg/L ise yetersiz kalıyor

Sakoulas G. J Clin Microbiol 2004

- ✓ MİK ≥2 olan S. aureus ve KNS izolatlarında 3x1g dahi yetersiz kalabiliyor

Kuti JL. Clin Microbiol Infect 2008

- ✓ Vankomisin MİK ≥2 MRSA pnömonisinde tedavi başarısızlığı için bağımsız faktör

Hidayat LK. Arch Intern Med 2006

Vancomycin Therapeutic Guidelines: A Summary of Consensus Recommendations from the Infectious Diseases Society of America, the American Society of Health-System Pharmacists, and the Society of Infectious Diseases Pharmacists

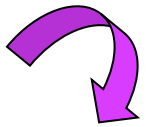
Michael J. Rybak,[1,2,3] Ben M. Lomaestro,[4] John C. Rotschafer,[5] Robert C. Moellering, Jr.,[6,7,8] Willam A. Craig,[9] Marianne Billeter,[10] Joseph R. Dalovisio,[11] and Donald P. Levine[3]

Clinical Infectious Diseases 2009; 49:325–7

- ✓ AUC / MİK > 400

  25-30 mg/kg yükleme; 15-20 mg/kg 8-12 saatte bir

- ✓ 1.5-2 saat infüzyon; 4. dozdan önce serum düzey



15-20 mg/l vadi düzeyi gerekli

Pharmacokinetics and preliminary safety of high dose linezolid for the treatment of Gram-positive bacterial infections

Table 2 Microbiological, pharmacokinetic and tolerability data.

Pt	Infection	Pathogen	$Cmin_{ss}/Cmax_{ss}$ (mg/L)	Baseline/final platelet count (cells/mcl)	Baseline/final Hb (cells/mcl)	Haematological toxicity	Clinical cure	All-cause mortality
1	Intra-abdominal	*E. faecium*	1.7/7.4	170/245	8.2/8.7	None	Yes	No
2	Intra-abdominal	Empirical	21.9/34.1	237/40	9.1/9.2	Thrombocytopenia	Yes	Yes
3	Central nervous system	MRSA	0.8/11.4	269/244	11.2/12.5	None	Yes	No
4	Respiratory	MRSA	11.5/27.4	177/69	8.4/9.1	Thrombocytopenia	No	Yes
5	Respiratory	Empirical	6.2/19.8	136/15	13.8/8.2	Thrombocytopenia + Anaemia	Yes	No
6	Post-surgical sepsis and urinary	*E. faecalis/E. faecium*/MRSA	38.6/46.7	369/90	8.2/8	Thrombocytopenia	Yes	No
7	Respiratory	MRSA	1.1/18.1	784/366	8.5/8.1	None	Yes	Yes

Lopez-Garcia B& Luque S. J Infect 2015; 71(1): 604–607

YBÜ izolatı ve Monte Carlo Simulasyonuna göre dozlar

Regimen	Probability of achieving bacteriostatic/bactericidal pharmacodynamic target (%)			
	Overall	Enterobacteriaceae	*P. aeruginosa*	*A. baumannii*
Aztreonam 1 g every 8 h[c]	75/64	87/84	78/57	35/10
Aztreonam 2 g every 8 h[c]	82/73	90/86	**90/73**	57/27
Cefepime 1 g every 8 h[c]	82/73	**95/92**	82/63	46/34
Cefepime 1 g every 12 h[c]	76/61	93/88	68/32	37/19
Cefepime 2 g every 8 h[c]	**88/81**	**96/95**	**92/80**	**61/45**
Cefepime 2 g every 12 h[c]	83/70	**95/91**	85/54	48/29
Ceftazidime 1 g every 8 h[c]	**80/75**	87/85	**85/77**	51/40
Ceftazidime 2 g every 8 h[c]	**93/79**	95/85	**95/83**	**83/49**
Ceftriaxone 1 g every 24 h[c]	46/39	81/78	3/1	7/3
Ceftriaxone 2 g every 24 h[c]	52/47	84/82	12/4	22/8
Ertapenem 1 g every 24 h[d]	63/56	**97/95**	22/8	29/11
Imipenem 0.5 g every 6 h[d]	**86/81**	**100/97**	79/70	**89/72**
Piperacillin/tazobactam 3.375 g every 4 h[b]	**80/75**	89/85	**84/78**	53/46
Piperacillin/tazobactam 3.375 g every 6 h[b]	78/67	87/78	82/67	49/39
Piperacillin/tazobactam 4.5 g every 6 h[b]	79/71	88/83	84/72	50/42
Piperacillin/tazobactam 4.5 g every 8 h[b]	67/46	86/54	79/43	47/25
Ticarcillin/clavulanate 3.1 g every 4 h[b]	75/68	84/81	65/52	**59/52**
Ticarcillin/clavulanate 3.1 g every 6 h[b]	68/53	81/74	56/29	**53/43**

