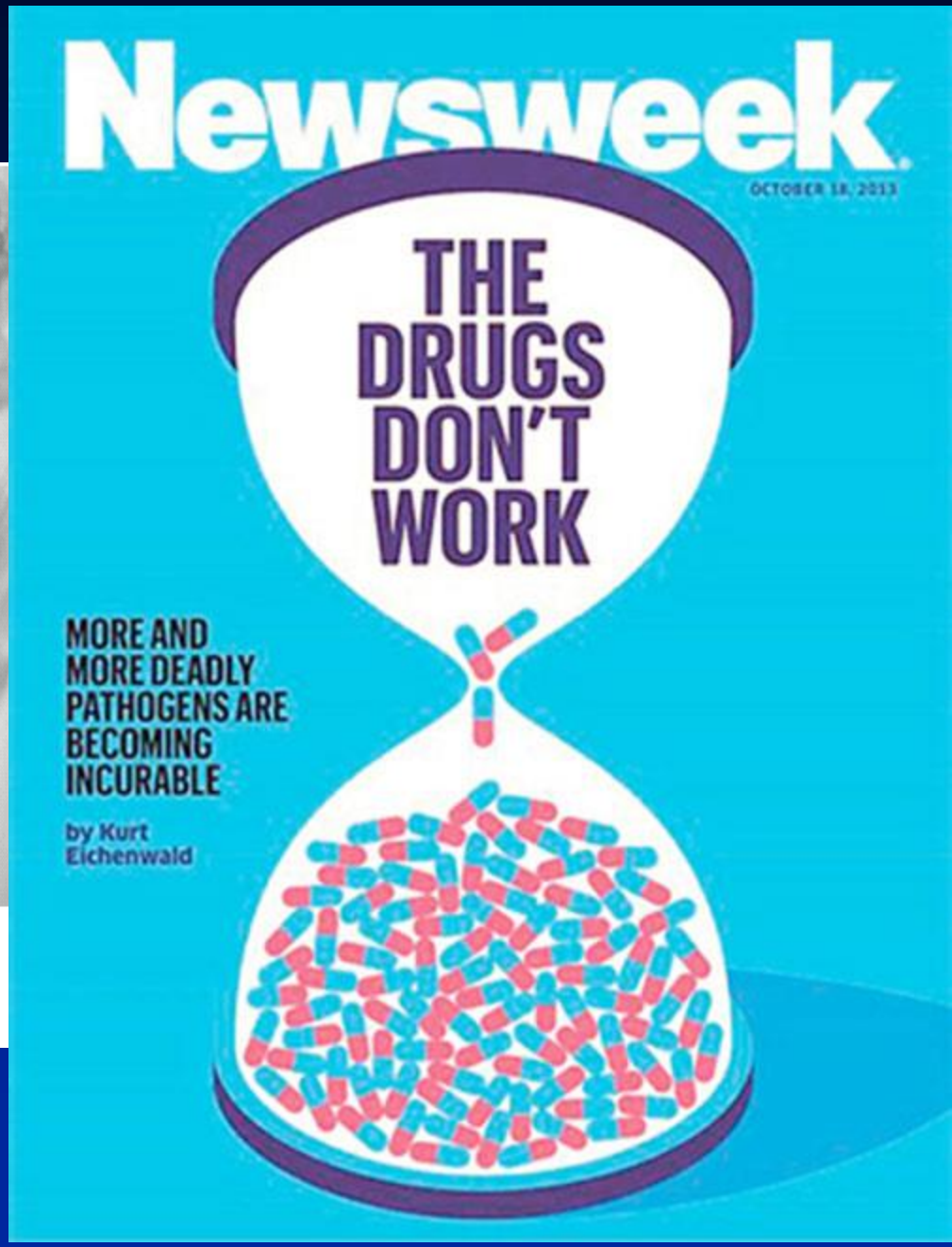
Dirençli Gram-negatif Çomak İnfeksiyonlarının “Akılcı” Tedavisi

Dr Gökhan AYGÜN
İÜ CTF Tıbbi Mikrobiyoloji AD

Dirençli GNÇ İnfeksiyonlarının Akılcı Tedavisi

"Infectious diseases physicians are alarmed by the prospect that effective antibiotics may not be available to treat seriously ill patients in the near future. There simply aren't enough new drugs in the pharmaceutical pipeline to keep pace with drug-resistant bacterial infections, so-called 'superbugs.'"

