

Antibiyotiklerin Sistemik Olmayan Uygulamaları

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Sunum Planı



- ▶ İnhaler uygulama
- ▶ İntraventriküler/intratekal uygulama
- ▶ Antibiyotik kilit tedavisi
- ▶ Antibiyotik içerikli çimento uygulaması
- ▶ İntraperitoneal uygulama

İnhaler uygulama

- ▶ İnhaler antibiyotikler ilk kullanım 1940
- ▶ Kistik fibrozisli hastalar için 1990 inhaler tobramisin



EFFICACY OF AEROSOLIZED TOBRAMYCIN IN PATIENTS WITH CYSTIC FIBROSIS

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Conclusions. The short-term aerosol administration of a high dose of tobramycin in patients with clinically stable cystic fibrosis is an efficacious and safe treatment for endobronchial infection with *P. aeruginosa*. (N Engl J Med 1993;328:1740-6.)

INTERMITTENT ADMINISTRATION OF INHALED TOBRAMYCIN IN PATIENTS WITH CYSTIC FIBROSIS**INTERMITTENT ADMINISTRATION OF INHALED TOBRAMYCIN IN PATIENTS WITH CYSTIC FIBROSIS**

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FOR THE CYSTIC FIBROSIS INHALED TOBRAMYCIN STUDY GROUP*

Conclusions In a 24-week study of patients with cystic fibrosis, intermittent administration of inhaled tobramycin was well tolerated and improved pulmonary function, decreased the density of *P. aeruginosa* in sputum, and decreased the risk of hospitalization. (N Engl J Med 1999;340:23-30.)

Table 1. Inhaled antibiotics for cystic fibrosis

Drug	FDA Indication	Established Clinical Use	Notes
Aztreonam solution (Cayston)	To improve respiratory symptoms in patients with CF and <i>Pseudomonas aeruginosa</i> infections \geq 6 yr of age and FEV ₁ > 25% and < 75%	Chronic pulmonary <i>P. aeruginosa</i> infection	Alternating-month use is common
Colistin solution (Colomycin)	An intravenous/intramuscular formulation to treat or prevent acute or chronic gram-negative bacterial infection (including <i>P. aeruginosa</i>)	Chronic pulmonary <i>P. aeruginosa</i> infection	
Colistin dry powder (Colobreathe)	N/A*	Chronic pulmonary <i>P. aeruginosa</i> infection	Not FDA approved
Tobramycin solution (TOBI, Novartis) Equivalent formulation: TEVA Pharmaceuticals, USA	Management of patients with CF with <i>P. aeruginosa</i> infection > 6 yr of age, FEV ₁ > 25% and < 75%. Treatment schedule is 28 d on therapy alternating with 28 d off therapy	Chronic pulmonary <i>P. aeruginosa</i> infection <i>P. aeruginosa</i> eradication	Alternating-month use
Tobramycin dry powder (TOBI Podhaler)	Management of patients with CF with <i>P. aeruginosa</i> infection > 6 yr of age, FEV ₁ > 25% and < 80%. Treatment schedule is 28 d on therapy alternating with 28 d off therapy	Chronic pulmonary <i>P. aeruginosa</i> infection	Alternating-month use Not currently used for <i>P. aeruginosa</i> eradication

Definition of abbreviations: CF = cystic fibrosis; FDA = U.S. Food and Drug Administration; N/A = not applicable.

*EMA approved but not FDA approved.

Uygulamanın avantajları

- ▶ İlacın enfeksiyon alanına doğrudan ulaşması
- ▶ Bronşiyal sekresyonlarda ilaç yoğunluğunun yüksek olması
- ▶ Gastrointestinal floranın antibiyotiğe maruz kalmaması
- ▶ Sistemik toksisitenin en düşük düzeyde olması

Uygulamanın yan etkileri

- ▶ Lokal etkiler
- ▶ Sistemik etkiler
- ▶ Antibiyotik direnç gelişimi
- ▶ Fungal kolonizasyon

Ventilatör ilişkili pnömoni (VİP)



İnhale antibiyotiklerin sistemik antibiyotiklere eklenerek veya alternatif ilaç olarak kullanımı

Çoklu ilaca dirençli (ÇİD) Gram negatif bakterilerle (GNB)
(*Acinetobacter baumannii*, *Pseudomonas aeruginosa* ve
karbapenemaz üreten *Enterobacteriaceae* spp.)