Burgess D, Frei CR. JAC 2005;56, 893–898

Clinical Infectious Diseases

IDSA GUIDELINE

Management of Adults With Hospital-acquired and Ventilator-associated Pneumonia: 2016 Clinical Practice Guidelines by the Infectious Diseases Society of America and the American Thoracic Society

Table 3. Suggested Empiric Treatment Options for Clinically Suspected Ventilator-Associated Pneumonia in Units Where Empiric Methicillin-Resistant *Staphylococcus aureus* Coverage and Double Antipseudomonal/Gram-Negative Coverage Are Appropriate

A. Gram-Positive Antibiotics With MRSA Activity	B. Gram-Negative Antibiotics With Antipseudomonal Activity: β-Lactam–Based Agents	C. Gram-Negative Antibiotics With Antipseudomonal Activity: Non-β-Lactam–Based Agents
Glycopeptides[a] Vancomycin 15 mg/kg IV q8–12h (consider a loading dose of 25–30 mg/kg × 1 for severe illness)	Antipseudomonal penicillins[b] Piperacillin-tazobactam 4.5 g IV q6h[b]	Fluoroquinolones Ciprofloxacin 400 mg IV q8h Levofloxacin 750 mg IV q24h
OR	OR	OR
Oxazolidinones Linezolid 600 mg IV q12h	Cephalosporins[b] Cefepime 2 g IV q8h Ceftazidime 2 g IV q8h	Aminoglycosides[a,c] Amikacin 15–20 mg/kg IV q24h Gentamicin 5–7 mg/kg IV q24h Tobramycin 5–7 mg/kg IV q24h
	OR	OR
	Carbapenems[b] Imipenem 500 mg IV q6h[d] Meropenem 1 g IV q8h	Polymyxins[a,e] Colistin 5 mg/kg IV × 1 (loading dose) followed by 2.5 mg × (1.5 × CrCl + 30) IV q12h (maintenance dose) [135] Polymyxin B 2.5–3.0 mg/kg/d divided in 2 daily IV doses
	OR	
	Monobactams[f] Aztreonam 2 g IV q8h	

Tigesiklin Klinik Başarı için Gereken FK/FD *(AUC/MİK)*

- ✓ Komplike İntraabdominal Enf ≥ 6.96

  Passarell JA, et al. AAC 2008; 52(1):204-210

- ✓ Komplike Cilt Yumuşak Doku Enf ≥ 17.9

  Meagher AK, et al. AAC 2007; 51(6):1939-1945

- ✓ Hastane Kökenli Pnömoni ≥ 5.70

  Bhavnani, IDSA 2007

De Pascale et al. Critical Care 2014, 18:R90
http://ccforum.com/content/18/3/R90

CRITICAL CARE

RESEARCH Open Access

High dose tigecycline in critically ill patients with severe infections due to multidrug-resistant bacteria

Gennaro De Pascale[1*], Luca Montini[1], Mariano Alberto Pennisi[1], Valentina Bernini[1], Riccardo Maviglia[1], Giuseppe Bello[1], Teresa Spanu[3], Mario Tumbarello[2] and Massimo Antonelli[1]

	SD TGC group (n = 30)	HD TGC group (n = 33)	*P*-value
Responsible pathogens, n (%)			
Acinetobacter baumannii XDR	13 (43.3)	15 (45.4)	0.86
Klebsiella pneumoniae MDR/XDR	10 (33.3)	20 (60.6)	0.03
Other bacteria	14 (46.6)	6 (18.1)	0.01
MIC value 1 to 2 mcg/mL[a]	8 (32)	23 (79.3)	<0.01
Clinical and microbiological outcome, n (%)			
ICU mortality	20 (66.6)	16 (48.4)	0.14
Clinical cure	10 (33.3)	19 (57.5)	0.05
Microbiological eradication	7 (30.4)	12 (57.1)	0.07