Joseph R. Dalovisio, MD
IDSA President



DİRENÇLİ GRAM NEGATİFLER

- Geçirgenlikte azalma (barikat)
- Parçalayıcı enzim (silah)
- Hedef değişimi (kamuflaj)
- Pompalama

  (sınır askerleri)

Süper Mikrop

Table 1e. *Acinetobacter* spp.; antimicrobial categories and agents used to define MDR, XDR and PDR

Antimicrobial category	Antimicrobial agent	Results of antimicrobial susceptibility testing (S or NS)
Aminoglycosides	Gentamicin	
	Tobramycin	
	Amikacin	
	Netilmicin	
Antipseudomonal carbapenems	Imipenem	
	Meropenem	
	Doripenem	
Antipseudomonal fluoroquinolones	Ciprofloxacin	
	Levofloxacin	
Antipseudomonal penicillins + β-lactamase inhibitors	Piperacillin-tazobactam	
	Ticarcillin-clavulanic acid	
Extended-spectrum cephalosporins	Cefotaxime	
	Ceftriaxone	
	Ceftazidime	
	Cefepime	
Folate pathway inhibitors	Trimethoprim-sulfamethoxazole	
Penicillins + β-lactamase inhibitors	Ampicillin-sulbactam	
Polymyxins	Colistin	
	Polymyxin B	
Tetracyclines	Tetracycline	
	Doxycycline	
	Minocycline	

Criteria for defining MDR, XDR and PDR in *Acinetobacter* spp.

MDR: non-susceptible to ≥ 1 agent in ≥ 3 antimicrobial categories

XDR: non-susceptible to ≥ 1 agent in all but ≤ 2 categories,

PDR: non-susceptible to all antimicrobial agents listed

- Magiorakos AP et al. Clin Microbiol Infect 2011

Sorun (MDR) Bakteriler

- *ESBL/GSBL E.coli, Klebsiella*
- *KARBAPENEMAZ (CRE)*
- *P. aeruginosa*
  - İmipenem ve seftazidime ve amikasin ve siprofloksasin
- *Acinetobacter spp.*
  - İmipenem
- *S. maltophilia*
  - TMP-SMX

E.coli/Klebsiella direnç sorunu

- HİTİT
- NPRS
- MYSTIC
- ....

*** Klebsiella karbapenem direnci var !

*** ESBL oranı % 30-50

HITIT-II-2007 Duyarlılık

- *Escherichia coli* - ESBL(+)-%42
- *Klebsiella pneumoniae* - ESBL(+)-%41
- *Pseudomonas aeruginosa*
  -İmipenem %70
  -Piperasilin/tazobaktam %82
- *Acinetobacter baumannii*
  -İmipenem %45
  -CFP/Sulb %48
- 2004-2005

CTX-M(%71.4), TEM (%49.4) ve SHV(%46.7)

Gür D et al. J Chemother 2009

Gür D et al. Mikrobiyol Bul 2008

Antibiyotik direncinin bedeli

- Maliyet artışı
- Hastanede daha uzun süre kalış
- Artmış mortalite

Clinical Infectious Diseases 2006; 42:S82–9

The Relationship between Antimicrobial Resistance and Patient Outcomes: Mortality, Length of Hospital Stay, and Health Care Costs

Sara E. Cosgrove
Division of Infectious Diseases, The Johns Hopkins Medical Institutions, Baltimore, Maryland

“Akılcı antibiyotik kullanımı”

- Doğru bir klinik tanı (kolonizasyon ?)
- Onlarca antibiyotik arasından en uygununun seçimi
- Uygun doz ve yolun kullanılması
- Toksisite
- MALİYET !
- Direnç gelişiminin izlenmesi gibi karmaşık bir süreci idare etme sanatıdır !

