Yoğun Bakım Ünitelerinde Doğru Antibiyotik Kullanımı

Prof. Dr. Emine ALP

Erciyes Üniversitesi Tıp Fakültesi
Enfeksiyon Hastalıkları ve Klinik Bakteriyoloji A.D.

Kayseri

Sunum Planı

- Niçin Önemli?
- Hangi Antibiyotik?
- Hangi Dozda?
- Nasıl?
- Ne Kadar Süre?
- Sonuç

YBÜ'lerinde Doğru Antibiyotik Kullanımı

Niçin Önemli?

- **Nozokomiyal enfeksiyonların %25'i YBÜ'lerinde gelişiyor**
- **Mortalite yüksek**
- **Doğru antibiyotik kullanımı mortaliteyi düşürüyor**

YBÜ'lerinde Doğru Antibiyotik Kullanımı

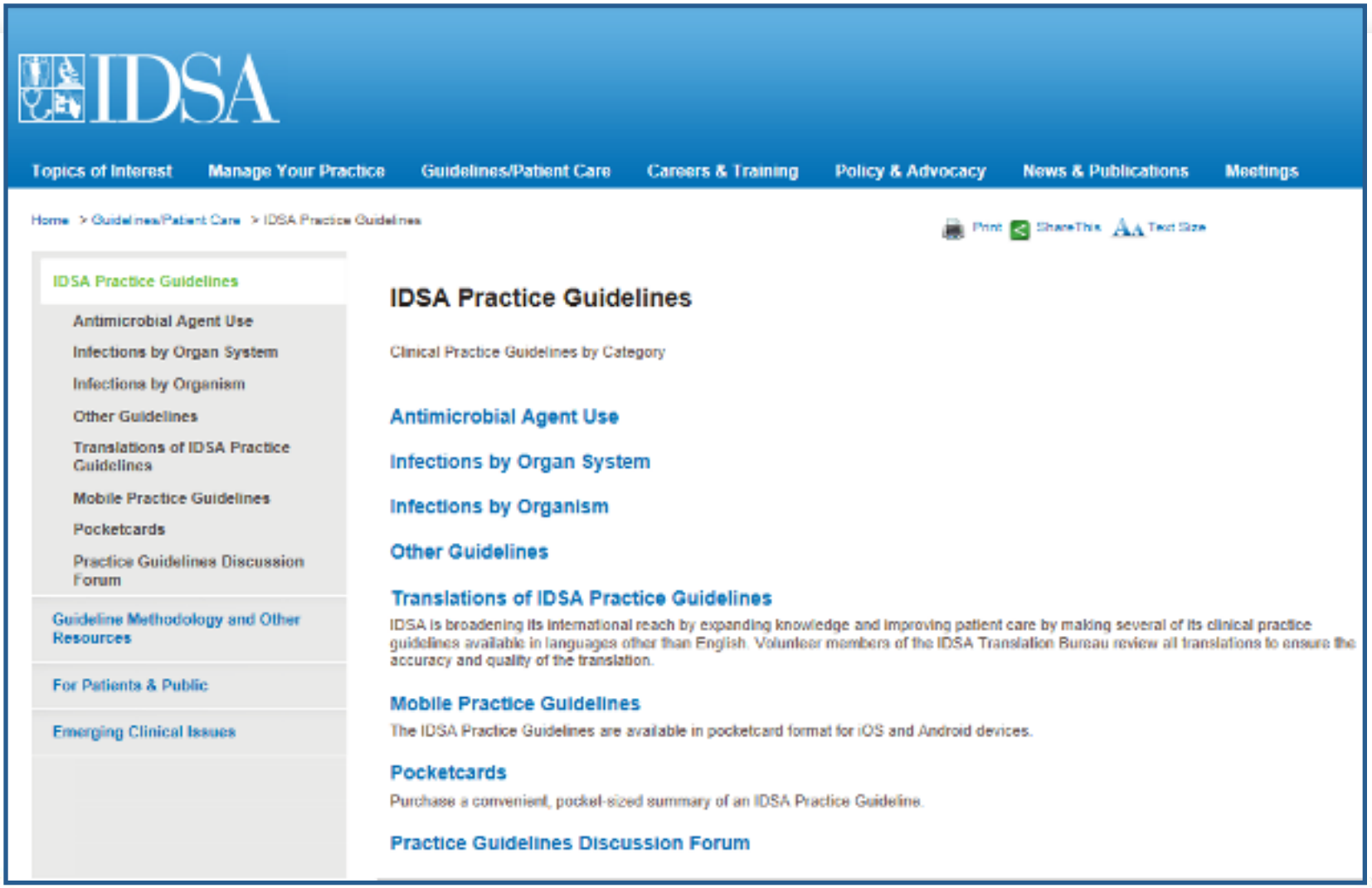
- **Enfeksiyonun erken tanısı**
- **Hedefe yönelik uygun antibiyotiklerin zamanında uygulanması**

YBÜ'lerinde Doğru Antibiyotik Kullanımı

Hangi Antibiyotik ?

- **Enfeksiyon bölgesi**
  - Akciğer
  - Karaciğer
  - Böbrek
  - BOS
  - ….
- **Hastaların özellikleri**
  - Alt hastalıkları
  - Yaş
  - Organ yetmezliği
  - Enfeksiyonun şiddeti
  - …..
- **YBÜ sürveyans sonuçları**
  - Etken mikroorganizmalar
  - Antimikrobiyal direnç
  - ….
- **Yan etki**
  - Hepatotoksite
  - Nefrotoksite
  - Kardiyotoksite
  - ….

Hangi Antibiyotik ?



Hangi Antibiyotik ?

Enfeksiyon odağı	Etkenler	Antibiyotik
Pnömoni	S.pneumoniae H.influenza P. aeruginosa A. baumannii E.coli MRSA	3. kuşak sefalosporin 4. kuşak sefalosporin Ampisilin/sulbaktam Kinolon (moksifloksasin/levofloksasin) Piperasilin/tazobaktam Karbapenem + Aminoglikozid Linezolid Vankomisin Colistin/sulbaktam
Üriner sistem enf.	E.coli Klebsiella spp. P. aeruginosa Proteus spp. Enterobacter spp. Staphylococcus spp. Candida spp.	3. kuşak sefalosporin 4. kuşak sefalosporin Kinolon Piperasilin/tazobaktam Karbapenem Flukonazol
Kan dolaşımı enf.	Staphylococcus spp. Enterococcus spp. E.coli Klebsiella spp. P.aeruginosa A.baumannii Candida spp.	Sefazolin Vankomisin Daptomisin Piperasilin/tazobaktam Karbapenem Colistin/sulbaktam Kaspofungin

Hangi Antibiyotik ?

Enfeksiyon odağı	Etkenler	Antibiyotik
İntraabdominal enf.	E.coli Klebsiella spp. P.aeruginosa P. mirabilis Enterobacter spp. Bacteroides fragilis Peptostreptococcus spp. Fusobacterium spp. Clostridium spp. Streptococcus spp. Enterococcus spp.	Sefoksitin 3.KSS+metronidazol Siprofloksasin+metronidazol Moksifloksasin Tigesiklin Piperasilin/tazobaktam Karbapenem
Yumuşak doku enf.	Staphylococcus spp. Streptococcus spp. E.coli Klebsiella spp. P.aeruginosa P. mirabilis Enterobacter spp.	Sefazolin Siprofloksasin±klindamisin Karbapenem Vankomisin Daptomisin

Monoterapi mi?
Kombine Antibiyotik mi?

- Ampirik tedavi uygunluğu
- Sinerjistik etki
- Direnç gelişiminin önlenmesi

Monoterapi mi?
Kombine Antibiyotik mi?

Beta lactam antibiotic monotherapy versus beta lactam-aminoglycoside antibiotic combination therapy for sepsis (Review)

Main results

We included 64 trials, randomizing 7586 patients. Twenty trials compared the same beta-lactam in both study arms, while the remaining compared different beta-lactams using a broader spectrum beta-lactam in the monotherapy arm. In studies comparing the same beta-lactam, we observed no difference between study groups with regard to all-cause fatality, RR 1.01 (95% CI 0.75 to 1.35) and clinical failure, RR 1.11 (95% CI 0.95 to 1.29). In studies comparing different beta-lactams, we observed an advantage to monotherapy: all cause fatality RR 0.85 (95% CI 0.71 to 1.01), clinical failure RR 0.77 (95% CI 0.69 to 0.86). No significant disparities emerged from subgroup and sensitivity analyses, including the assessment of patients with Gram-negative and *Pseudomonas aeruginosa* infections. We detected no differences in the rate of resistance development. Adverse events rates did not differ significantly between the study groups overall, although nephrotoxicity was significantly more frequent with combination therapy, RR 0.30 (95% CI 0.23 to 0.39). We found no heterogeneity for all comparisons. We included a small subset of studies addressing patients with Gram-positive infections, mainly endocarditis. We identified no difference between monotherapy and combination therapy in these studies.

Authors' conclusions

The addition of an aminoglycoside to beta-lactams for sepsis should be discouraged. All-cause fatality rates are unchanged. Combination treatment carries a significant risk of nephrotoxicity.

THE COCHRANE COLLABORATION®

Journal of Infection (2014) 68, 131–140

ELSEVIER

BIAM
British Infection Association

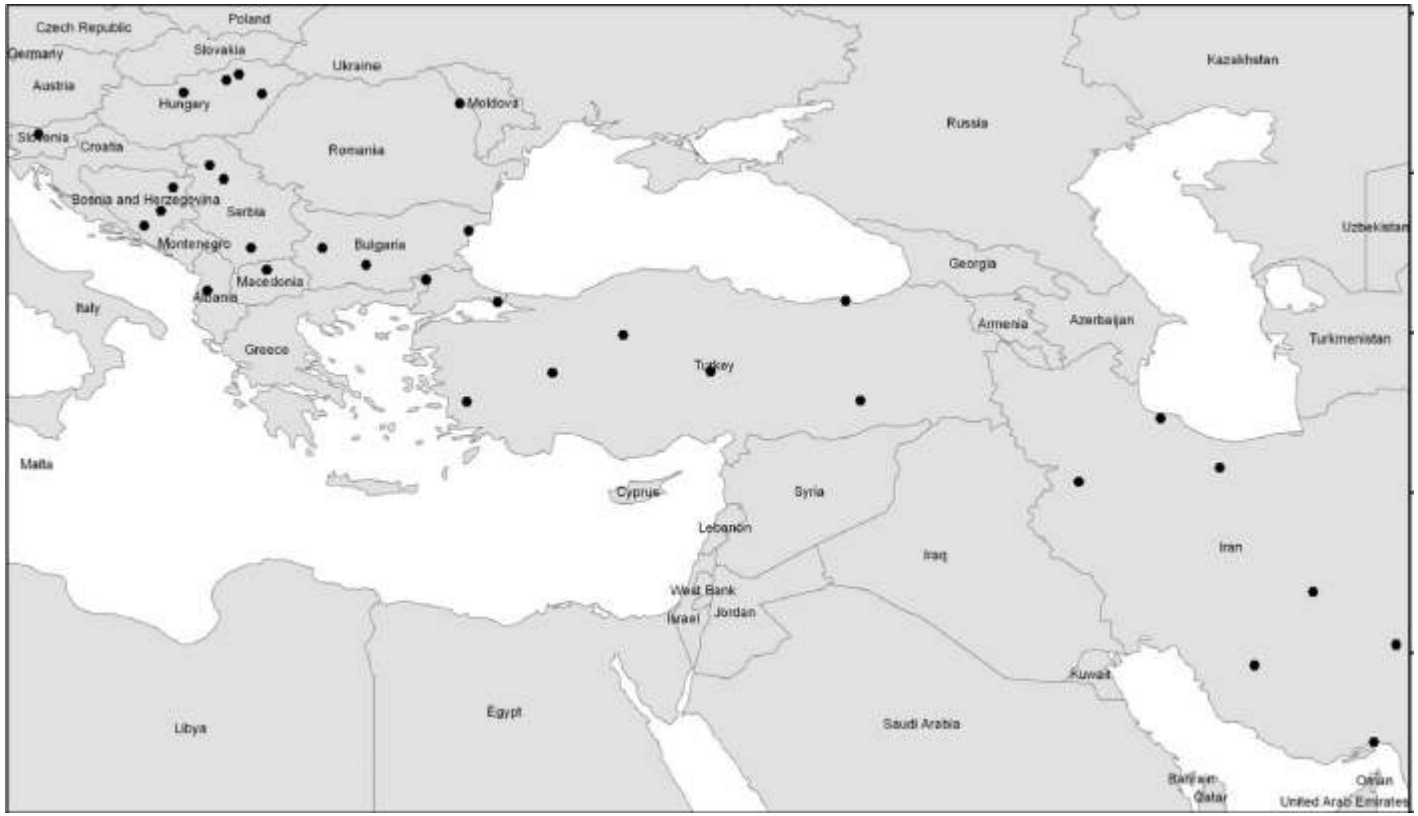
www.elsevierhealth.com/journals/jinf

Surveillance, control and management of infections in intensive care units in Southern Europe, Turkey and Iran – A prospective multicenter point prevalence study