Tigesiklin Yüksek Doz

Logistic regression analysis of factors associated with clinical cure in 63 patients with ventilator-associated pneumonia

Variable	Multivariate analysis		
	Odds ratio	95% CI	*P*-value
SOFA score at infection occurrence	0.66	0.51, 0.87	0.003
Initial inadequate treatment	0.18	0.05, 0.68	0.01
High-dose tigecycline group	6.25	1.59, 24.57	0.009

Critical Care 2014;18:R90

Table 4. Recommended Initial Empiric Antibiotic Therapy for Hospital-Acquired Pneumonia (Non-Ventilator-Associated Pneumonia)

Not at High Risk of Mortality[a] and no Factors Increasing the Likelihood of MRSA[b,c]	Not at High Risk of Mortality[a] but With Factors Increasing the Likelihood of MRSA[b,c]	High Risk of Mortality or Receipt of Intravenous Antibiotics During the Prior 90 d[b,c]
One of the following:	One of the following:	Two of the following, avoid 2 β-lactams:
Piperacillin-tazobactam[d] 4.5 g IV q8h	Piperacillin-tazobactam[d] 4.5 g IV q8h	Piperacillin-tazobactam[d] 4.5 g IV q8h
OR	OR	OR
Cefepime[d] 2 g IV q8h	Cefepime[d] or ceftazidime[d] 2 g IV q8h	Cefepime[d] or ceftazidime[d] 2 g IV q8h
OR	OR	OR
Levofloxacin 750 mg IV daily	Levofloxacin 750 mg IV daily	Levofloxacin 750 mg IV daily
	Ciprofloxacin 400 mg IV q8h	Ciprofloxacin 400 mg IV q8h
	OR	OR
Imipenem[d] 500 mg IV q8h	Imipenem[d] 500 mg IV q8h	Imipenem[d] 500 mg IV q8h
Meropenem[d] 1 g IV q8h	Meropenem[d] 1 g IV q8h	Meropenem[d] 1 g IV q8h

PHARMACOKINETIC/PHARMACODYNAMIC OPTIMIZATION OF ANTIBIOTIC THERAPY

Remarks: PK/PD-optimized dosing refers to the use of antibiotic blood concentrations, extended and continuous infusions, and weight-based dosing for certain antibiotics.

empiric regimen for HAP.

If patient has severe penicillin allergy and aztreonam is going to be used instead of any β-lactam-based antibiotic, include coverage for MSSA.

Zamana Bağlı Etki T>MİK

- ✓ 2-log'luk öldürme (maksimal) için iki doz aralığında ilaç konsantrasyonunun MİK düzeyi üzerinde kaldığı sürenin yüzdesi

Antibiyotik	Üremenin durması	2-log öldürme
Penisilin	%30	%50
Sefalosporin	%40	%60-70
Karbapenem	%20	%40