BAZEN HİÇ BİR ETKİLİ ANTİBİYOTİK YOKKEN

Akılcı ?

- Riskleri ortadan kaldırmaya çalış !
- Kolonizasyonu tedavi etme
- Ampirik tedavi etkene uygun olmalı !
- Antibiyotik baskısına dikkat et
- Direnç geliştirme potansiyeli var mı?
- Antibiyotikleri –zamanında- kes !
- Laboratuvar ile dinamik bir ilişki içinde !
- Doz, FK/FD ilişkilerini gözeterek !

Sorun mikroorganizmalar için risk

- Kötü Hastalıklar
- İnvaziv Girişimler
- Ünitede sorun mikroorganizma varlığı
- YBÜ yatışı
- ANTİBİYOTİK

Kolonizasyonu tedavi etme

INFECTION CONTROL AND HOSPITAL EPIDEMIOLOGY MARCH 2014, VOL. 35, NO. 3

ORIGINAL ARTICLE

Ventilator-Associated Pneumonia: Overdiagnosis and Treatment Are Common in Medical and Surgical Intensive Care Units

Veronique Nussenblatt, MD, MHS;[1] Edina Avdic, PharmD, MBA;[2] Sean Berenholtz, MD, MHS;[3,4] Elizabeth Daugherty, MD, MPH;[5] Eric Hadhazy, MS;[1] Pamela A. Lipsett, MD, MHPE;[3,4] Lisa L. Maragakis, MD, MPH;[1] Trish M. Perl, MD, MSc;[1] Kathleen Speck, MPH;[3] Sandra M. Swoboda, RN, MS;[3] Wendy Ziai, MD;[3,6] Sara E. Cosgrove, MD, MS[1]

OBJECTIVE. Diagnosing ventilator-associated pneumonia (VAP) is difficult, and misdiagnosis can lead to unnecessary and prolonged antibiotic treatment. We sought to quantify and characterize unjustified antimicrobial use for VAP and identify risk factors for continuation of antibiotics in patients without VAP after 3 days.