Hakan Erdem [a,*], Asuman Inan [b], Selma Altındis [c], Biljana Carevic [d], Mehrdad Askarian [e], Lucy Cottle [f], Bojana Beovic [g], Akos Csomos [h], Krassimir Metodiev [i], Sead Ahmetagic [j], Arjan Harxhi [k], Lul Raka [l], Krsto Grozdanovski [m], Mihai Nechifor [n], Emine Alp [o], Fatma Bozkurt [p], Salih Hosoglu [p], Ismail Balik [q], Gulden Yilmaz [q], Matjaz Jereb [g], Fatemeh Moradi [r], Nikolay Petrov [s], Selcuk Kaya [t], Iftihar Koksal [t], Turan Aslan [u], Nazif Elaldi [v], Yasemin Akkoyunlu [u], Seyyed Alireza Moravveji [w], Gabor Csato [x], Balazs Szedlak [y], Filiz Akata [z], Serkan Oncu [aa], Svjetlana Grgic [ab], Gorana Cosic [ac], Chavdar Stefanov [ad], Mehrdad Farrokhnia [ae], Mária Müller [af], Catalina Luca [n], Nada Koluder [ag], Volkan Korten [ah], Viliyan Platikanov [ai], Petja Ivanova [ai], Soheil Soltanipour [aj], Mahmood Vakili [ak], Saman Farahangiz [al], Abdorrahim Afkhamzadeh [am], Nicholas Beeching [f], Salman Shaheer Ahmed [o], Alma Cami [an], Ramin Shiraly [ao], Anja Jazbec [ap], Tomislav Mirkovic [aq], Hakan Leblebicioglu [ar], Kurt Naber [as]

Surveillance, control and management of infections in intensive care units in Southern Europe, Turkey and Iran – A prospective multicenter point prevalence study

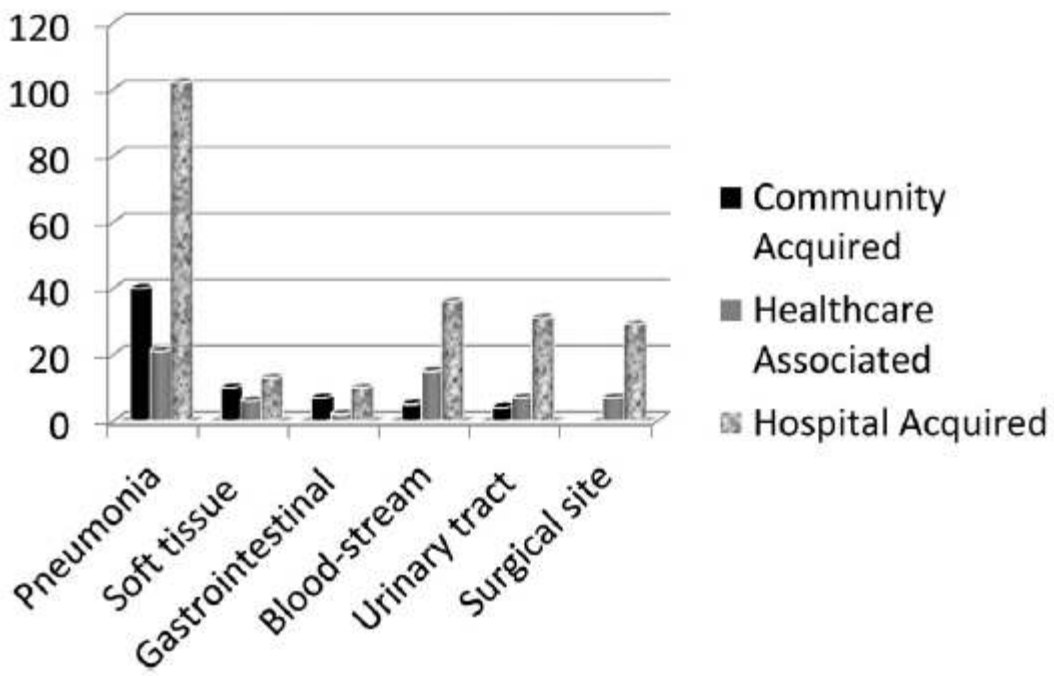
Journal of Infection (2014) 68, 131-140



11 ülke, 88 YBÜ, 749 hasta

Surveillance, control and management of infections in intensive care units in Southern Europe, Turkey and Iran – A prospective multicenter point prevalence study

Journal of Infection (2014) 68, 131-140



305 (%40.7) hastada en az bir enfeksiyon bölgesi
69 (%22) hastada toplum kaynaklı
61 (%20) hastada sağlık hizmeti ilişkili
176 (%58)hastada nozokomiyal enfeksiyon

Surveillance, control and management of infections in intensive care units in Southern Europe, Turkey and Iran — A prospective multicenter point prevalence study

Journal of Infection (2014) 68, 131-140

Table 5 The distribution of resistance patterns of isolated microorganisms from clinical specimens, according to country groups.[a]

Microorganism	Overall	Southeast Europe	Turkey	p Value[b]	Iran
Enteric Gram-negative bacilli (n = 62)					
Multidrug resistant	39 (63%)	20/34 (58.8)	18/26 (69.2)	0.43	1/2 (50)
Extensively drug resistant	5 (8%)	4/34 (11.8)	1/26 (3.8)	0.38	0
Pandrug resistant	0	0	0	ND	0
***Acinetobacter spp.* (n = 47)**					
Multidrug resistant	31 (66%)	19/25 (80)	11/19 (57.9)	0.33	0
Extensively drug resistant	13 (28%)	4/25 (20)	8/19 (42.1)	0.09	0
Pandrug resistant	5 (11%)	2/25 (4)	0	ND	3/3 (100)
***Pseudomonas aeruginosa* (n = 29)**					
Multidrug resistant	16 (55%)	7/13 (53.8)	7/14 (50)	1.0	1/2 (50)
Extensively drug resistant	7 (14%)	4/13 (30.8)	3/14 (21.4)	0.82	0
Pandrug resistant	2 (7%)	2/13 (15.4)	0	ND	0
***Staphylococcus aureus* (n = 17)**					
Multidrug resistant	8 (47%)	7/16 (43.8)	0	ND	1/1 (100)
Extensively drug resistant	0	0	0	ND	0
Pandrug resistant	0	0	0	ND	0
***Enterococcus spp.* (n = 17)**					
Multidrug resistant	10 (59%)	6/9 (66.7)	3/7 (42.9)	1.0	1/1 (100)
Extensively drug resistant	1 (6%)	0	1/7 (14.3)	ND	0
Pandrug resistant	0	0	0	ND	0

[a] Data expressed as *n*/*N* (%), ND: Not determined.
[b] Comparisons were performed between Southeast Europe and Turkey.

Changing pattern of antibiotic susceptibility in intensive care units: Ten years experience of a university hospital

Emine Alp [a,*], Bilge Kiran [b], Dilek Altun [b], Gamze Kalin [a], Ramazan Coskun [c], Murat Sungur [c], Aynur Akin [d], Duygu Percin [c], Mehmet Doganay [a]

Anaerobe 17 (2011) 422-425

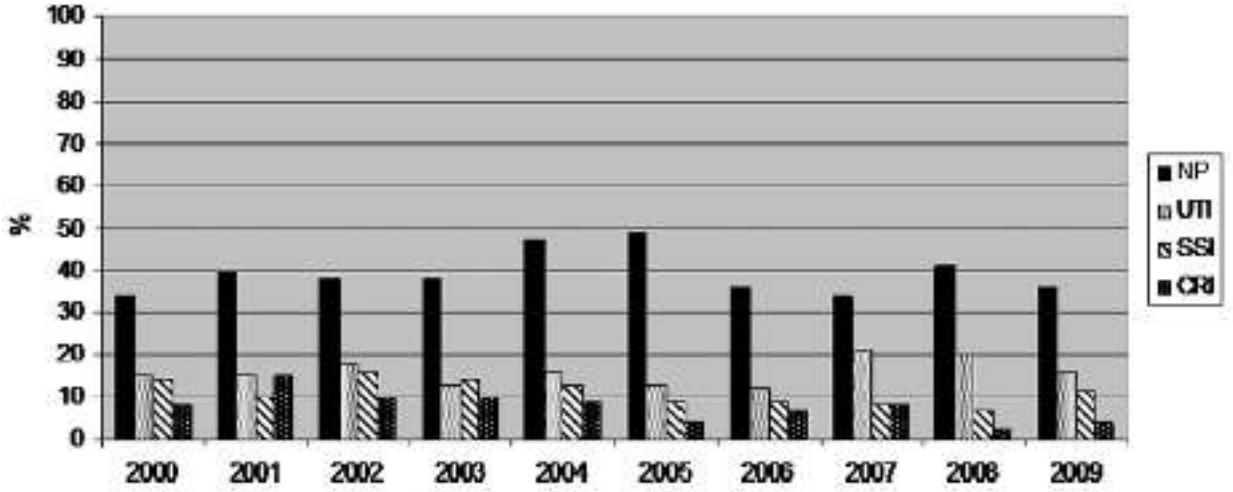
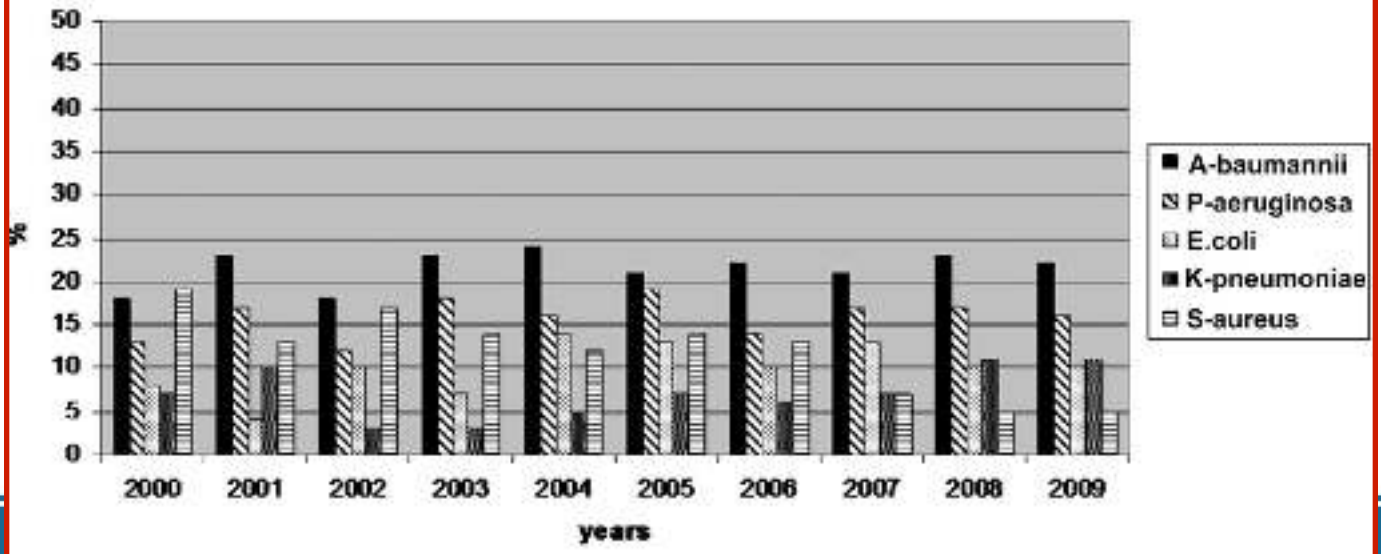


Fig. 1. Nosocomial infections in ICUs from 2000 to 2009.



Changing pattern of antibiotic susceptibility in intensive care units: Ten years experience of a university hospital

Emine Alp [a,*], Bilge Kiran [b], Dilek Altun [b], Gamze Kalin [a], Ramazan Coskun [c], Murat Sungur [c], Aynur Akin [d], Duygu Percin [c], Mehmet Doganay [a]

Anaerobe 17 (2011) 422-425

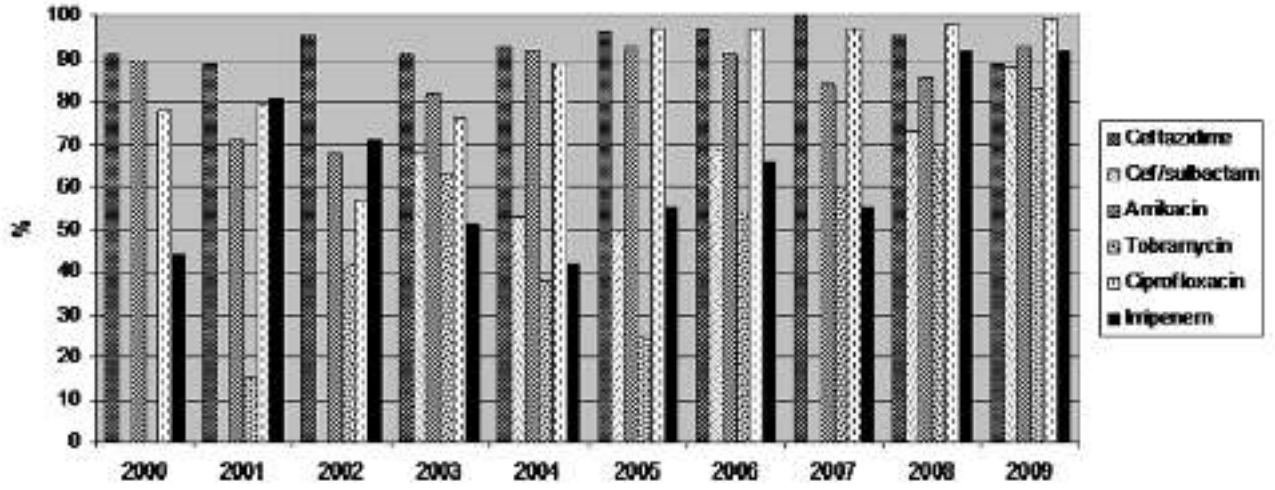


Fig. 3. Antimicrobial resistance rates of *A. baumannii*.