%T>MİK oranı aynı olduğunda aynı mikrobiyolojik sonuçlar alınmıştır

Drusano GL. Clin Infect Dis 2003

Drusano GL. Clin Infect Dis 2003

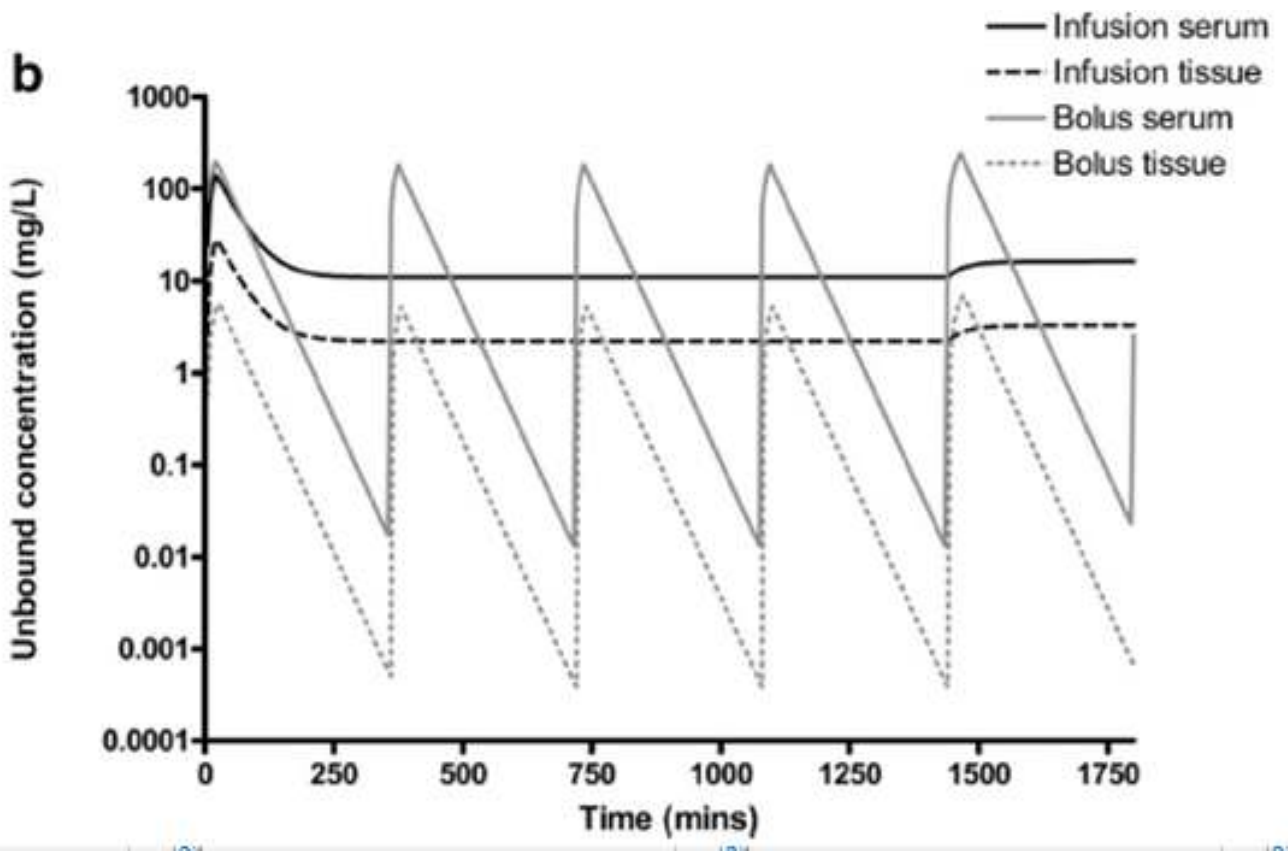
Seftazidim Devamlı İnfüzyon

BJ. Br J Clin Pharmacol 49; 184-191

Piperacillin penetration into tissue of critically ill patients with sepsis—Bolus versus continuous administration?

Jason A. Roberts, BPharm (Hons); Michael S. Roberts, DSc; Thomas A. Robertson, PhD; Andrew J. Dalley, PhD; Jeffrey Lipman, FJFICM, MD

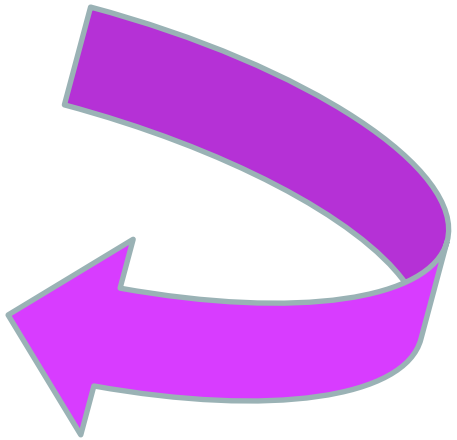
Tümü VİP 13 hasta (7 bolus, 6 devamlı infüzyon; 12/1.5 gr/gün



Crit Care Med 2009; 37:926 –933

Piperasilin/Tazobaktam
Bolus, Uzun veya Devamlı İnfüzyon

- ✓ Karşılaştırılan Uygulama
  - 3.375 gr - 30dk - 4 saat ara ile
  - 4.5 gr - 4 st infüzyon - 6 saat ara ile
  - 18 gr - devamlı inf - 24 saat ara ile