American Thoracic Society Documents

Guidelines for the Management of Adults with Hospital-acquired, Ventilator-associated, and Healthcare-associated Pneumonia

THIS OFFICIAL STATEMENT OF THE AMERICAN THORACIC SOCIETY AND THE INFECTIOUS DISEASES SOCIETY OF AMERICA WAS APPROVED BY THE ATS BOARD OF DIRECTORS, DECEMBER 2004 AND THE IDSA GUIDELINE COMMITTEE, OCTOBER 2004

2. Aerosolized antibiotics have not been proven to have value in the therapy of VAP (**Level I**) (256). However, they may be considered as adjunctive therapy in patients with MDR gram-negatives who are not responding to systemic therapy (**Level III**) (255).

4. Adjunctive therapy with an inhaled aminoglycoside or polymyxin for MDR gram-negative pneumonia should be considered, especially in patients who are not improving with systemic therapy (**Level III**) (255). More studies of this type of therapy are needed.

Sistemik tedaviye cevap alınamayan ÇİD GNB'lere bağlı pnömonide sistemik tedaviye inhaler antibiyotiklerin eklenmesi düşünülmelidir (Düzey III)

J Antimicrob Chemother 2010; 65: 2645–2649
doi:10.1093/jac/dkq390 Advance Access publication 28 September 2010

**Randomized controlled trial of nebulized colistimethate sodium
as adjunctive therapy of ventilator-associated pneumonia
caused by Gram-negative bacteria**

Piyo Rattansumpowan, Jintana Lamsathitham, Puangpaka Ungprasert, Neeleam Angkasekwinai
and Visara Thamlikitkul*

**Nebulized Ceftazidime and Amikacin in
Ventilator-associated Pneumonia Caused
by *Pseudomonas aeruginosa***

Qin Lu¹, Jianxin Yang¹, Zhihai Liu¹, Claudia Gutierrez¹, Guy Aymard¹, Jean-Jacques Rouby¹,
and the Nebulized Antibiotics Study Group*

Am J Respir Crit Care Med Vol 184, pp 106–115, 2011

İki araştırma sonucu sistemik tedaviye eklenen inhaler antibiyotikler mikrobiyolojik eradikasyonda üstün ama klinik yarar saptanmamış

Reduction of Bacterial Resistance with Inhaled Antibiotics in the Intensive Care Unit

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Am J Respir Crit Care Med Vol 189, Iss 10, pp 1225-1233, May 15, 2014

Randomize, çift-kör, plasebo kontrollu, tek merkezli

Sonuç:

- İnhale antibiyotikler ÇİD bakterileri eradike edebilir
- Direnç gelişimini önleyebilir

Table 3. Clinical response in aerosolized antibiotic group vs. placebo group^a

	Randomization			EOT		
	AA (n=24)	Placebo (n=18)	P value	AA (n=24)	Placebo (n=18)	P value
CPIS*	9.3±2.7	8.0±2.1	0.5000 ^b	5.3±2.6	8.6±2.6	0.0006 ^b
Volume/4 h ^c	8.9±4.2	9.9±0.69	0.12	1.1±1.3	6.3±4.3	<0.001
Systemic WBC ^{***}	12.1±1.9	12.6±1.2	0.18	13.3±1.3	13.9±1.5	0.726

The Role of Aerosolized Colistin in the Treatment of Ventilator-Associated Pneumonia: A Systematic Review and Metaanalysis*

Antonios Valachis, MD, PhD¹; George Samonis, MD, PhD²; Diamantis P. Kofteridis, MD, PhD³

Conclusion: Based on the present results and awaiting further evidence from randomized trials, aerosolized colistin is associated with improved outcome in the treatment of ventilator-associated pneumonia although the level of evidence was low. (*Crit Care Med* 2015; 43:527–533)

The Role of Aerolized Colistin in the Treatment of Hospital-Acquired Pneumonia: Experience of Multicenter From Turkey

To the Editor:

We read with great interest, in a recent issue of *Critical Care Medicine*, the meta-analysis and systematic review by Valachis et al (1), which evaluated the efficacy and safety of aerosolized colistin as adjunctive therapy to parenteral antimicrobials or as monotherapy in the treatment of ventilator-associated pneumonia.

remaining authors have disclosed that they do not have any potential conflicts of interest.