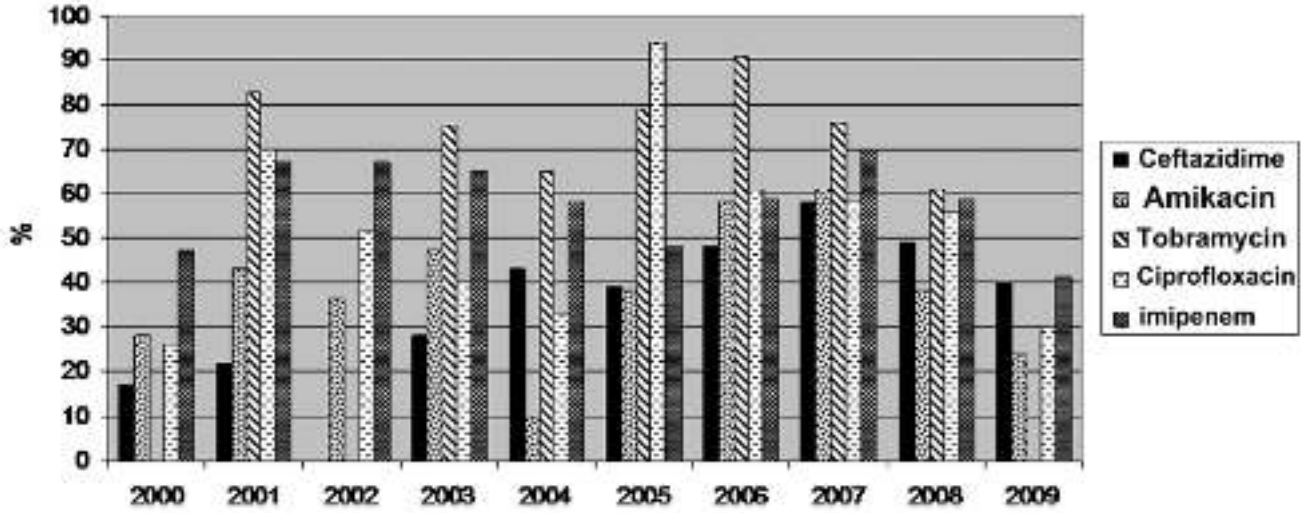


Fig. 4. Antimicrobial resistance rates of *P. aeruginosa*.

Dirençli Mikroorganizma Ne Zaman Düşünülmeli?

- Antibiyotik kullanımı: 90 gün içinde
- Hastanede yatış öyküsü: (>5 gün)
- Toplumda ve hastanede antibiyotik direncinin yüksek olması
- Sağlık hizmeti ilişkili enfeksiyon
  - Hastanede yatış : 90 gün içinde > 2gün
  - Bakımevinde yaşamak
  - Evde antibiyotik infüzyonu
  - Kronik diyaliz: 30 gün içinde
  - Evde yara bakımı
  - Evde beraber yaşayan kişilerde ilaca dirençli patojen taşıyıcılığı
- İmmünosüpressif hastalık veya tedavi

Dirençli Mikroorganizmalarda Antibiyotik Tedavisi Nasıl Olmalı?

- Standart antibiyotikleri **yüksek dozda** uygulama
  (Yan etki !!!!)

- **Standart olmayan**, henüz direnç gelişmemiş antibiyotikleri (kolistin/sulbaktam/tigesiklin/rifampisin) uygulama

  (Tedavi başarısızlığı-yan etki !!!)

- **Kombinasyon tedavisi** uygulama
  (Doz ???)

Kolistin

Farmakokinetik

- Kolistimethanosulfonate (KMS)-kolistine hidrolize olur
- **Atılım:** KMS böbrekten atılır, ancak kolistin renal tübüler absorbsiyon ile alınır ve böbrek dışı yollarla atılır
- Yoğun bakım hastalarında klirens ↓ ve yarı ömrü uzun
- Yüksek doz ve uzun aralıklarla uygulama

Farmakodinamik

- Konsantrasyona bağlı etki
- Kalıcı etki

Kolistin

	Colomycin injection	Coly-Mycin M Parenteral
Manufacturer	Dumex-Alpharma A/S, Copenhagen, Denmark	Parkedale Pharmaceuticals, Rochester, MN, USA
Main distributors	Pharmax Limited, Bexley, Kent, UK; Bex	Monarch Pharmaceuticals, Inc, Bristol,
Labelled content per vial	50(IU;	
Mass of colistimethate sodium dry powder per vial	40	
Appearance	Cre	
Recommended dose*	≤6(75 (divi 4–6 sod >6(thr 80- sod	
Product-recommended upper limit dose for a 60 kg patient*	480 mg of colistimethate sodium per day	800 mg of colistimethate sodium per day

*For patients with normal renal function.

Kolistin Doz

- 1 mg kolistin baz =2.4 mg kolistimetat sodyum
- 150 mg kolistin baz =5 MU=400 mg kolistimetat sodyum
- 1 MU =80 mg kolistimetat sodyum
- 1 mg kolistimetat sodyum=12 500 IU

Use of high-dose IV and aerosolized colistin for the treatment of multidrug-resistant *Acinetobacter baumannii* ventilator-associated pneumonia: do we really need this treatment?

Gamze Kalin · Emine Alp · Ramazan Coskun · Hayati Demiraslan · Kürsat Gündogan · Mehmet Doganay

J Infect Chemother (2012) 18:872–877

	High-dose ($n = 15$) n (%)	Normal-dose ($n = 20$) n (%)	Low-dose ($n = 10$) n (%)	p value
Age in years (mean ± SD)	48.07 ± 24.86	53.75 ± 17.86	45.70 ± 18.89	0.55
APACHE II score (median)	22	22	22	0.92
Male	9 (60)	16 (80)	7 (70)	0.44
Diabetes mellitus	2 (13)	1 (5)	2 (20)	0.59
Chronic liver failure	0 (0)	1 (5)	0 (0)	1.00
Congestive cardiac failure	0 (0)	0 (0)	0 (0)	–
Chronic obstructive lung disease	2 (13)	7 (35)	1 (10)	0.22
Malignancy	0 (0)	2 (10)	1 (10)	0.59
Chemotherapy	0 (0)	1 (5)	1 (10)	0.70
Steroid	5 (33)	9 (45)	3 (30)	0.79
Trauma	5 (33)	8 (40)	1 (10)	0.27
Smoking	5 (33)	9 (45)	5 (50)	0.79
Sepsis	1 (7)	5 (25)	0 (0)	0.34
Severe sepsis	11 (73)	11 (55)	7 (70)	
Septic shock	3 (20)	4 (20)	3 (30)	
Multi-organ failure	0 (0)	0 (0)	0 (0)	
Previous antibiotic use	15 (100)	20 (100)	10 (100)	–
Another infection site	13 (87)	19 (95)	10 (100)	0.45
Concomitant glycopeptide use	8 (53)	7 (35)	5 (50)	0.55
Concomitant aminoglycoside use	5 (33)	5 (25)	3 (30)	0.91
Hospital admission before ICU admission	6 (40)	11 (55)	6 (60)	0.59

Standart 2*2.5mg/kg (max 300 mg)
Yüksek doz 4*2.5 mg/kg (max 600 mg)
İnhale:2*75 mg

Use of high-dose IV and aerosolized colistin for the treatment of multidrug-resistant *Acinetobacter baumannii* ventilator-associated pneumonia: do we really need this treatment?

Gamze Kalin · Emine Alp · Ramazan Coskun · Hayati Demiraslan · Kürsat Gündogan · Mehmet Doganay

J Infect Chemother (2012) 18:872–877

	High-dose ($n = 15$) n (%)	Normal-dose ($n = 20$) n (%)	Low-dose ($n = 10$) n (%)	p value
On the 5th day of COL therapy				
Good response	4 (27)	10 (50)	3 (30)	0.45
Poor response	11 (73)	10 (50)	7 (70)	
On the 14th day of COL therapy				
Clinical cure	1 (7)	6 (30)	3 (30)	0.25
Clinical failure	14 (93)	14 (70)	7 (70)	
Bacteriological clearance	9 (64)	13 (65)	6 (75)	0.19
Bacteriological failure	5 (36)	7 (35)	2 (25)	
Presence of fever (median, days)	11 (73)	5 (25)	5 (50)	0.01
Nephrotoxicity	6 (40)	7 (35)	2 (20)	0.66
Length of ICU stay (mean ± SD, days)	33 ± 39.87	34 ± 34.97	42 ± 32.24	0.25
Mortality	10 (67)	9 (45)	4 (40)	0.18

Application of a Loading Dose of Colistin Methanesulfonate in Critically Ill Patients: Population Pharmacokinetics, Protein Binding, and Prediction of Bacterial Kill

Ami F. Mohamed,[a,b] Ilias Karaiskos,[c] Diamantis Plachouras,[c] Matti Karvanen,[d] Konstantinos Pontikis,[e] Britt Jansson,[a] Evangelos Papadomichelakis,[e] Anastasia Antoniadou,[c] Helen Giamarellou,[c] Apostolos Armaganidis,[e] Otto Cars,[d] and Lena E. Friberg[a]

Antimicrob Agents Chemotherapy 2012;56:4241-4249

TABLE 1 Demographic and clinical data[a]

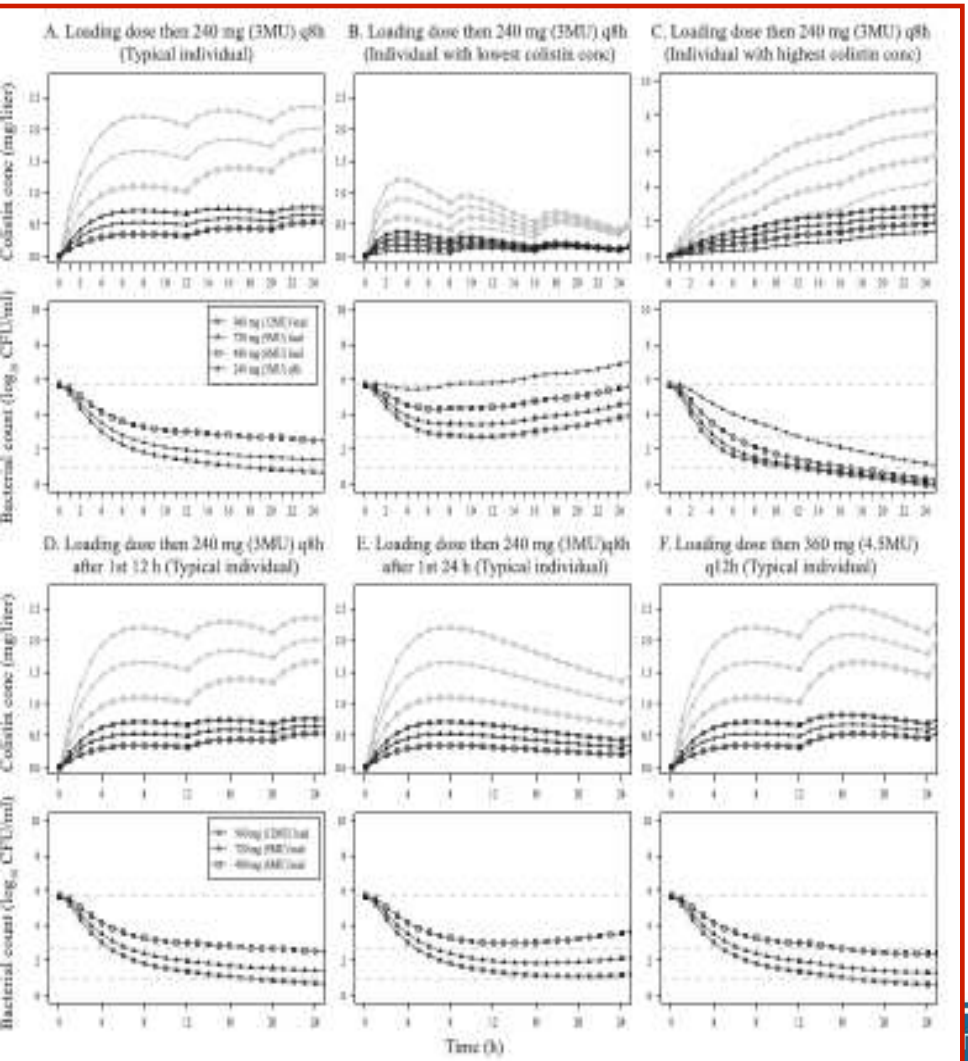
Patient no.	Gender	Age (yr)	Body wt (ideal body wt) (kg)	Total maintenance daily dose (mg [MU])	Serum creatinine concn at baseline, day 3 (mg/dl)	CrCL at baseline, day 3 (ml/min)	Serum albumin concn (g/dl)	APACHE II score	Diagnosis	Reason for colistin administration
19	M	46	80 (70)	720 (9)	1, 0.9	91.6, 101.7	2.3	8	Necrotizing fasciitis	Necrotizing fasciitis
20	F	51	60 (65)	720 (9)	0.8, 0.5	120.5, 134.8	3	17	Multiple sclerosis	VAP
21	M	59	140 (75)	720 (9)	1.1, 0.8	76.8, 105.7	2.7	9	Pneumonia	VAP
22	M	66	75 (75)	480 (6)	1.1, 0.8	70.2, 96.5	3.5	23	Cirrhosis-hepatic encephalopathy	VAP
23	M	32	80 (70)	720 (9)	0.6, 0.6	191.5, 191.5	1.9	17	Pneumonia	VAP
24	F	88	80 (70)	240 (3)	1.7, 1.7	24.9, 24.9	2.1	24	Acute mesenteric ischemia	VAP
25	M	60	85 (75)	720 (9)	1, 1	83.5, 83.5	3.2	7	Pneumonia	VAP
26	F	48	65 (65)	720 (9)	0.7, 0.5	99.5, 139.4	3.1	16	Trauma	VAP
27	M	52	80 (70)	720 (9)	0.4, 0.5	214.3, 171.4	3.8	18	NHL-pneumonia	VAP
28	F	52	65 (65)	720 (9)	0.7, 0.8	95.2, 83.3	2.5	15	H1N1 infection-pneumonia	Bacteremia