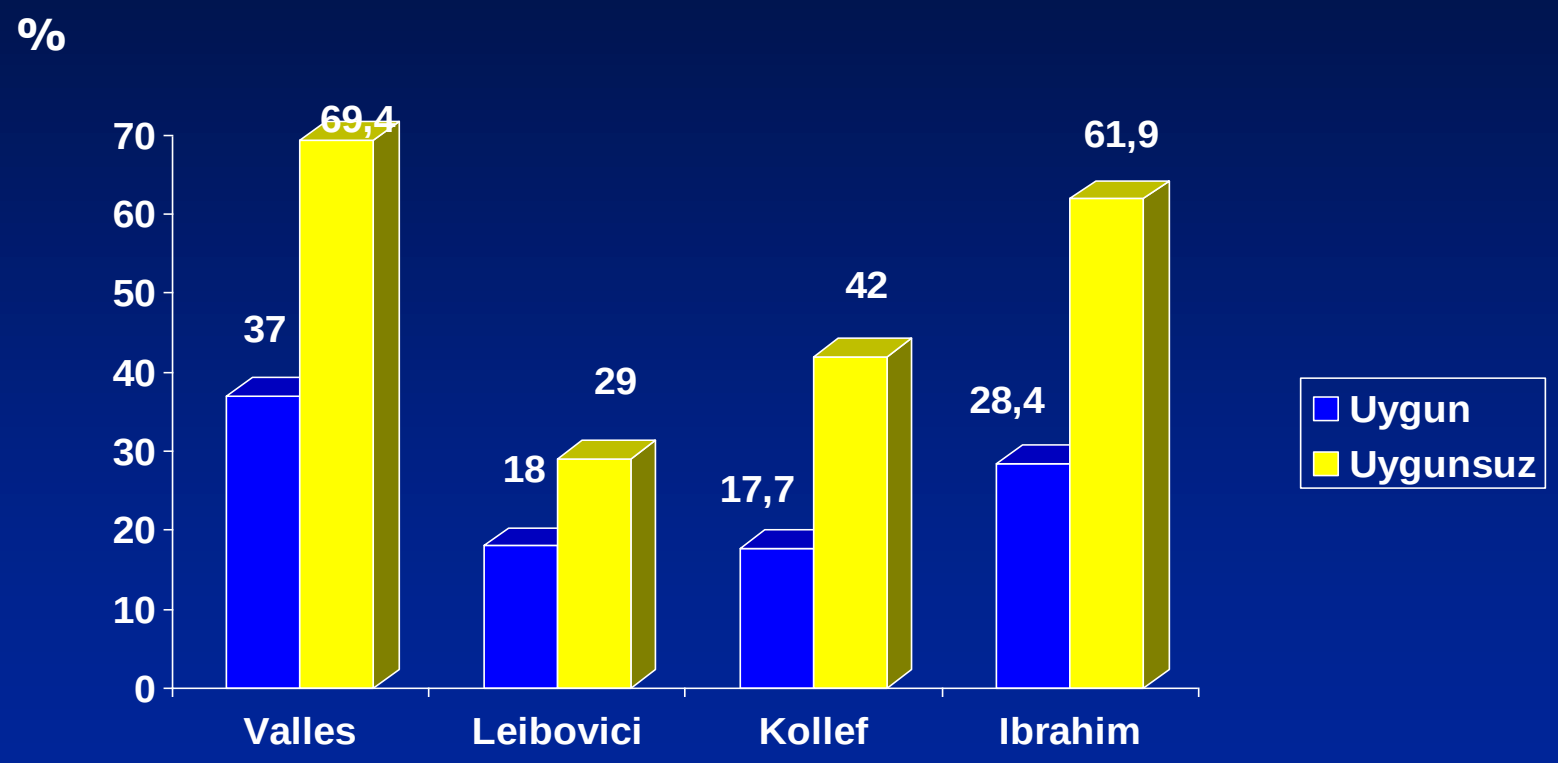
METHODS. Patients suspected of having VAP were identified in 6 adult intensive care units (ICUs) over 1 year. A multidisciplinary adjudication committee determined whether the ICU team's VAP diagnosis and therapy were justified, using clinical, microbiologic, and radiographic data at diagnosis and on day 3. Outcomes included the proportion of VAP events misdiagnosed as and treated for VAP on days 1 and 3 and risk factors for the continuation of antibiotics in patients without VAP after day 3.

RESULTS. Two hundred thirty-one events were identified as possible VAP by the ICUs. On day 1, 135 (58.4%) of them were determined to not have VAP by the committee. Antibiotics were continued for 120 (76%) of 158 events without VAP on day 3. After adjusting for acute physiology and chronic health evaluation II score and requiring vasopressors on day 1, sputum culture collection on day 3 was significantly associated with antibiotic continuation in patients without VAP. Patients without VAP or other infection received 1,183 excess days of antibiotics during the study.

CONCLUSIONS. Overdiagnosis and treatment of VAP was common in this study and led to 1,183 excess days of antibiotics in patients with no indication for antibiotics. Clinical differences between non-VAP patients who had antibiotics continued or discontinued were minimal, suggesting that clinician preferences and behaviors contribute to unnecessary prescribing.