Pervin Korkmaz Ekren, MD, Nur Toreyin, MD, Abdullah Sayiner, MD, PhD, Feza Bacakoglu, MD, PhD, on behalf of Colistin Study Group, Department of Chest Diseases, Ege University Faculty of Medicine, Bornova, Turkey

Critical Care Medicine 2016; 44; 5

Hastanede gelişen pnömonili olgular

Sonuçta kombine tedavi ile klinik ve bakteriyolojik cevap

oranlarının daha yüksek olduğu, mortalite ve nefrotoksisitenin

de benzer olduğu



Antibiyotiklerin dozu

Uygulamada
kullanılacak araç

Sistemik antibiyotik
kullanımı azaltılabilir
mi?

Dirençli bakterilerin
ortaya çıkışı
önlenebilir mi?

Intraventriküler (İVT)–intratekal (İT) uygulamalar

- ▶ İlk İVT uygulaması 50 yıl önce

Clifford HE et al. Lancet 1961;2;177–80

- ▶ İVT/İT uygulama endikasyonları



Ventrikülit/menenjit olgularında

Beyin apsesi rüptürlerinde

BOS şant/drenaj
enfeksiyonlarında

Sistemik uygulama
+
İVT/İT uygulama

Table 7. Recommended dosages of antimicrobial agents administered by the intraventricular route (A-III).

Antimicrobial agent	Daily intraventricular dose, mg
Vancomycin	5–20 ^a
Gentamicin	1–8 ^b
Tobramycin	5–20
Amikacin	5–50 ^c
Polymyxin B	5 ^d
Colistin	10
Quinupristin/dalfopristin	2–5
Teicoplanin	5–40 ^e

NOTE. There are no specific data that define the exact dose of an antimicrobial agent that should be administered by the intraventricular route.

^a Most studies have used a 10-mg or 20-mg dose.

^b Usual daily dose is 1–2 mg for infants and children and 4–8 mg for adults.

^c The usual daily intraventricular dose is 30 mg.

^d Dosage in children is 2 mg daily.

^e Dosage of 5–10 mg every 48–72 h in one study [112].

Practice Guidelines for the Management of Bacterial Meningitis

Allan R. Tunkel,¹ Barry J. Hartman,² Sheldon L. Kaplan,³ Bruce A. Kaufman,⁴ Karen L. Roos,¹ W. Michael Scheld,⁴ and Richard J. Whitley⁷

Clinical Infectious Diseases 2004; 39:1267–84



Review

Post-neurosurgical multidrug-resistant *Acinetobacter baumannii* meningitis successfully treated with intrathecal colistin. A new case and a systematic review of the literature

Antonio Cascio ^{a,*}, Alfredo Conti ^b, Luca Sinardi ^c, Chiara Iaria ^d, Filippo Flavio Angileri ^b,
Giovanna Stassi ^e, Teresa David ^c, Antonio Versaci ^c, Maurizio Iaria ^f, Antonio David ^c

36 yaşında erkek hasta

Operasyon sonrası BOS kültüründe *A. baumannii*

10 gün İT kolistin (10 mg/gün) ile tedavi ediliyor

Intrathecal Colistin For Treatment Of *Acinetobacter* Spp Meningitis: Case Report

S Sahin, A Selik, D Memis

Neurosurgical Gram-Negative Bacillary Ventriculitis and Meningitis: A Retrospective Study Evaluating the Efficacy of Intraventricular Gentamicin Therapy in 31 Consecutive Cases

Thomas Tängdén,¹ Per Enblad,² Måns Ullberg,³ and Jan Sjölin¹

Clinical Infectious Diseases 2011;52(11):1310–1316

Nonrandomize, retrospektif araştırma

Sistemik tedavi alan (n:18)

Sistemik antibiyotik tedavisine ek olarak İVT gentamisin alan (n:13) hasta grupları

Uygun sistemik tedaviye ek olarak İVT gentamisin uygulanan grupta anlamlı yüksek kür ve düşük relaps oranları

Intraventricular and lumbar intrathecal administration of antibiotics in postneurosurgical patients with meningitis and/or ventriculitis in a serious clinical state