Doz: Yükleme dozu (480 mg), ardından 3*240 mg

Application of a Loading Dose of Colistin Methanesulfonate in Critically Ill Patients: Population Pharmacokinetics, Protein Binding, and Prediction of Bacterial Kill

Antimicrob Agents Chemotherapy 2012;56:4241-4249

Ami F. Mohamed,[a,b] Ilias Karaiskos,[c] Diamantis Plachouras,[c] Matti Karvanen,[d] Konstantinos Pontikis,[e] Britt Jansson,[a] Evangelos Papadomichelakis,[e] Anastasia Antoniadou,[c] Helen Giamarellou,[c] Apostolos Armaganidis,[e] Otto Cars,[d] and Lena E. Friberg[a]



- Yüksek yükleme dozlarında serbest ilaç düzeyi artıyor
- Yüksek yükleme dozlarında bakteriyi öldürme zamanı kısalıyor
- Hidrasyon ile yüksek yükleme dozu (480 mg) nefrotoksite için riski artırmıyor
- **480-720 mg yükleme doz** öneriliyor

High-Dose, Extended-Interval Colistin Administration in Critically Ill Patients: Is This the Right Dosing Strategy? A Preliminary Study

Lidia Dalfino,[1] Filomena Puntillo,[1] Adriana Mosca,[2] Rosa Monno,[2] Maria Luigia Spada,[1] Sara Coppolecchia,[1] Giuseppe Miragliotta,[2] Francesco Bruno,[1] and Nicola Brienza[1]

- 25 hasta, 28 kolistin tedavisi değerlendiriliyor
- **Doz:** 9 MU (720 mg) yükleme dozu sonrası 2*4.5 MU (720 mg/gün)
- Klinik kür 23 (%82) hastada var
- 5 (%18) hastada ABY var

Table 1. Patients' Characteristics and Clinical Features of Infectious Episodes Among 23 Infectious Episodes With and 5 Without a Favorable Response to Colistimethate Sodium Therapy

Variable	CMS Response[a]	No CMS Response
Age (years), mean ± SD	62 ± 18	76 ± 3
Charlson comorbidity index, mean ± SD	2 (1.5)	3.2 (2.2)[b]
Surgical admission, No. (%) of patients	8/20 (40)	4/5 (80)
APACHE II score, mean ± SD	18 ± 6	25 ± 7[b]
SOFA score, mean ± SD	7.6 ± 2	9.1 ± 2
ICU LOS (days)	56 (30–85)	75 (52–86)
ICU mortality, No. (%) of patients	5/20 (25)	5/5 (100)[b]
Infectious episodes, No. (%) of cases	23/28 (82.1)	5/28 (17.9)
CMS-associated pathogens, No. of isolates		
Acinetobacter baumannii	6	2
Klebsiella pneumoniae	6	3
Pseudomonas aeruginosa	1	0
Bacteriological clearance, No. (%) of cases	13/13 (100)	0/5[b]
VAP, No. (%) of cases	10/23 (43.5)	0/5
VAP-associated pathogens, No. of isolates		
Acinetobacter baumannii	5	0
Klebsiella pneumoniae	4	0
Pseudomonas aeruginosa	1	0
Bacteriological clearance, No. (%) of cases	4/10 (40)	0/5 (0)
Clinical presentation, No. (%) of cases		
Severe sepsis	16/23 (69.5)	0/5 (0)[b]
Septic shock	7/23 (30.5)	5/5 (100)[b]
Daily CMS dose (MU/d)	8.5 (7.3–9)	7.7 (5–8.5)
Cumulative CMS dose (MU/course)	91 (61–122)	105 (17–142)
CMS monotherapy, No. (%) of courses	12/23 (52.2)	2/5 (40)
CMS treatment duration (days)	11 (10–14.5)	15.5 (7–21)

COLOMYCIN® / COLISTIN

Ağır enfeksiyonlarda yüksek doz etkili

Table 2. Potential Risk Factors for Acute Kidney Injury Associated With Colistimethate Sodium Therapy

Factor	No AKI (n = 23)	AKI (n = 5)
Septic shock	10 (43.5)	2 (40)
Concomitant nephrotoxic agents	20 (86.9)	4 (80)
Antibiotics	7 (30.4)	3 (60)
Diuretics	15 (65.2)	3 (60)
Radiocontrast agents	1 (4.3)	4 (80)*
Mannitol	4 (17.4)	1 (20)
Daily CMS dose (MU/day)	8.3 (6.5–9)	7.1 (6–8.6)
CMS treatment duration (days)	11 (8.5–17.5)	12 (10–15)
Cumulative CMS dose	92 (66–126)	81 (64–92)

Clin Infect Dis 2012;54:1720-6

Comparison of colistin and colistin/sulbactam for the treatment of multidrug resistant *Acinetobacter baumannii* ventilator-associated pneumonia

G. Kalin · E. Alp · A. Akin · R. Coskun · M. Doganay

Infection 2013

Table 1 In vitro antibiotic resistance rates of 87 *A. baumannii* strains isolated from endotracheal aspirates or bronchial lavage samples

Antibiotic agent	Resistance rate (%)
Cefepim	78
Cefoperazone-sulbactam	77
Ceftazidim	84
Cefotaxim	85
Piperacillin tazobactam	96
Ciprofloxacin	85
Amikacin	79
Gentamicin	85
Netilmicin	55
Tobramicin	84
İmipenem	91
Meropenem	94
Trimetoprim-sulfametoxazol	91
Tigecycline	25
Colistin	0

Table 2 The characteristics of patients who were treated with colistin and colistin/sulbactam

	Colistin ($n = 52$), n (%)	Colistin/sulbactam ($n = 37$), n (%)	p
Age in years (median, range)	52 (19–96)	63 (20–89)	0.10
APACHE II (median, range)	22 (14–36)	27 (18–35)	0.00
Male	36 (69.2)	18 (48.6)	0.08
Diabetes mellitus	5 (9.6)	10 (27)	0.04
Chronic renal disease	2 (3.8)	5 (13.5)	0.12
Chronic liver disease	1 (1.9)	0 (0)	1.00
Chronic cardiac disease	0 (0)	1 (2.7)	0.42
Chronic obstructive lung disease	13 (25.0)	10 (27.0)	1.00
Malignancy	4 (7.7)	5 (13.5)	0.48
Chemotherapy	2 (3.8)	2 (5.4)	1.00
Steroid	20 (38.5)	10 (27.0)	0.36
Trauma	15 (28.8)	5 (13.5)	0.12
Smoking	22 (42.3)	12 (32.4)	0.38
Severity of sepsis on diagnosis of VAP			
Sepsis	9 (17.3)	8 (21.6)	0.53
Severe sepsis	33 (63.5)	19 (51.4)	
Septic shock	10 (19.2)	10 (27.0)	
Multi organ failure	0	0	
Previous antibiotic use	52 (100)	34 (94.6)	0.17
Other infection sites	49 (94.2)	34 (91.9)	0.69
Hospital admission before ICU admission	27 (51.9)	18 (48.6)	0.83
Concomitant aminoglycoside use	15 (28.8)	2 (5.4)	0.006
Concomitant glycopeptide use	23 (44.2)	10 (27)	0.12

TESİ TIP FA

Comparison of colistin and colistin/sulbactam for the treatment of multidrug resistant *Acinetobacter baumannii* ventilator-associated pneumonia

G. Kalin · E. Alp · A. Akin · R. Coskun · M. Doganay

Infection 2013

Table 3 Clinical and microbiological evaluation of patients on colistin and colistin/sulbactam therapy

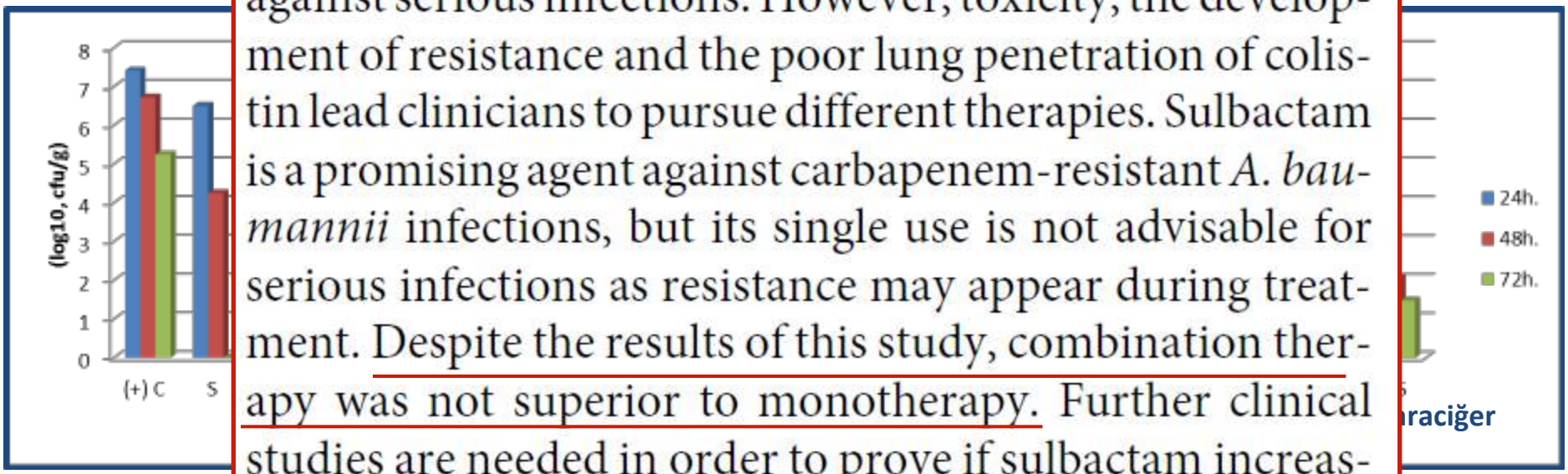
On the fifth day of therapy	Colistin ($n = 52$), n (%)	Colistin/sulbactam ($n = 37$), n (%)	p
Good response	21 (40.4)	16 (43.2)	0.84
Poor response	31 (59.6)	21 (56.8)	
On the 14th day of therapy	**Colistin ($n = 47$), n (%)**	**Colistin/sulbactam ($n = 35$), n (%)**	**p**
Clinical cure	14 (29.8)	14 (40)	0.50
Clinical failure	33 (70.2)	21 (60)	
Bacteriological clearance	34 (72.3)	30 (85.7)	0.28
Bacteriological failure	13 (27.7)	5 (14.3)	
Length of ICU stay (mean ± SD)	42.33 ± 33.03	37.73 ± 24.29	0.81
Mortality	27 (51.9)	27 (73)	0.53[a]

Efficacy of Sulbactam and Its Combination with Imipenem, Colistin and Tigecycline in an Experimental Model of Carbapenem-Resistant *Acinetobacter baumannii* Sepsis

Gokcen Dinc[a] Havati Demiraslan[b] Ferhan Elmali[c] Salman Shabeer Ahmed[b]
Gokhan Metan[b]

y 2014

In conclusion, the treatment of life-threatening carbapenem-resistant *A. baumannii* infections is a serious concern. Colistin appears to be the most effective agent against serious infections. However, toxicity, the development of resistance and the poor lung penetration of colistin lead clinicians to pursue different therapies. Sulbactam is a promising agent against carbapenem-resistant *A. baumannii* infections, but its single use is not advisable for serious infections as resistance may appear during treatment. Despite the results of this study, combination therapy was not superior to monotherapy. Further clinical studies are needed in order to prove if sulbactam increases the clinical effectiveness and reduces the mortality which also prevents colistin-resistant mutants.



Antimicrobial Efficacy of Doripenem and its Combinations with Sulbactam, Amikacin, Colistin, Tigecycline in Experimental Sepsis of Carbapenem Resistant *Acinetobacter baumannii*

Gokcen Dinc[1], Hayati Demiraslan[2], Ferhan Elmali[3], Salman Shaheer Ahmed[2], Emine Alp[2], Mehmet Doganay[2]

New Microbiologica

SUMMARY

Acinetobacter baumannii is the most common species that have developed resistance to antibiotics. Due to increasing levels of drug resistance, the therapeutic options are limited in *A. baumannii* infections. We investigated the efficacy of doripenem monotherapy versus doripenem combination therapy with sulbactam, amikacin, colistin and tigecycline in an experimental sepsis. The carbapenem resistant *A. baumannii* was used to develop sepsis model in 8-10 weeks old Balb-c mice by intraperitoneal injection. Two hours later from injection of bacterial suspension, antibiotic therapies were initiated. Mice were sacrificed at 24, 48 and 72 hours and cultures were made from heart, lung, liver and spleen samples and the bacterial loads of lung and liver were calculated as cfu/g. Combination therapies with doripenem were more effective than monotherapy at 24 and 48 hours of infection but any differences between groups were detected at 72 hours. The combination of doripenem with tigecycline and amikacin began to eradicate bacterial load of lung and liver after 48 hours of infection, whereas doripenem+sulbactam and doripenem+colistin were started to eradication at 72 hours. These results suggested that combination therapies with doripenem is more effective than monotherapy and the combination of doripenem with tigecycline or amikacin has more rapid bactericidal effect than sulbactam or colistin.