*Devamlı veya uzun inf ile

MİK=32 için T>MİK %90

*Bolus ile

MİK=8 için T>MİK %90

Kim, et al. Pharmacotherapy 2007; 27: 1290-7

Alveolar concentrations of piperacillin/tazobactam administered in continuous infusion to patients with ventilator-associated pneumonia*

Emmanuel Boselli, MD, PhD; Dominique Breilh, PharmD, PhD; Thomas Rimmelé, MD; Christian Guillaume, MD; Fabien Xuereb, PharmD; Marie-Claude Saux, PharmD, PhD; Lionel Bouvet, MD; Dominique Chassard, MD, PhD; Bernard Allaouchiche, MD, PhD

- ✓ >16 mg/L alveolar konsantrasyonu sağlamak için 35–40 mg/L serum düzeyi gerekli
- ✓ **16/2 g /gün dozun devamlı infüzyonu gerekli**
- ✓ Renal yetmezlikte düzey takibi gerekebilir

Crit Care Med 2008; 36:1500–1506

ANTIMICROBIAL AGENTS AND CHEMOTHERAPY, Apr. 2009, p. 1476–1481 Vol. 53, No. 4
0066-4804/09/$08.00+0 doi:10.1128/AAC.01141-08

Population Pharmacokinetics of High-Dose, Prolonged-Infusion Cefepime in Adult Critically Ill Patients with Ventilator-Associated Pneumonia▽

Anthony M. Nicasio,[1] Robert E. Ariano,[2] Sheryl A. Zelenitsky,[2] Aryun Kim,[1] Jared L. Crandon,[1] Joseph L. Kuti,[1] and David P. Nicolau[1]*

✓3x 2 gr;3 saat infüzyon ile T>MİK %50

MİK

8 → **%91.8**

16 → **%78.1**

32 → **%50.3**

Uzun / Devamlı İnfüzyon Gerekliliği…

- ✓ Seftazidim; VİP; 4 gr Dİ

  Boselli, et al. Intensive Care Med 2004; 30:939

- ✓ Sefepim;
  - VİP; 3x2 gr- 3st infüzyon

    Nicasio, et al. AAC 2009; 53: 1476

  - HKP; **2Y**+ 4g Dİ

    Boselli, et al. Crit Care Med 2003; 31:2102–2106

Uzun / Devamlı İnfüzyon Gerekliliği…

- ✓ Meropenem; VİP, 3 st infüzyon

  Jaruratanasirikul, et al. AAC 2005; 49:1337

- ✓ Doripenem; Faz II, III; 1-6 st infüzyon

  Bhavnani, et al. AAC; 49: 3944

- ✓ İmipenem;
  - VİP; Dİ

    Sakka, et al. AAC 2007; 51: 3304.

  - VİP; 2st infüzyon

    Jaruratanasirikul & Sudsai. JAC 2009; 63: 560-63

ELSEVIER

International Journal of Antimicrobial Agents 31 (2008) 122–129

International Journal of Antimicrobial Agents

www.ischemo.org

Linezolid pharmacokinetic/pharmacodynamic profile in critically ill septic patients: intermittent versus continuous infusion☆

Pharmacokinetic/pharmacodynamic parameters of linezolid after intermittent infusion (Group I) or continuous infusion (Group C) of 1200 mg daily in critically ill septic patients

Parameter	Group I	Group C
$AUC_{0-24\,h}$ (mg h/L)	154.21 ± 59.59^{a}	179.72 ± 59.01^{a}
$AUC_{24-48\,h}$ (mg h/L)	210.91 ± 66.01^{a}	200.64 ± 80.15^{a}
$AUC_{48-72\,h}$ (mg h/L)	188.16 ± 136.58^{a}	245.75 ± 104.81^{a}
Mean AUC/2 mg/L MIC	92.2 ± 45.2^{a}	103.03 ± 39.8^{a}
AUC/2 mg/L MIC ≥80	5/8 (62.5%)[b]	7/8 (87.5%)[b]
$T_{total} > 1$ mg/L MIC (%)[c]	99	100
$T_{free} > 1$ mg/L MIC (%) ≥85%	4/8 (50%)[b,*]	8/8 (100%)[b]
$T_{total} > 2$ mg/L MIC (%)[d]	94.3	100
$T_{free} > 2$ mg/L MIC (%) ≥85%	3/8 (40%)[b,*]	8/8 (100%)[b]

Time (h)