Clinical article

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VÁCLAV VANÍŠ, M.D.,² AND MICHAL ŠETLÍK, M.D.¹

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Menenjit/ventrikülit gelişen 34 hasta retrospektif
Sistemik tedaviye cevap vermeyen olgulara İVT/İT yolla çeşitli
antibiyotikler uygulanmış
23 hastada 48. saatte BOS kültürlerinde üreme görülmemiş
Sonuçta kombine tedavinin etkin ve güvenilir olduğunu
belirtmişlerdir



Systematic Review of Efficacy, Pharmacokinetics, and Administration of Intraventricular Vancomycin in Adults

**Karen Ng · Vincent H. Mabasa · Ivy Chow ·
Mary H. H. Ensom**

- 17 makalenin sonuçları değerlendirilmiş
- Ventrikülit, menenjit ve alet ilişkili SSS enfeksiyonlu vakalarda İVT vankomisin kullanımının etkili ve güvenilir olduğu belirtilmiştir

Antibiyotiklerin İVT/İT yol ile uygulaması

- Parenteral tedaviye rağmen BOS sterilizasyonu sağlanamayan olgularda
- Sadece BOS'a geçişi zayıf olan antibiyotiklere karşı duyarlı olan dirençli bakterilerle gelişen enfeksiyonlarda uygulanabilir

Antibiyotik kilit tedavisi (AKT)

- ▶ Kateter ilişkili kan dolaşımı enfeksiyonlarını tedavi etmek için kateter lümeninin antibiyotik solüsyonu ile doldurulup belli bir süre kilitlenmesi

Antibiyotik → Katater lümeni →



Messing B, Peitra-Cohen S, Debure A, Beliah M, Bernier JJ. Antibiotic-lock technique: a new approach to optimal therapy for catheter-related sepsis in home-parenteral nutrition patients. *J Parenter Enteral Nutr* 1988; 12: 185-9

- Uzun süreli (>14 gün) damar içi kateter varlığında (tünelli kateterler ve implante portlar)
- Klinik ve hemodinamik stabil hastada
- Koagülaz negatif stafilokoklar, gram negatif basiller ve vankomisin duyarlı enterokoklarda

Sistemik antibiyotik ile birlikte AKT önerilmektedir.

Mermel LA, et al. IDSA Guidelines. Clin Infect Dis. 2009;49(1):1-45

Treatment of long-term intravascular catheter-related bacteraemia with antibiotic lock: randomized, placebo-controlled trial

**Bart J. Rijnders^{1*}, Eric Van Wijngaerden², Stefaan J. Vandecasteele², Marguerite Stas³
and Willy E. Peetermans²**

- ❖ 44 KİKDE atağı incelenmiş
- ❖ Sistemik antibiyotik tedavisi verilen bir grup ile sistemik antibiyotik ve AKT verilen hasta grupları karşılaştırılmış
- ❖ Sistemik antibiyotik alan grupta tedavi başarısızlığı %57 diğer grupta %33 saptanmıştır

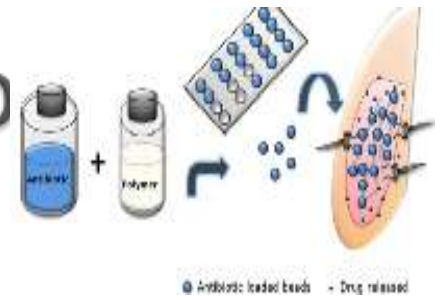
Table 9. Final concentrations of antibiotic lock solutions used for the treatment of catheter-related bloodstream infection.

Antibiotic and dosage	Heparin or saline, IU/mL	Reference(s)
Vancomycin, 2.5 mg/mL	2500 or 5000	[100, 275]
Vancomycin, 2.0 mg/mL	10	[275]
Vancomycin, 5.0 mg/mL ^a	0 or 5000	[276, 277]
Ceftazidime, 0.5 mg/mL	100	[123]
Cefazolin, 5.0 mg/mL	2500 or 5000	[100, 277]
Ciprofloxacin, 0.2 mg/mL ^b	5000	[130]
Gentamicin, 1.0 mg/mL	2500	[100]
Ampicillin, 10.0 mg/mL	10 or 5000	[275]
Ethanol, 70% ^c	0	[131]