Antimicrobial Original Research Paper

Carbapenem-resistant *Klebsiella pneumoniae* sepsis in corticosteroid receipt mice: tigecycline or colistin monotherapy versus tigecycline/colistin combination

J Infect 2013

Hayati Demiraslan[1], Gokcen Dinc[2], Salman Shaheer Ahmed[1], Ferhan Elmali[3], Gokhan Metan[1], Emine Alp[1], Mehmet Doganay[1]

[1]Department of Infectious Diseases, [2]Department of Medical Microbiology, [3]Department of Biostatistics, Faculty of Medicine, Erciyes University, Melikgazi, 38039, Kayseri, Turkey

This study compared the effect of monotherapy of colistin, tigecycline, and their combination in sepsis model of mice. OXA-48 producing Carbapenem-resistant Klebsiella pneumoniae (CRKP) strain was used in Balb/c mice. The mice were divided into competent and Methylprednisolone acetate (MPA)-treated groups. Each group was sub-divided into (1) colistin or (2) tigecycline monotherapy and (3) colistin/ tigecycline combination therapy. After 3 hours of intraperitoneal bacterial inoculation, antimicrobials were administered, and mice were sacrificed at 24 and 48 hours Time-kill curve study demonstrated that colistin sulphate had early bactericidal activity following re-growth. In competent and MPA-treated groups of mice at 24 hours, bacterial counts in liver samples significantly lowered compared to control, however, there were no statistically differences between monotherapy and combination therapy subgroup. Bacterial count in lung samples of competent group was significantly lesser than control for all three antimicrobial subgroups at 24 hours Colistin plus tigecycline combination therapy was not superior against colistin or tigecycline monotherapy.

Comparison of colistin–carbapenem, colistin–sulbactam, and colistin plus other antibacterial agents for the treatment of extremely drug-resistant *Acinetobacter baumannii* bloodstream infections

A. Batirel • I. I. Balkan • O. Karabay • C. Agalar • S. Akalin • O. Alici • E. Alp • F. A. Altay • N. Altin • F. Arslan • T. Aslan • N. Bekiroglu • S. Cesur • A. D. Celik • M. Dogan • B. Durdu • F. Duygu • A. Engin • D. O. Engin • I. Gonen • E. Guclu • T. Guven • C. A. Hatipoglu • S. Hosoglu • M. K. Karahocagil • A. U. Kilic • B. Ormen • D. Ozdemir • S. Ozer • N. Oztoprak • N. Sezak • V. Turhan • N. Turker • H. Yilmaz

Eur J Clin Microbiol Infect Dis 2014

Comparison of colistin–carbapenem, colistin–sulbactam, and colistin plus other antibacterial agents for the treatment of extremely drug-resistant *Acinetobacter baumannii* bloodstream infections

Eur J Clin Microbiol Infect Dis 2014

Table 1 Baseline demographic and clinical characteristics and outcomes of 214 patients with extremely drug-resistant *Acinetobacter* spp. bloodstream infections (XDR-ABSI) who received colistin-based combination therapy and 36 patients who received colistin monotherapy

Characteristic/variable	Colistin combination group, *n* (%)	Colistin monotherapy group, *n* (%)	*p*-Value
Total (*n*)	214	36	
Age (mean + SD) (years)	59.1±19.6	58.3±20.5	0.81
Gender (male)	141 (65)	21 (58)	0.46
Hospital stay prior to XDR-ABSI (mean + SD, days)	23.9±21.9	22.3±19.9	0.69
ICU stay prior to XDR-ABSI (mean ± SD, days)	19.1±19.3	18.9±20.8	0.96
Pitt bacteremia score (mean ± SD)	7.1±3.6	6.8±2.9	0.62
APACHE II score[a] (mean ± SD)	18.6±6.9	17.9±7.1	0.82
Charlson comorbidity index (mean ± SD)	3.3±2.2	3.5±2.2	0.55
Concomitant other infection	128 (59)	20 (56)	0.63
Initiation of effective therapy			0.13
Early (within 24 h)	152 (71)	21 (58.3)	
Late (after 24 h)	62 (29)	15 (41.7)	
Nephrotoxicity	36 (21.8)	9 (25)	0.88
Neurotoxicity[b]			
Present	3 (1.4)	0 (0)	
Unconscious/pharmacologic sedation	211 (98.6)	36 (100)	
Clinical outcome			0.19
Complete response/cure	99 (46.3)	11 (30.6)	
Partial response/improvement	68 (31.8)	16 (44.4)	
No response/failure	47 (22)	9 (25)	
Microbiologic outcome			0.001
Eradication present	171 (79.9)	20 (55.6)	
Redundant	43 (20.1)	16 (44.4)	
14-day survival	146 (68.2)	20 (55.5)	0.14
In-hospital crude mortality	112 (52.3)	26 (72.2)	0.03

Comparison of colistin–carbapenem, colistin–sulbactam, and colistin plus other antibacterial agents for the treatment of extremely drug-resistant *Acinetobacter baumannii* bloodstream infections

Eur J Clin Microbiol Infect Dis 2014

Table 2 Demographic and clinical characteristics and outcomes of 214 patients with extremely drug-resistant *Acinetobacter* spp. bloodstream infection (XDR-ABSI), according to the three different combination treatment modalities

Characteristic/variable	Colistin–carbapenem group, *n* (%)	Colistin–sulbactam group, *n* (%)	Colistinplusother agent group, *n* (%)	*p*-Value
Total, *n*	102	69	43	
Age (mean ± SD) (years)	58.94±19.8	58.2±20	60.9±19.1	0.77
Gender (male)	67 (65.7)	50 (72.5)	24 (55.8)	0.19
Hospital stay p… days)				0.25
ICU stay prior… days)				0.58
Pitt bacteremi…				0.85
APACHE II s…				0.48
Charlson com…				0.62
Primary bacte…				0.28
Secondary ba…				0.3
Catheter-relat…				0.33
Concomitant …				0.17
Initiation of e…				
Early (with…				0.38
Late (after …				
Nephrotoxicity…				0.36
Neurotoxicity…				0.16
Present				
Unconscious/pharmacologic sedation	59 (57.8)	40 (58)	19 (44.2)	
Clinical outcome				0.97
Complete response/cure	50 (49)	32 (46.4)	17 (39.5)	
Partial response/improvement	28 (27.5)	23 (33.3)	17 (39.5)	
No response/failure	24 (23.5)	14 (17.4)	9 (21)	
Microbiologic outcome				0.92
Control hemoculture obtained	95 (93)	62 (90)	39 (90.7)	
Eradication present	77 (81)	49 (79)	32 (82)	
Redundant	18 (18.9)	13 (20.9)	7 (17.9)	
14-day survival	72 (70.6)	47 (68.1)	27 (62.8)	0.79
In-hospital crude mortality	56 (55)	32 (46.4)	24 (55.8)	0.44

Colistin-based combination therapy resulted in significantly higher microbiological eradication rates, relatively higher cure and 14-day survival rates, and lower in-hospital mortality compared to colistin monotherapy. CC, CS, and CO combinations for XDR-ABSI did not reveal significant differences with respect to 14-day survival and clinical or microbiological outcome before and after propensity score matching (PSM). PBS, age, and length of ICU stay were independent risk factors for 14-day mortality.

Hangi Antibiyotik ?

- Antibiyotik de-eskalasyonu
- Lokal rehberler
- Kısıtlı/dönüşümlü antibiyotik

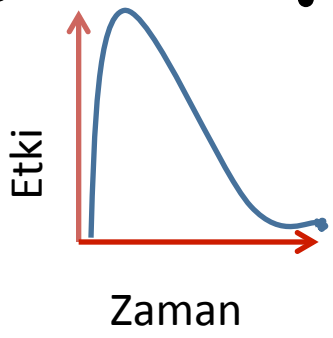
Hangi Dozda ve Nasıl Uygulanmalı?

FARMAKODİNAMİK ÖZELLİKLER

- Etki Spektrumu
- Antibakteriyel Etki
  - Zamana bağlı
  - Konsantrasyona bağlı

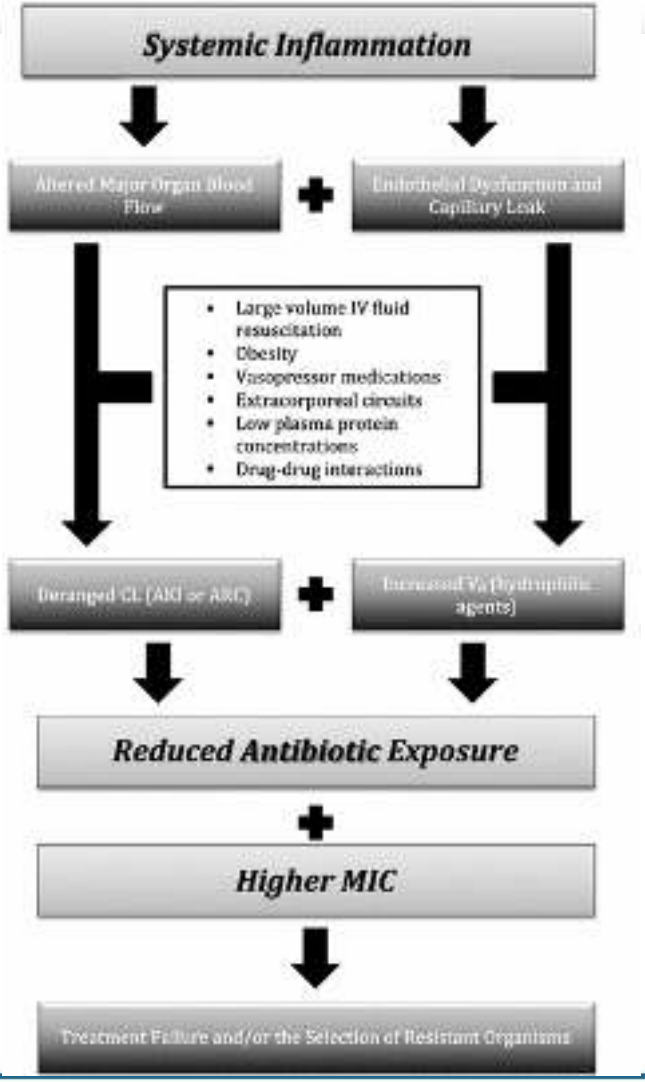
FARMAKOKİNETİK ÖZELLİKLER

- Emilimi
- Dağılım
- Proteine bağlanma
- Metabolizma
- Atılım



KLİNİK BAŞARI

YBÜ Hastalarında FK/FD Parametreleri Neden Değişir?



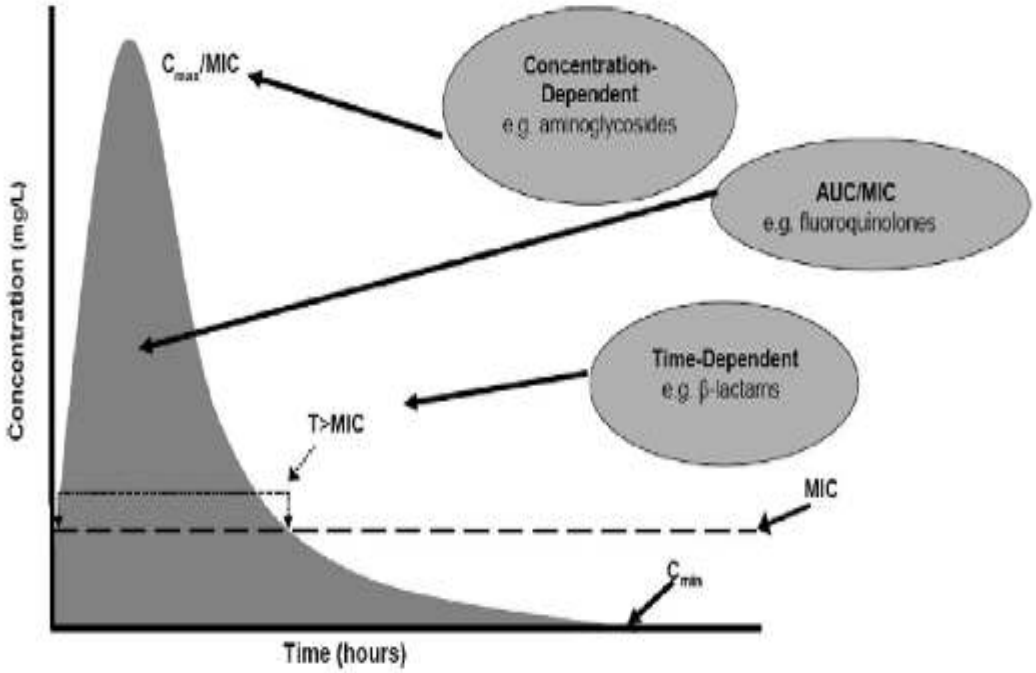
 Udy AA, et al. Intensive Care Med 2013;39:2070-2082

Hangi Dozda ve Nasıl Uygulanmalı?