*p< 0.05 **p< 0.01

C. Adembri ,et al. IJAA 31 2008;122–129

Piperacillin-Tazobactam for *Pseudomonas aeruginosa* Infection: Clinical Implications of an Extended-Infusion Dosing Strategy

Thomas P. Lodise, Jr.,[1,2] Ben Lomaestro,[3] and George L. Drusano[2]

- ✓ Çalışma grubu (2002-2004): 3.375 g, 8 saatte, 4 s uzamış infüzyon
- ✓ Kontrol grubu (2000-2002): 3.375, 6 saatte bir, 30 dk infüzyon

APACHE II >17 grupta

Piperasilin/Tazobaktam	30dk	4 st infüzyon	p
14. gün mortalite	31.6	12.2	0.04
Hastanede yatış*	38 gün	21 gün	0.02

Lodise, et al. CID 2007; 44: 357-63

Beta-laktamların devamlı infüzyonla kullanımı – sistematik derleme

- ✓ 30 makaleden 14'ü değerlendirmeye alınmış
- ✓ Devamlı infüzyon klinik sonucu anlamlı olarak değiştirmiyor ancak belirgin faydaları var
- ✓ Hastanede yatan tüm hastalar için uygulanması bir avantaj olmayabilir ancak spesifik gruplarda ör. Kritik hastalarda faydalı olabilir.

Roberts JA. Crit Care Med 2009

Management of Ventilator-Associated Pneumonia

Diaz E, Ulldemolins M, Lisboa T, Rello J.
Infect Dis Clin N Am 2009; 23: 521–533.

Table 2
Final recommendation for antibiotic treatment in patients withVAP

Patient Category	Antibiotic Treatment
No risk factors for MDR organisms	Amoxicillin-clavulanate Ampicillin-sulbactam Ertapenem Ceftriaxone
At risk for: Pseudomonas aeruginosa	Initial empiric antibiotic treatment Imipenem/cilastatin: 2 h infusion Meropenem: 3 h infusion Doripenem: 4 h infusion Piperacillin-tazobactam: 4 infusion Ceftazidime/cefepime: continuous infusion Combination with Ciprofloxacin
MRSA	Linezolid Vancomycin: continuous infusion to trough levels of 15–20 microg/mL
Acinetobacter baumannii	Carbapenem Sulbactam Colistin
Previously treated with antibiotic:	
Previous β-lactam Ciprofloxacin Carbapenem Aminoglycoside	Recommendation Carbapenem Avoid imipenem Piperacillin-tazobactam Ciprofloxacin or change aminoglycoside type

Continuous versus intermittent infusions of antibiotics for the treatment of severe acute infections (Review)

Shiu JR, Wang E, Tejani AM, Wasdell M

Authors' conclusions

No differences in mortality, infection recurrence, clinical cure, super-infection post-therapy, and safety outcomes were reported when continuous infusions of intravenous antibiotics were compared with traditional intermittent infusions of antibiotics. However, the wide confidence intervals suggest that beneficial or harmful effects cannot be ruled out for all outcomes. Therefore, the current evidence is insufficient to recommend the widespread adoption of continuous infusion antibiotics in the place of intermittent infusions of antibiotics. Additinal large prospective randomised trials, with consistent and complete reporting of clinical outcome measures, conducted with concurrent pharmacokinetic and pharmacodynamic studies in special populations, are required to determine whether adoption of continuous antibiotic infusions is warranted in specific circumstances.

- Klinik Başarı
  - n = 975, RR 1.00, %95 GA 0.93 - 1.08, P = 0.98
- Tedavi sonrası süperinfeksiyon
  - n = 813, RR 1.08, % 95 GA 0.60 -1.94, P = 0.79

Cochrane Database of Systematic Reviews 2013, Issue 3. Art. No.: CD008481.

Continuous versus Intermittent β-Lactam Infusion in Severe Sepsis. A Meta-analysis of Individual Patient Data from Randomized Trials.