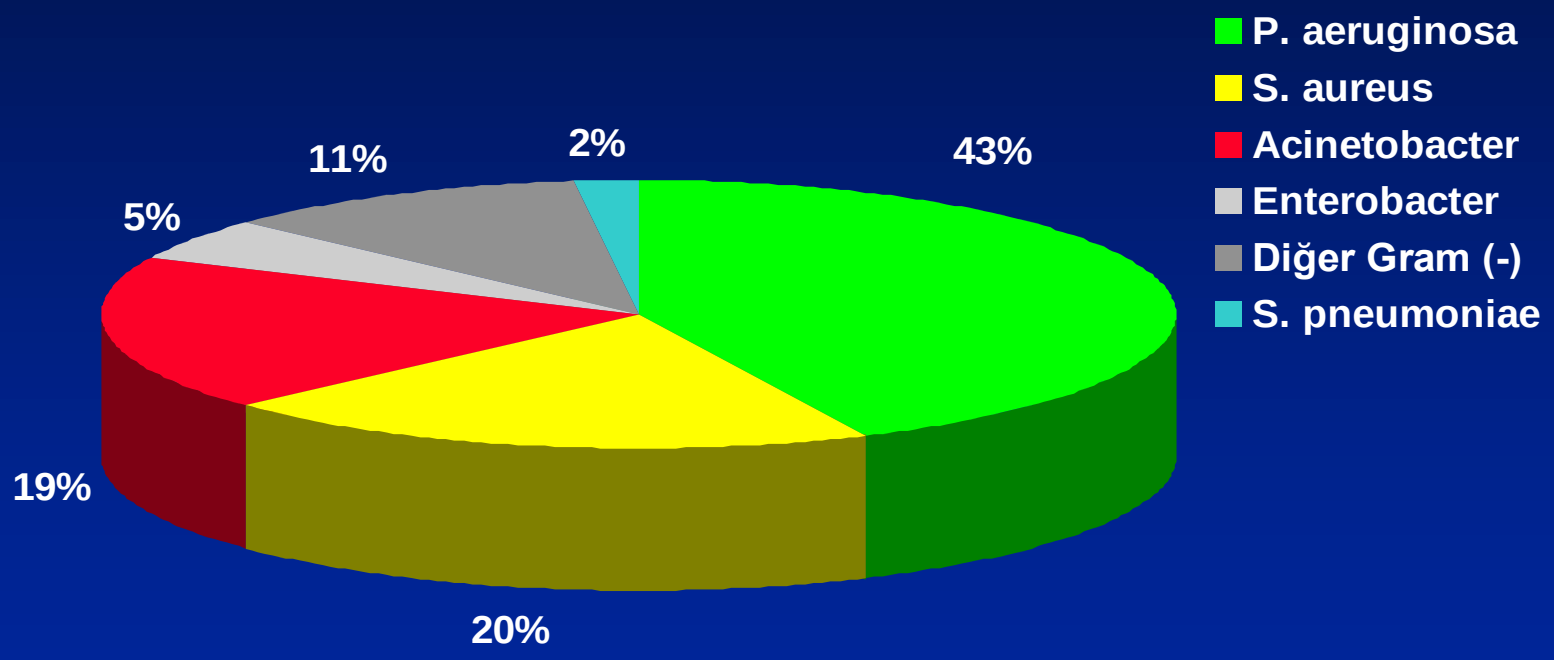
Infect Control Hosp Epidemiol 2014;35(3):278–284

Uygunsuz Antibiyotik Kullanımı (Mortalite)



Leibovici L, et al. J Intern Med 1998;244:379-386
Ibrahim EH, et al, Chest 2000;118:146–155
Valles J, et al. Chest 2003;123:1615–1624
Kollef M, et al. Chest 1999;115:462-74