AKT yan etkiler

- ▶ Mantar enfeksiyonu
- ▶ Kullanılan antibiyotik/antikoagulana bađlı sistemik toksisite
- ▶ Direncin ortaya çıkışı ve tedavi başarısızlığı

Antibiyotik içerikli çimento uygulaması



- ▶ Total eklem artroplastisinde protez enfeksiyonu
- ▶ Tedavide sistemik antibiyotikler
- ▶ Antibiyotik içerikli çimento (gentamisin, tobramisin, sefuroksim ve vankomisin)
- ▶ Buchholz ve ark.ları ilk kez 1970 yılında
- ▶ 2003 yılında iki aşamalı revizyon FDA onaylı

A Systematic Review and Meta-Analysis of Antibiotic-Impregnated Bone Cement Use in Primary Total Hip or Knee Arthroplasty

Jiaxing Wang¹*, Chen Zhu^{1,2}*, Tao Cheng¹, Xiaochun Peng¹, Wen Zhang¹, Hui Qin¹, Xianlong Zhang^{1*}

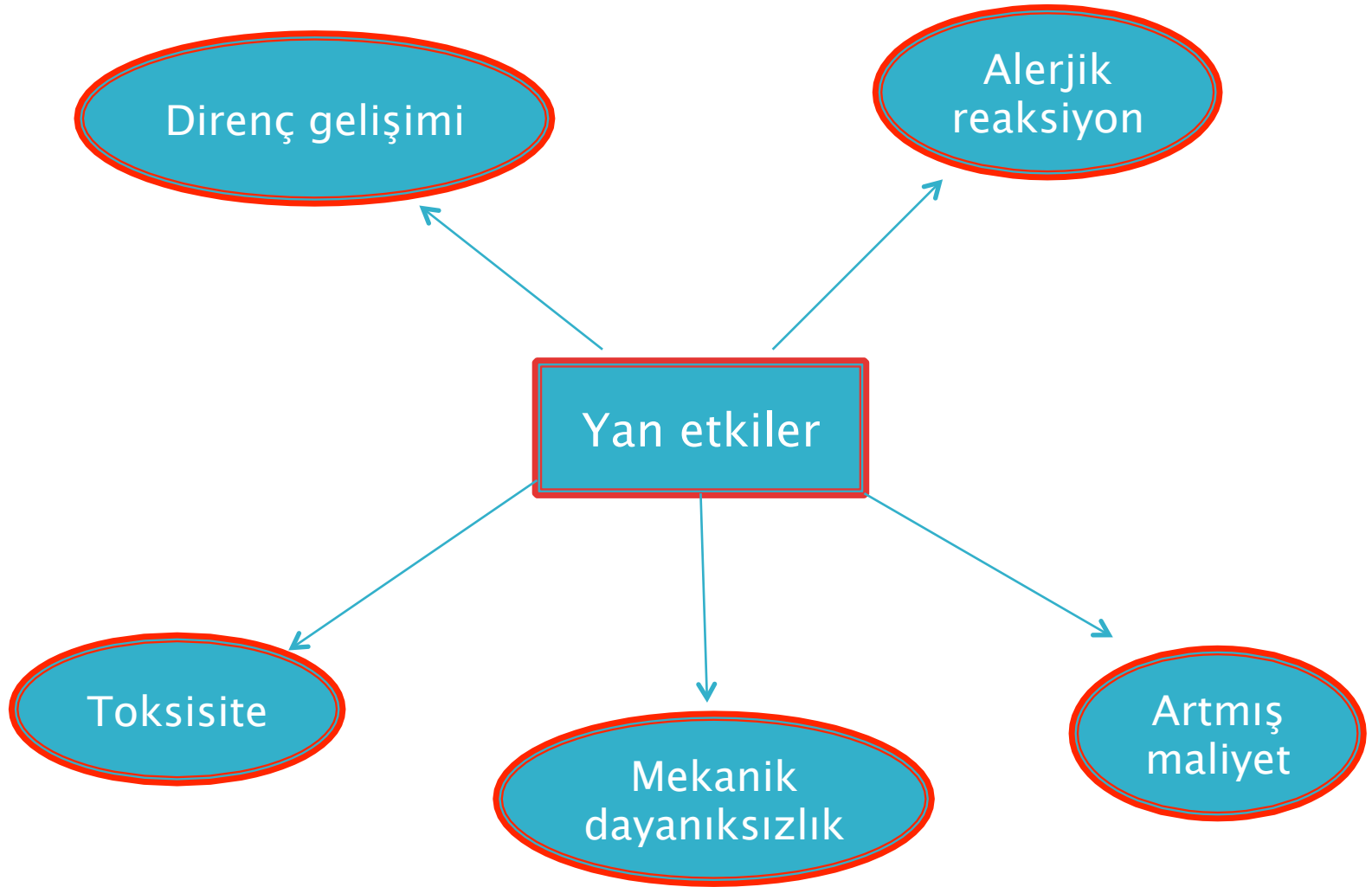
1 Department of Orthopaedic Surgery, Shanghai Sixth People's Hospital, Shanghai Jiao Tong University School of Medicine, Shanghai, China, 2 Department of Orthopaedic Surgery, Anhui Provincial Hospital of Anhui Medical University, Hefei, China