- ✓ 3 RKÇ + ../ 632 hasta
  - yaş, cins, hastalık ciddiyeti

	Devamlı	İntermittan	RR (%95 GAA)	p
H. Ölüm	19.6%	26.3%	0.74 (0.56-1.00)	0.045
Şifa	55.4%	46.3%	1.20 (1.03-1.40)	0.021

- ✓ Çok Değişkenli analiz / Hastanede mortalite
  - intermittan β-laktam
  - Yüksek APACHE II SKORU
  - Renal replasman tedavisi
  - Nonfermentatif GNB

Roberts JA,et al. AJRCCM 2016

Continuous Infusion of Beta-Lactam Antibiotics in Severe Sepsis: A Multicenter Double-Blind, Randomized Controlled Trial

Joel M. Dulhunty,[1] Jason A. Roberts,[1] Joshua S. Davis,[2] Steven A. R. Webb,[3] Rinaldo Bellomo,[4] Charles Gomersall,[5] Charudatt Shirwadkar,[6] Glenn M. Eastwood,[4] John Myburgh,[7] David L. Paterson,[8] and Jeffrey Lipman[1]

Endpoint	Intervention Group	Control Group	*P*
Plasma antibiotic concentration >MIC	18 (81.8%)[a]	6 (28.6%)[a]	.001
Clinical cure (test of cure date)	23 (76.7%)	15 (50.0%)	.032
Clinical cure (test of cure date with treatment exclusions)	21 (70.0%)	13 (43.3%)	.037
Clinical cure (last day of blinding)	9 (30.0%)	6 (20.0%)	.37
Time to clinical resolution (days)	11 (6.75–24.25)[b]	16.5 (7–28)[b]	.14
Time to resolution of CRP (days)	6 (2.5–22.5)[c]	5 (3–27)[c]	.79
ICU length of stay (postrandomization)	7.5 (4–12)	9 (5–14.25)	.50
ICU-free days			
All	19.5 (12.75–24)	17 (.75–22)	.14
ICU survivors	20.5 (16–24)[d]	18 (12.75–22)[d]	.22
ICU survival	28 (93.3%)	26 (86.7%)	.67
Hospital survival	27 (90.0%)	24 (80.0%)	.47

Clinical Infectious Diseases 2013;56(2):236–44

Intensive Care Med (2016) 42:1535–1545
DOI 10.1007/s00134-015-4188-0

ORIGINAL

CrossMark

- ✓ **Klinik Başarı**
  - Dİ %56; İB %34 ; p = 0.011
- ✓ ***ventilator-free* gün**
  - Dİ 22 ; İB 14 gün; p<0.043
- ✓ **PK/PD hedefi fT>MIK sağlama**
  - 1 .gün %97 vs %70 ; p<0.001
  - 3. gün %97 vs %68 ; p<0.001
- ✓ **Survi**
  - 14. ve 30. günde fark yok

Table 2 Pri

Primary end				Significance (p value)[a,b]
Clinical cur				**0.011**
Clinical cur				
Piperacillin				**0.016**
Meropenem				0.064
Cefepime				1.000
Clinical cur				
Yes				0.802
No				**0.001**
Clinical cur				
Lung				**0.022**
Clinical cure by *A. baumannii* or *P. aeruginosa* infection, *n* (%)[c]				
Yes	13 (52)	6 (25)	27 (−0.5 to 0.1)	0.052
No	10 (44)	12 (38)	6 (−0.3 to 0.2)	0.655