- **Zamana bağlı etki:** Etki, ilaç konsantrasyonu MİK düzeylerinin 2-4 katına ulaştığında ve sürekli bu konsantrasyonda kaldığında **(sürekli infüzyon)** artar

- **Konsantrasyona bağlı etki:** Etki, ilaç konsantrasyonu arttıkça artar

- **Konsantarsyona bağlı kalıcı etkisi olan, zamana bağlı etki gösteren antibiyotikler**



Antibakteriyel Etki İle İlişkili FK/FD Parametreler

Antibiyotik Sınıfı	FK/FD Parametre
Beta-laktamlar Karbapenemler Linezolid Eritromisin Klaritromisin Linkozamid	T>MİK Zamana bağlı etki Minimum veya orta düzeyde postantibiyotik etki
Aminoglikozidler Metronidazol Kinolonlar Telitromisin Daptomisin Kinopristin/dalfopristin Kolistin	C_{maks}/MİK Konsantrasyona bağlı etki
Kinolonlar Aminoglikozidler Azitromisin Tetrasiklinler Glikopeptidler Tigesiklin Kinopristin/dalfopristin Linezolid	AUC_{0-24}/MİK Konsantrasyona bağlı kalıcı etki Zamana bağlı etki

Proteİne Bağlanma

- Serbest ilaç düzeyi farmakolojik etkiden ve yan etkilerden sorumludur
- Serbest ilaç düzeyi arttıkça, eliminasyon ve dağılım hacmi artar
- Hipoalbuminemi, proteine bağlanma oranı yüksek (>%90) olan ve böbrekten atılan antibiyotiklerin FK'ini etkiler
  - Ertapenem
  - Seftriakson
  - Teikoplanin
  - Oksasilin, vb.

DAĞILIM HACMİ

Lipofilik antibiyotikler:

- Yüksek dağılım hacmi
-
-
  - Kinolonlar
  - Makrolidler
  - Tetrasiklinler (Tigesiklin)
  - Kloramfenikol
  - Rifampisin

Hidrofilik antibiyotikler:

- Düşük dağılım hacmi
  - Beta-laktamlar
  - Aminoglikozidler
  - Daptomisin
  - Glikopeptid
  - Linezolid
  - Kolistin

Dağılım Hacminin Değişmesi Hidrofilik Antibiyotiklerin FK Etkiler

DAĞILIM HACMİ

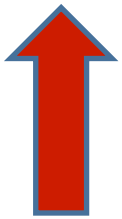
ANTİBİYOTİK ELİMİNASYONU

- Akut böbrek yetmezliği ve aralıklı veya sürekli renal replasman tedavisi antibiyotiklerin FK/ FD değişmektedir

- Beta-laktam antibiyotiklerde, tedavinin ilk 48 saatinde böbrek dozu ayarlanmasına gerek yok

ANTİBİYOTİK ELİMİNASYONU

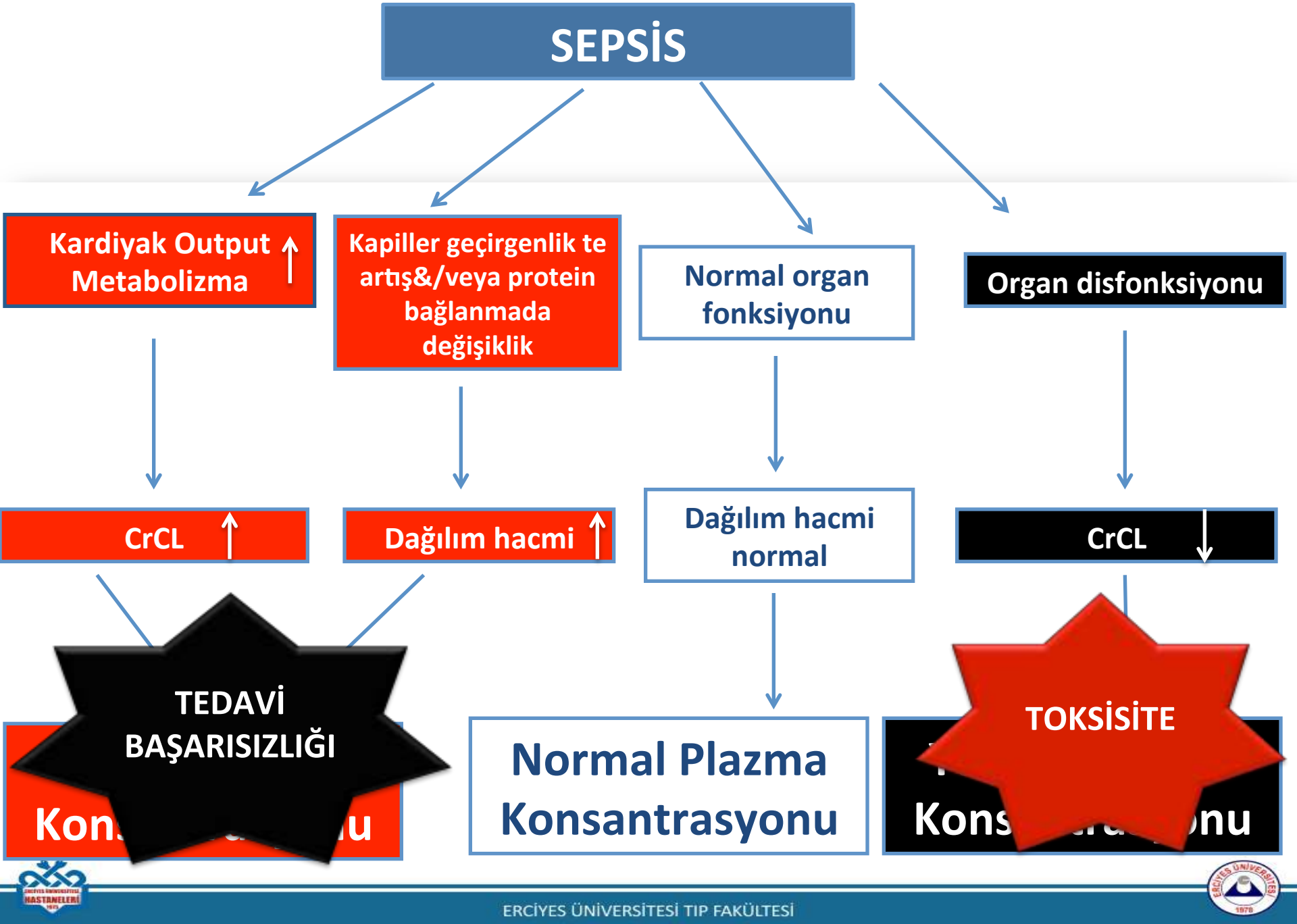
- Multiple travma
- Travmatik beyin hasarı
- Menenjit
- Postoperatif hastalar
- Yanık
- VİP
- Gebelik
- SIRS

Renal klirens 

ANTİBİYOTİK ELİMİNASYONU

- İdrarda Kreatin Klirens (CL_{CR}) (8 saatlik idrarda) ölçümü göstergedir
- CL_{CR} ≥130 ml/dk/1.73m^2 böbrekten atılan antibiyotiklerde tedavi başarısızlığına neden olur
- Serum kreatinin normal olması CL_{CR} normal olduğunu göstermez
- Hidrofilik antibiyotiklerde doz ayarlaması gerekir

CL_{Cr} was calculated according to formula: $CL_{Cr} = (U_{Cr}/S_{Cr}) \times (24\text{-h urinary output}/1440) \times (1.73/BSA)$. The DuBois and DuBois formula was used to calculate BSA: $BSA = 0.007184 \times [\text{height (cm)}]^{0.725} \times [\text{weight (kg)}]^{0.425}$.


SEPSİS
Kardiyak Output ↑ Metabolizma
Kapiller geçirgenlik te artış&/veya protein bağlanmada değişiklik
Normal organ fonksiyonu
Organ disfonksiyonu
CrCL ↑
Dağılım hacmi ↑
Dağılım hacmi normal
CrCL ↓
TEDAVİ BAŞARISIZLIĞI
TOKSİSİTE
Normal Plazma Konsantrasyonu

Augmented renal clearance in septic patients and implications for vancomycin optimisation

João Pedro Baptista*, Eduardo Sousa, Paulo J. Martins, Jorge M. Pimentel

Int J Antimicrob Agents 2012;39:420-423

- Vankomisin verilen 93 hasta
- Ventilatörde ve ağır sepsis veya septik şokta hastalar

Augmented renal clearance in septic patients and implications for vancomycin optimisation

João Pedro Baptista*, Eduardo Sousa, Paulo J. Martins, Jorge M. Pimentel

Int J Antimicrob Agents 2012;39:420-423

Vankomisin dozu

- **Yükleme dozu:**1000 mg (≤70 kg) veya 1500 mg (>70 kg)
- 30 mg/kg/gün sürekli infüzyon
- **Serum düzeyi:** 13.8-20.7µmol/L

Augmented renal clearance in septic patients and implications for vancomycin optimisation

João Pedro Baptista*, Eduardo Sousa, Paulo J. Martins, Jorge M. Pimentel

Int J Antimicrob Agents 2012;39:420-423

Baseline characteristics of the studied population (93 patients) in Group A [control group without augmented renal clearance (ARC)] and Group B (study group with ARC).

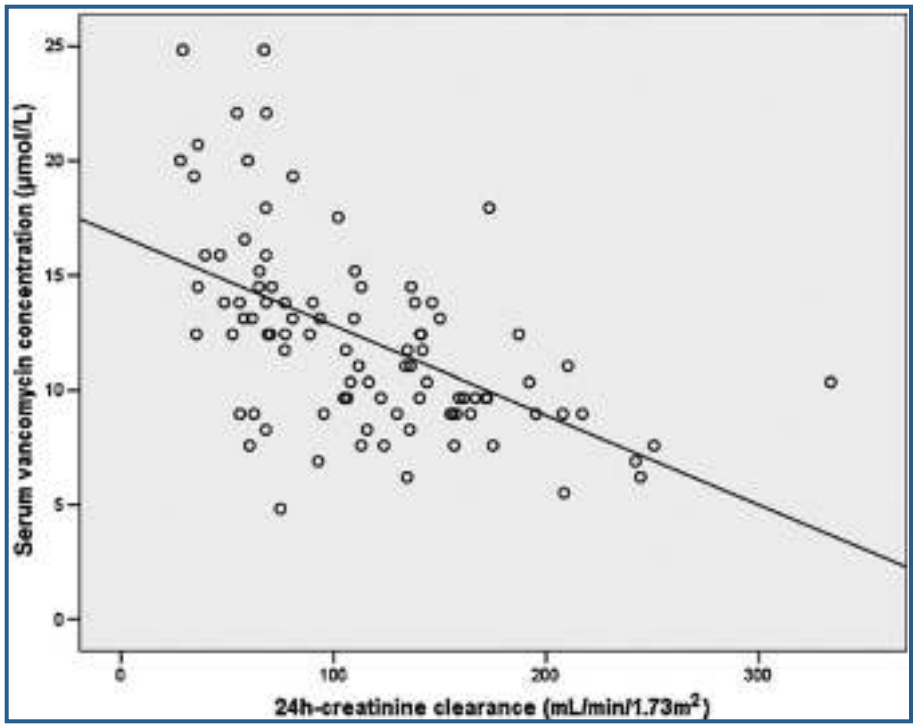
	All patients ($N=93$)	Group A ($N=56$)	Group B ($N=37$)	P-value
Males [n (%)]	69 (74.2)	40 (71.4)	29 (78.4)	N/S
Septic shock incidence [n (%)]	30 (32.3)	20 (35.7)	10 (27.0)	N/S
Urine output (mL/day) [mean (S.D.)]	2618 (826)	2459 (740)	2862 (899)	<0.05
Age (years) [median (IQR)]	58 (34–75)	70 (52–79)	41 (32–56)	<0.05
Use of diuretics [n (%)]	60 (64.5)	35 (62.5)	25 (67.6)	N/S
Actual body weight (kg) [median (IQR)]	73.5 (65–85)	74 (61–80)	77 (68.5–88.5)	N/S
APACHE II score [mean (S.D.)]	17.2 (6)	19.1 (6)	14.1 (5.7)	<0.05
SAPS II [mean (S.D.)]	42.2 (14.3)	45.9 (14)	36.3 (12.9)	<0.05
Serum creatinine (μmol/L) [median (IQR)]	70.7 (61.9–79.6)	70.7 (61.9–88.4)	61.9 (53–79.6)	N/S
BUN (μmol/L) [median (IQR)]	8 (5.6–10.4)	8.6 (6.6–11)	5.7 (4.8–8.6)	<0.05
Serum proteins (g/L) [median (IQR)]	53 (48–60)	52 (47–57)	57 (51–62)	<0.05
Serum albumin (g/L) [median (IQR)]	30 (25–34)	27 (24–31)	32 (29–36)	<0.05
CL_{Cr} (mL/min/m^2) [median (IQR)]	109.6 (68.1–152.5)	69.6 (57.8–104.2)	158.9 (140.9–193.6)	<0.05
Admission diagnosis [n (%)]				
Trauma	45 (48.4)	23 (41.1)	22 (59.5)	<0.05
Sepsis	28 (30.1)	22 (39.3)	6 (16.2)	<0.05
Respiratory failure without sepsis	11 (11.8)	8 (14.3)	3 (8.1)	N/S
Post surgery	5 (5.4)	2 (3.6)	3 (8.1)	N/S
Other	4 (4.3)	1 (1.8)	3 (8.1)	N/S