PLOS ONE 2013;8(12):e82745

Proflaktik antibiyotik
içerikli çimento
kullanımı

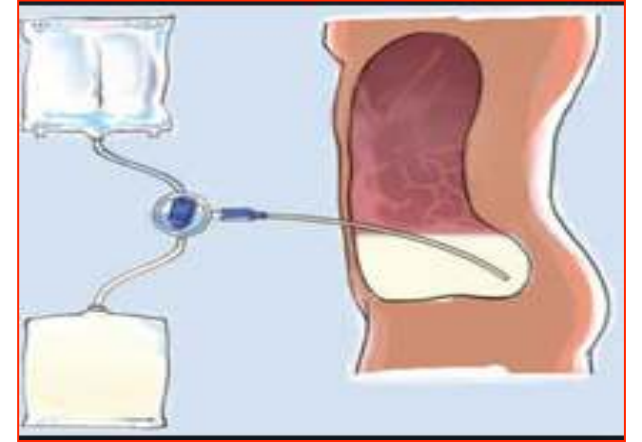


Düşük enfeksiyon
oranları



Intraperitoneal uygulama

- ▶ Peritonit peritoneal diyaliz komplikasyonu
- ▶ Tedavide intraperitoneal uygulama
- ▶ Antibiyotikler devamlı ya da aralıklı
- ▶ Aralıklı uygulamada en az 6 saat peritonda kalmalı



ISPD GUIDELINES/RECOMMENDATIONS

PERITONEAL DIALYSIS-RELATED INFECTIONS RECOMMENDATIONS: 2010 UPDATE

	Intermittent (per exchange, once daily)	Continuous (mg/L; all exchanges)
Aminoglycosides		
Amikacin	2 mg/kg	LD 25, MD 12
Gentamicin, netilmicin, or tobramycin	0.6 mg/kg	LD 8, MD 4
Cephalosporins		
Cefazolin, cephalothin, or cephadrine	15 mg/kg	LD 500, MD 125
Cefepime	1000 mg	LD 500, MD 125
Ceftazidime	1000-1500 mg	LD 500, MD 125
Ceftizoxime	1000 mg	LD 250, MD 125
Penicillins		
Amoxicillin	ND	LD 250-500, MD 50
Ampicillin, oxacillin, or nafcillin	ND	MD 125
Azlocillin	ND	LD 500, MD 250
Penicillin G	ND	LD 50 000 units, MD 25 000 units
Quinolones		
Ciprofloxacin	ND	LD 50, MD 25
Others		
Aztreonam	ND	LD 1000, MD 250
Daptomycin (115)	ND	LD 100, MD 20
Linezolid (41)	15 mg/kg	LD 400, MD 20
Teicoplanin	15-30 mg/kg every 5-7 days	LD 1000, MD 25
Vancomycin	NA	
Antifungals		
Amphotericin	200 mg IP every 24-48 hours	1.5
Fluconazole	200 mg IP every 24-48 hours	
Combinations		
Ampicillin/sulbactam	2 g every 12 hours	LD 1000, MD 100
Imipenem/cilastin	1 g b.i.d.	LD 250, MD 50
Quinupristin/dalfopristin	25 mg/L in alternate bags ^b	
Trimethoprim/sulfamethoxazole		Oral 960 mg b.i.d.



*Teşekkür
ederim*