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

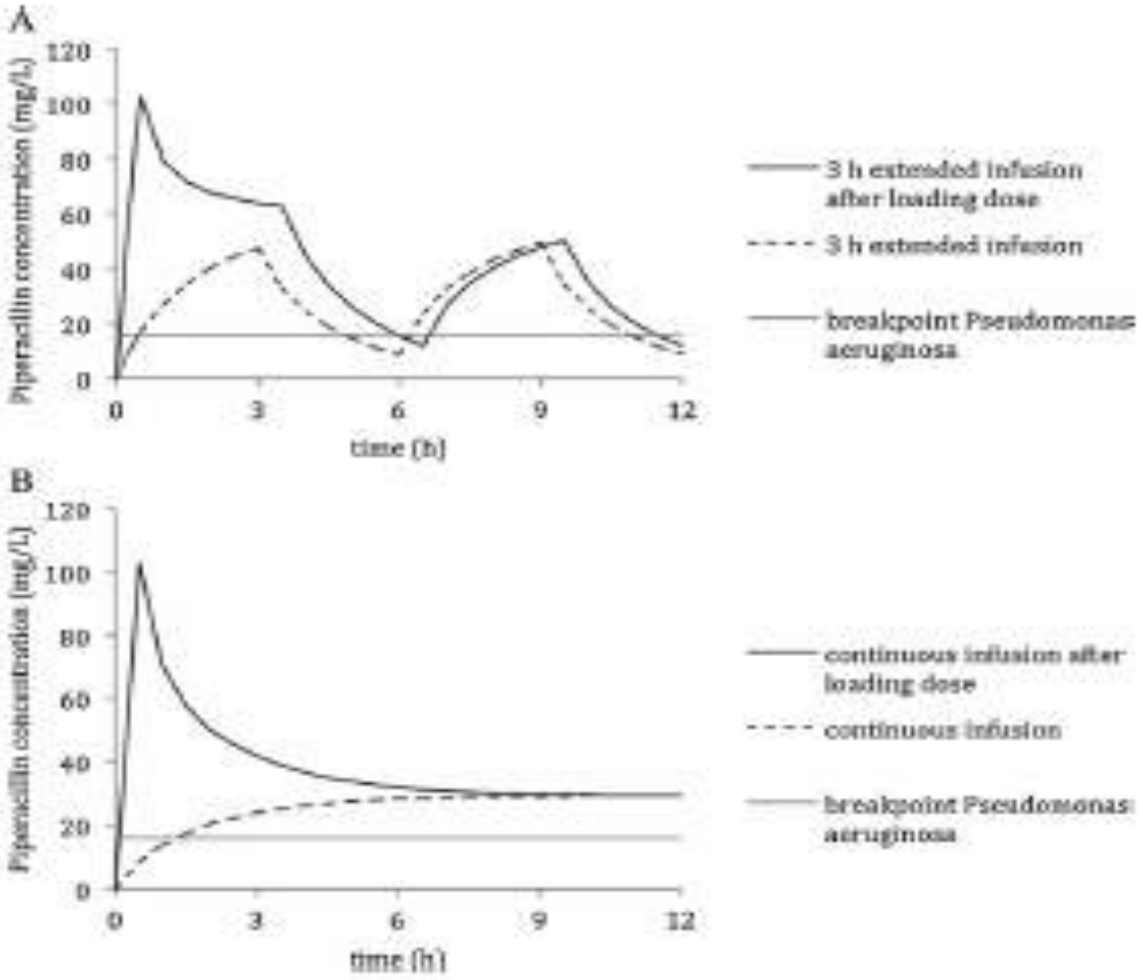
Short Communication

Might real-time pharmacokinetic/pharmacodynamic optimisation of high-dose continuous-infusion meropenem improve clinical cure in

- ✓ **Klinik Başarı: ort. 14 gün sonunda %73.3**
- ✓ **<u>Belirleyiciler</u>:**
  - ○ ***C*ss/MIC ≥1 (OR = 10.556, 95% GA 1.612–69.122; *P* = 0.014)**
  - ○ ***C*ss/MIC ≥4 (OR = 12.250, 95% GA 1.268–118.361; *P* = 0.030)**
  - ○ **Charlson komorbidite indeksi ≥4 (OR = 0.158, 95% CI 0.025–0.999; *P* = 0.05).**
- ✓ **Gerçek zamanlı TDM ile uygulanan yüksek doz Dİ meropenem**

MİK ≤ 64 mg/L KPC-KP' de klinik sonuçları düzeltebilir

Dİ: Yükleme Dozunun Önemi



- ✓ Stabilite
- ✓ Ölü boşluk
- ✓ Artık-set yıkanması

De Waele JJ, et al. IJAA 2015;45:461

Özetle Yüksek Doz

- ✓ Çoğu ajan için özellikle HKP/VİP'te standart uygulama olmalı
- ✓ İdeal olan Terapötik İlaç Monitorizasyonu
  - ○ Özellikle beta-laktam dışı ajanlarda
- ✓ Seçili ajanlarda mecbur kalındığında doğru doz seçimine özen gösterilmeli

Özetle;
Uzamış/devamlı infüzyon

- FK/FD veriler kesinlikle destekleyici
- Klinik sonuçlar daha fazla veri gerektirse de kritik hastada yararlı olabilir
- Panresistan bakteri enfeksiyonları; direncin hakim olduğu ortamda ampirik tedavi başlıca araştırma konuları olacaktır

Teşekkür ederim