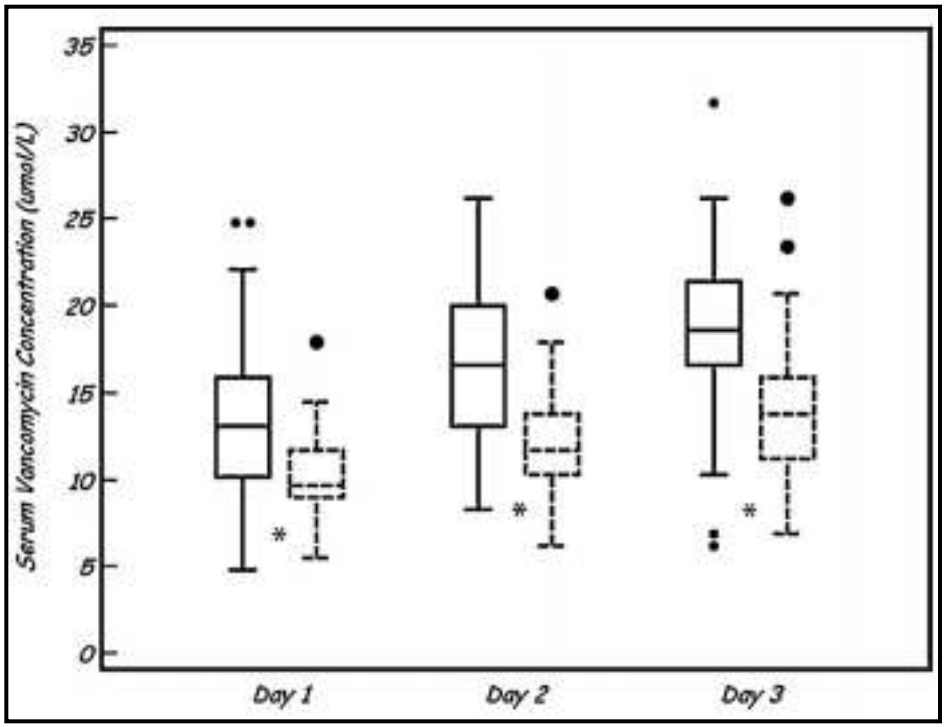
	Group A	Group B	P-value
Loading dose (g)	1.0 (1.0–1.1)	1.0 (1.0–1.5)	N/S
Perfusion dose (g)	2.0 (1.9–2.4)	2.1 (2.0–2.4)	N/S
Total dose (g)	3.1 (2.9–3.8)	3.4 (3.0–3.9)	N/S
Loading dose/actual weight (mg/kg)	15.4 (12.5–18.2)	14.5 (12.5–18.2)	N/S
Perfusion dose/actual weight (mg/kg)	30 (26.7–34.4)	30 (25.0–32.3)	N/S
Total dose/actual weight (mg/kg)	47.7 (40.0–51.8)	45.4 (38.8–48.6)	N/S
Time interval between loading dose and TDM of vancomycin on D_0 (h)	17 (16–17)	17 (17–18)	N/S

Augmented renal clearance in septic patients and implications for vancomycin optimisation

João Pedro Baptista*, Eduardo Sousa, Paulo J. Martins, Jorge M. Pimentel

Int J Antimicrob Agents 2012;39:420-423





Renal klirensin artışı vankomisin serum konsantrasyonunu anlamlı ölçüde düşürüyor
Sepsiste daha yüksek yükleme dozlarına ihtiyaç var !!!!

ANTİBİYOTİK DUYARLILIĞI

- MİK yükselince etkinlik 

YBÜ'si Hastalarında FK/FD Değişikliklerde Ne Yapılmalıdır?

FK Değişiklikler	Doz önerileri
Dağılım hacminin artması	Kiloya göre doz ayarlaması İlaç düzeyinin takibi
Renal eliminasyonun değişimi	Toplam günlük dozun artırılması Dozun daha sık aralıklarla uygulanması Sürekli/uzamış infüzyon İlaç düzeyinin takibi
Serbest ilaç düzeyinin değişimi	Yükleme dozunun artırılması Doz sıklığının artırılması Sürekli/uzamış infüzyon Serbest ilaç düzeyinin takibi
Antibiyotik duyarlılığının azalması	Toplam günlük dozun artırılması Sürekli/uzamış infüzyon İlaç düzeyinin takibi (erken dönemde)

ANTİBİYOTİK TEDAVİSİNDE BAŞARI

Yükleme dozu

- ✓ **Etkin tedavi konsantrasyonlarına hızla ulaşılır**

- ✓ **Yükleme dozu sonrası organ fonksiyonlarına göre doz ayarlaması yapılır**
  - Aminoglikozidler
  - Beta-laktamlar
  - Glikopeptidler
  - Tigesiklin
  - Kolistin

ANTİBİYOTİK TEDAVİSİNDE BAŞARI

Sürekli veya Uzamış İnfüzyon

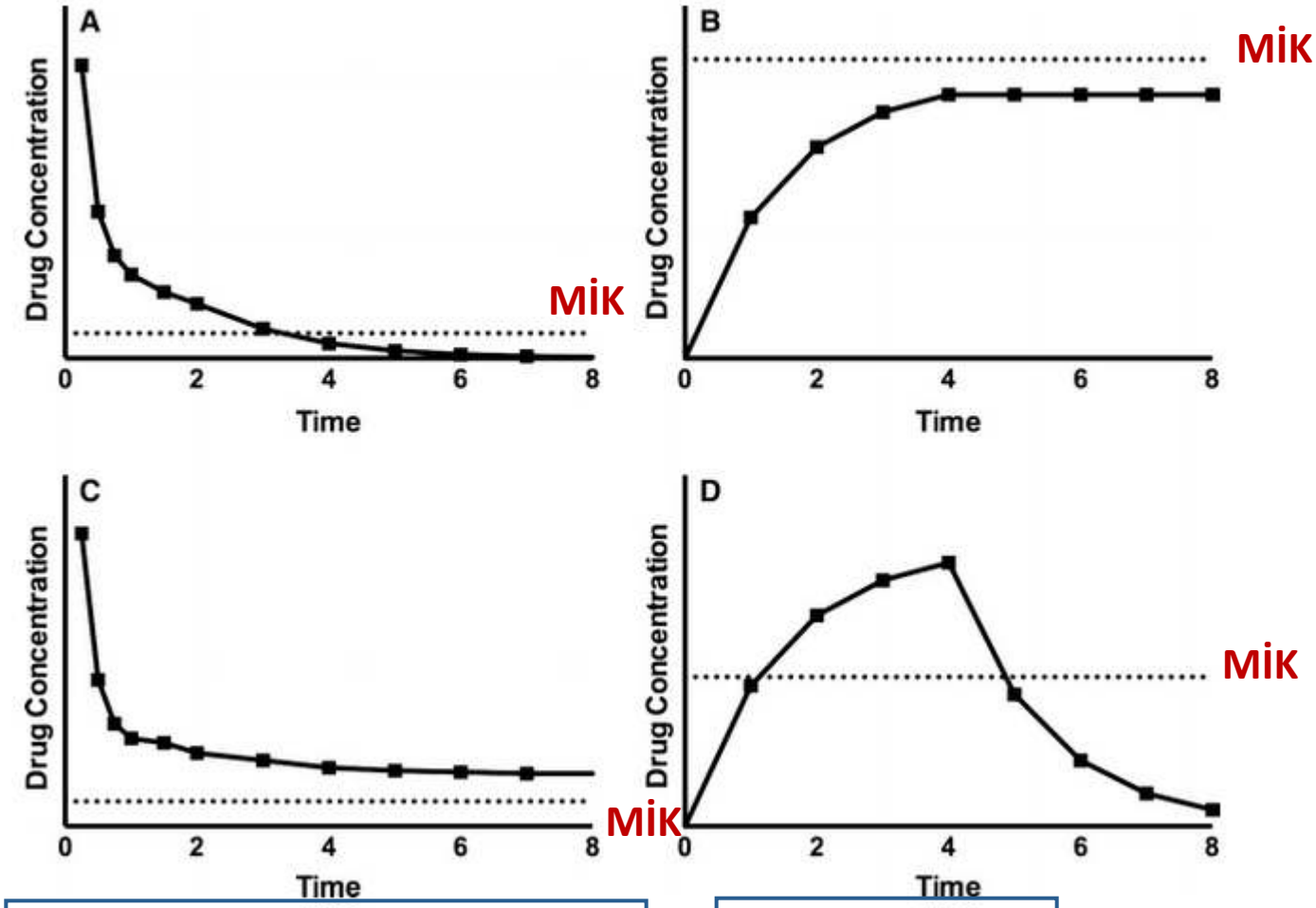
- **Zamana bağlı antibiyotiklerde, doz aralıklarında yeterli ilaç konsantrasyonunun (>MİK) olması önemlidir**
- **Sık aralıklarla uygulama veya sürekli veya uzamış infüzyon uygulanabilir**
- **Yükleme dozunu sürekli veya uzamış infüzyon takip etmeli**
  - Beta-laktamlar
  - Vankomisin

ANTİBİYOTİK TEDAVİSİNDE BAŞARI

Zamana Bağlı Antibiyotikler

Tek yükleme doz

Yükleme yapmadan sürekli infüzyon



Yükleme sonrası sürekli infüzyon

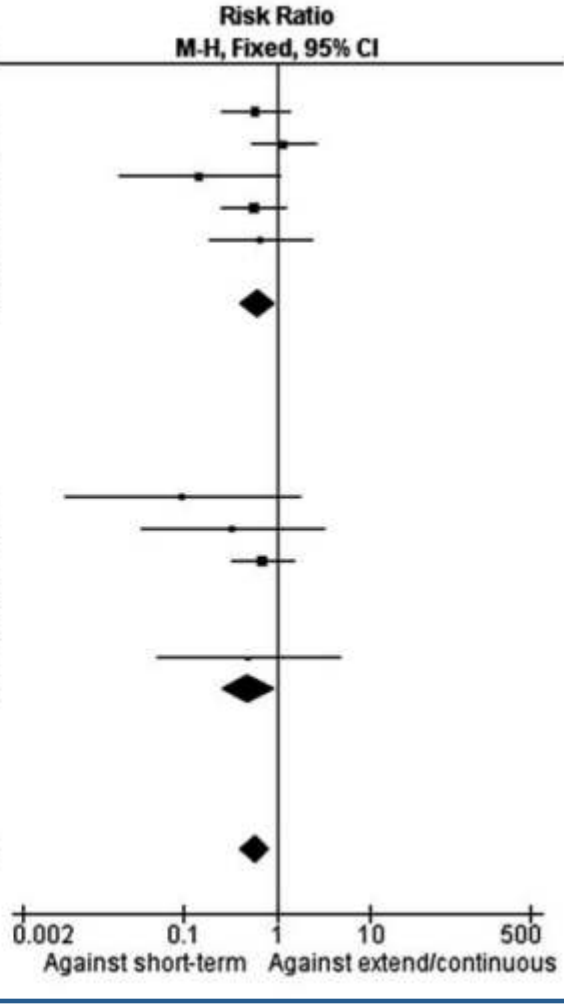
Uzamış infüzyon

Clinical Outcomes With Extended or Continuous Versus Short-term Intravenous Infusion of Carbapenems and Piperacillin/ Tazobactam: A Systematic Review and Meta-analysis

Matthew E. Falagas,[1,2,4] Giannoula S. Tansarli,[1] Kazuro Ikawa,[3] and Konstantinos Z. Vardakas[1]

Clin Infect Dis 2013;56:272-82

Study or Subgroup	Extended or continuous Deaths	Total	Short-term Deaths	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
1.1.1 Extended vs short-term						
Dow 2011	8	67	11	54	17.1%	0.59 [0.25, 1.35]
Esterly 2010	12	42	7	29	11.7%	1.18 [0.53, 2.64]
Itabashi 2007	1	18	9	24	10.9%	0.15 [0.02, 1.07]
Lodise 2007	9	102	14	92	20.7%	0.58 [0.26, 1.28]
Patel 2009	4	70	5	59	7.6%	0.67 [0.19, 2.40]
Wang 2009	0	15	0	15		Not estimable
Subtotal (95% CI)		**314**		**273**	**68.0%**	**0.63 [0.41, 0.95]**
Total events	34		46			
Heterogeneity: Chi² = 4.54, df = 4 (P = 0.34); I² = 12%						
Test for overall effect: Z = 2.18 (P = 0.03)						
1.1.2 Continuous vs short-term						
Grant 2002	0	47	5	51	7.4%	0.10 [0.01, 1.73]
Lau 2006	1	130	3	132	4.2%	0.34 [0.04, 3.21]
Lorente 2009	8	37	14	46	17.6%	0.71 [0.33, 1.51]
Okimoto 2009	0	25	0	25		Not estimable
Roberts 2010	0	8	0	8		Not estimable
Sakka 2007	1	10	2	10	2.8%	0.50 [0.05, 4.67]
Subtotal (95% CI)		**257**		**272**	**32.0%**	**0.50 [0.26, 0.96]**
Total events	10		24			
Heterogeneity: Chi² = 2.18, df = 3 (P = 0.54); I² = 0%						
Test for overall effect: Z = 2.07 (P = 0.04)						
Total (95% CI)		**571**		**545**	**100.0%**	**0.59 [0.41, 0.83]**
Total events	44		70			
Heterogeneity: Chi² = 6.84, df = 8 (P = 0.55); I² = 0%						
Test for overall effect: Z = 2.97 (P = 0.003)						
Test for subgroup differences: Chi² = 0.32, df = 1 (P = 0.57), I² = 0%						



Clinical Outcomes With Extended or Continuous Versus Short-term Intravenous Infusion of Carbapenems and Piperacillin/Tazobactam: A Systematic Review and Meta-analysis

Matthew E. Falagas,[1,2,4] Giannoula S. Tansarli,[1] Kazuro Ikawa,[3] and Konstantinos Z. Vardakas[1,2]

Clin Infect Dis 2013;56:272-82

- Uzamış veya sürekli infüzyon alanlarda mortalite ↓
- Pnömoni hastalarında mortalite ↓
- İyi planlanmış randomize çalışmalara ihtiyaç var !!!!

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]

Clin Infect Dis 2013;56:272-82

- Prospektif
- Çok merkezli
- Çift kör
- Randomize kontrollü çalışma

- Ağır sepsis olguları

- Her iki grupta 30'ar hasta

- Tikarsilin-klavulanat
- Piperasilin-tazobaktam
- Meropenem

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]

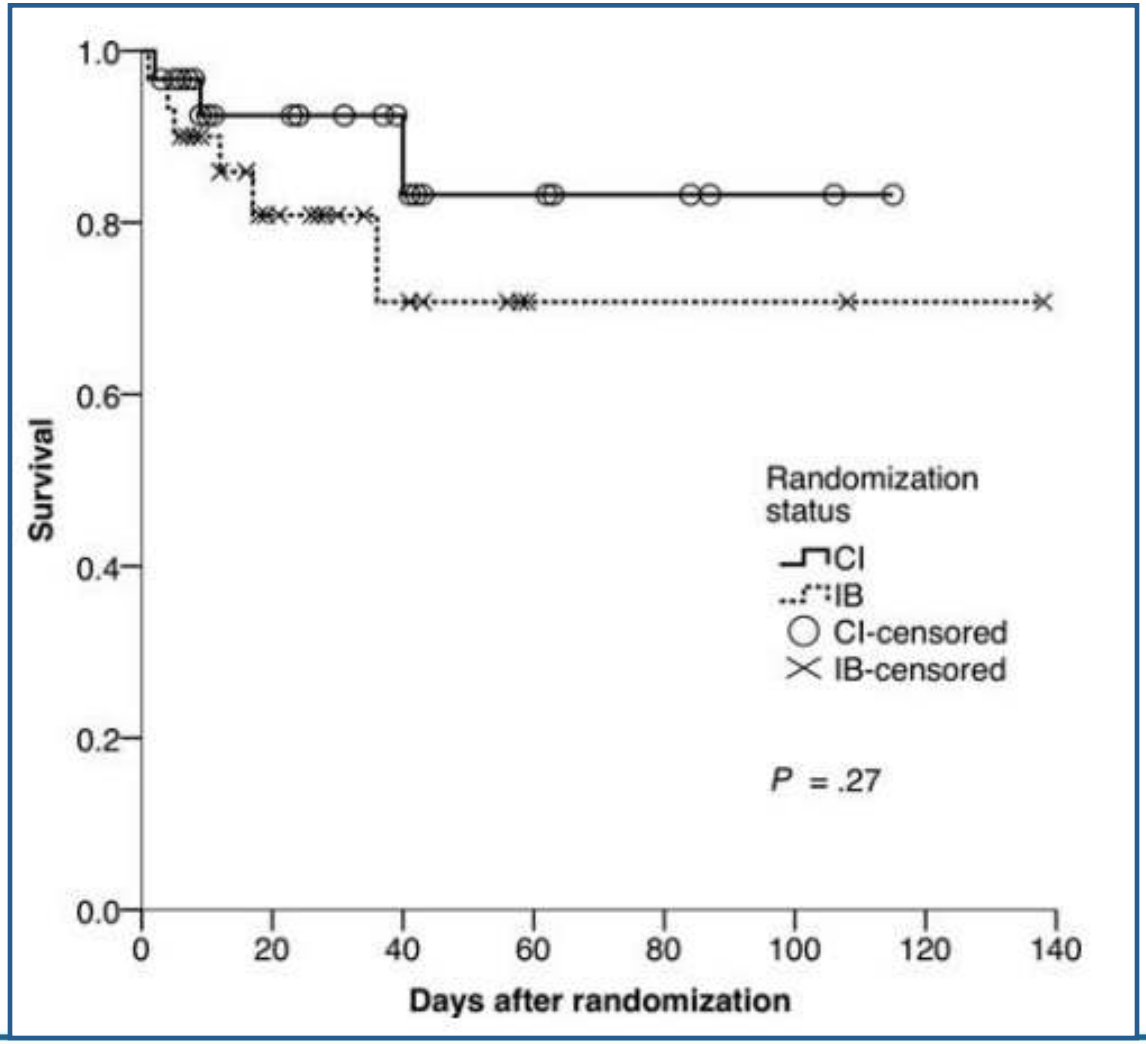
Clin Infect Dis 2013;56:272-82

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

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]

Clin Infect Dis 2013;56:272-82



ANTİBİYOTİK TEDAVİSİNDE BAŞARI

İlaç Düzeyinin Takibi

- Beta-laktamlar
- Karbapenemler (meropenem 4-10 mg/L)
- Glikopeptidler (vankomisin 20-40 mg/L, teikoplanin 10-20mg/L)
- Aminoglikozidler (gentamisin,tobramisin,netilmisin 6-10 mg/L, amikasin 12-20 mg/L)
- Kolistin (8 mg/L)

YBÜ Hastalarında Antibiyotik Dozu ve Uygulanması

	Önerilen Doz	
Antibiyotik Sınıfı	**Normal Böbrek Fonksiyonları**	**Orta ve Ağır Böbrek Yetmezliği**
Beta-laktamlar (penisilinler, sefalosporinler,monobaktamlar) Karbapenemler	Uzamış veya sürekli infüzyon veya daha sık uygulama	Eğer aralıklı doz uygulanıyorsa, daha düşük doz veya daha az sıklıkta
Aminoglikozidler	Yüksek doz (Cmax:MİK=10) Endokardit ve nötropenik hastalar dışında tek doz	Mümkün olduğunca yüksek doz kullanılır. Doz azaltılması MİK değerine göre yapılmalıdır
Glikopeptidler	Vankomisin 30-40 mg/kg/gün, 2 saat infüzyon Plazma konsantrasyonu 15-20 mg/L olmalı Sürekli infüzyon kullanılabilir	İlk gün yüksek doz kullanılır, daha sonra Cmin göre doz ayarlaması yapılır
Kinolonlar	Yüksek Cmax:MİK hedeflenmeli Siproflokasasin 1200 mg/gün Levofloksasisn 1000 mg/gün	Sıklık azaltılması
Tigesiklin	100 mg yükleme dozu, 2*50 mg	Doz ayarlaması gerekmez Ağır kolestaz varlığında 50 mg yükleme ardından 2*25 mg
Linezolid	2*600 mg	Doz ayarlaması gerekmez
Kolistin	5 mg/kg/gün iv-3 doz	Doz veya sıklık azaltılması

Ne Kadar Süre?

- Enfeksiyon odağı
- Enfeksiyon şiddeti
- Odak kontrolü
- Etken mikroorganizma
- Komplikasyon varlığı

Ne Kadar Süre?

• Pnömoni	10-14 gün
• Üriner sistem enfeksiyonu	3-14 gün
• Kan dolaşımı enfeksiyonu	10-14 gün
• Intraabdominal enf.	4-7 gün
• Yumuşak doku enf.	7-10 gün

Biomarker-guided antibiotic therapy in adult critically ill patients: a critical review

Pedro Póvoa[1,2*] and Jorge I F Salluh[3,4]

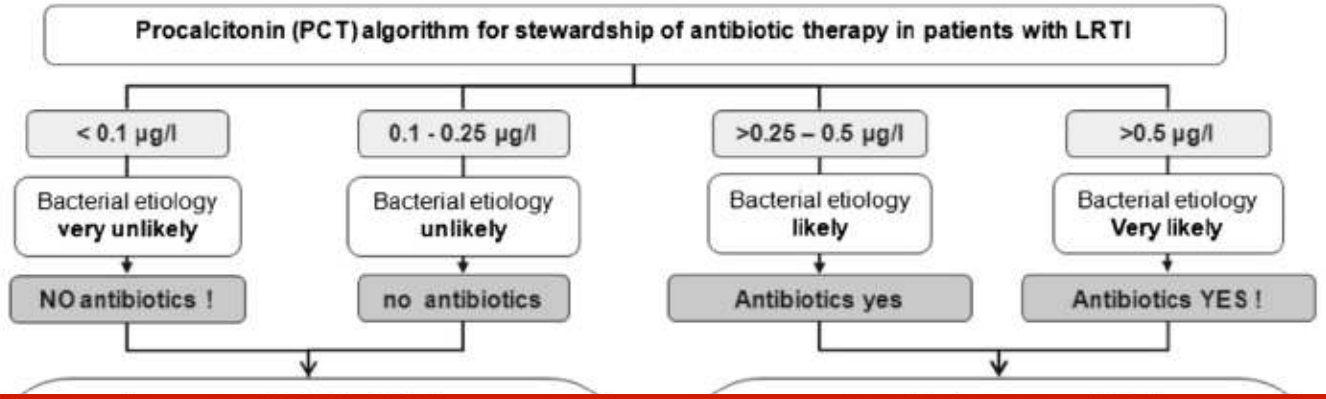


Figure 1 Procalcitonin algorithm for stewardship of antibiotic therapy; adapted from [10].

TEDAVİ SÜRESİ

PCT düzeyi 3,5,7. günlerde değerlendir

Eğer başlangıç değerinden >%80 düşmüş ise veya <0.5 ng/mL ise tedaviyi kes

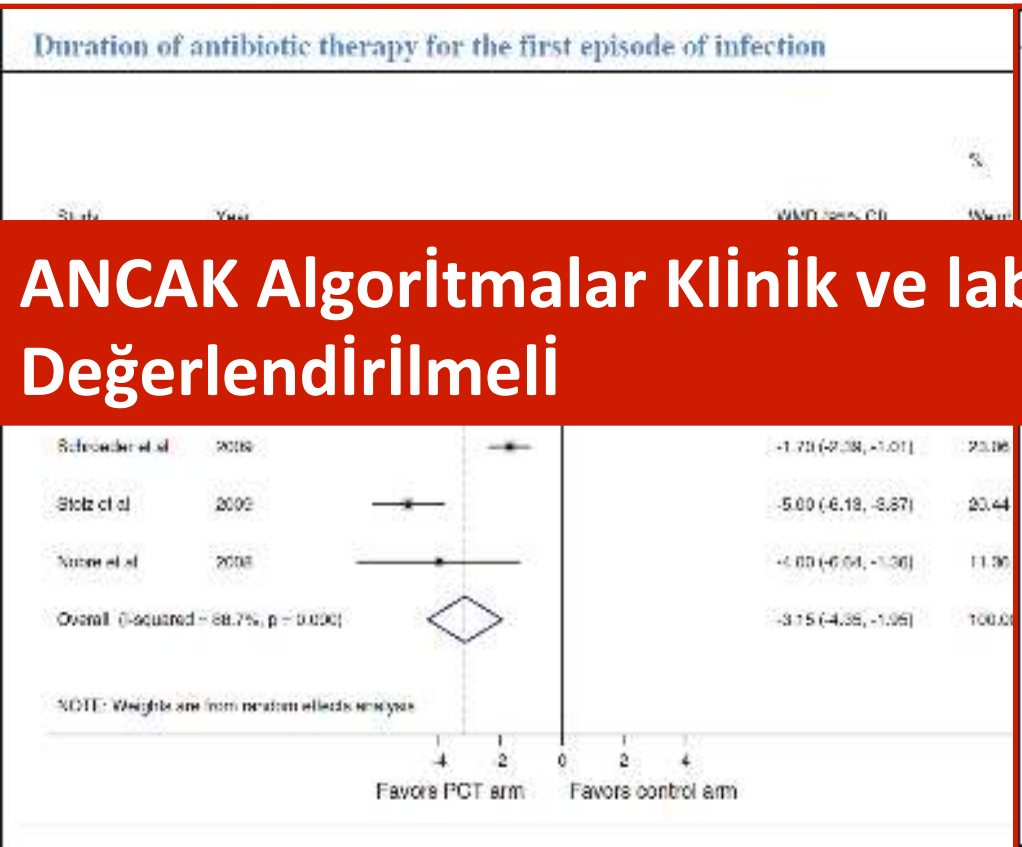
Eğer PCT yüksek ise tedavi başarısızlığı, enfeksiyöz komplikasyonlar veya süperenfeksiyon düşün

Ne Kadar Süre?

Dimitrios K. Matthaiou
Georgia Ntani
Marina Kontogiorgi
Garyfallia Poulakou
Apostolos Armaganidis
George Dimopoulos

An ESICM systematic review and meta-analysis of procalcitonin-guided antibiotic therapy algorithms in adult critically ill patients

Intensive Care Med (2012) 38:940–949



ANCAK Algoritmalar Klinik ve laboratuvar Bulguları İle Değerlendirilmeli

YBÜ Hastalarında Antibiyotik Dozu ve Uygulanması

Önerilen Dozlar Her Hastaya Uyar mı?

SONUÇ

YBÜ Uzmanı

Enfeksiyon Hastalıkları Uzmanı

Klinik Mikrobiyoloji&Biyokimya Uzmanı

Klinik Farmakolog

GERÇEK BAŞARI ENFEKSİYON KONTROLÜNDE

TEŞEKKÜRLER