Yetersiz Ampirik Tedavi Sonunda Etkenler



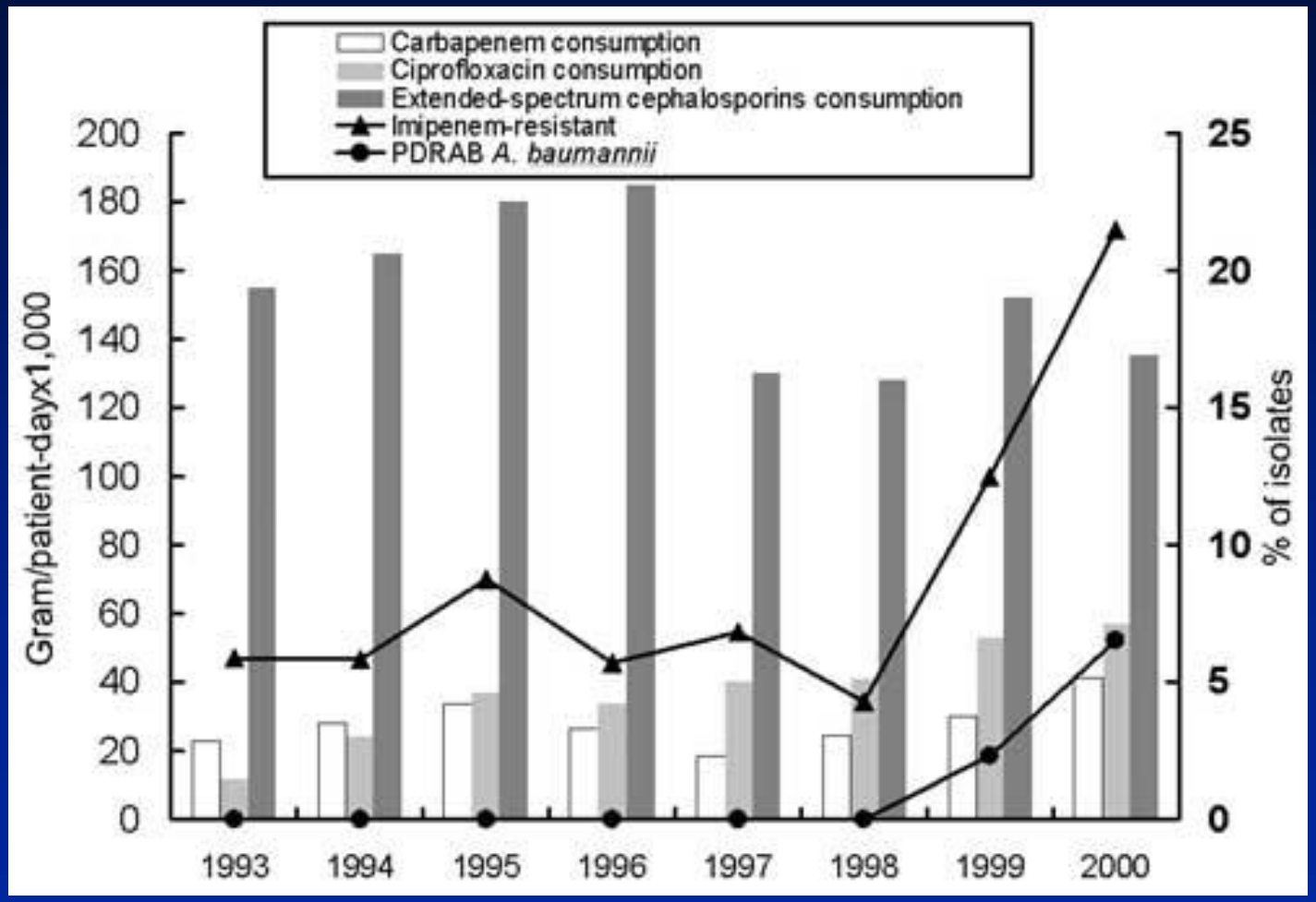
Alvarez-Lerma F. Intensive Care Med 1996;22:387

Ampirik tedavi etkene uygun olmalı !

- “Kültür”lü bir dayanağı olan
- Tamamen lokal verilere dayanan
- Dinamik
- Sıkı işbirliği içinde uygulanan
- “Erken başlanan ampirik tedavi

uygun ampirik tedavidir!!

Antibiyotik baskısına dikkat et



Hsueh PR, et al. Emerg Infect Dis 2002;8:827

K. pneumoniae (ESBL) Salgınları

Uygulama

- Seftazidim kullanımının kontrol altına alınması
- İnfeksiyon kontrol önlemleri
- Dirençli suşların tedavisinde imipenem

Sonuçlar

- K. pneumoniae insidansında azalma
- YBÜ'de polimiksin B ve sulbaktam dışında tüm antibiyotiklere karşı da dirence sahip olan imipeneme dirençli A. baumannii salgını

Go ES et al. Lancet 1994;344:1329-1332
Meyer KS et al. Ann Intern Med 1993;119:353-358
Urban C et al. Antimicrob Agents Chemother 1994;38:392-395

Hastanede “sorunlu” antibiyoterapi

	KAR	TZP	SEF	SCF
Antips	+	++	+	++
Anti Ab	++	-	+	++
ESBL	+++	+?	+?	+?
İBL	++	-	+	-
Direnç gelişimine etki	+++	-/+	+++	?
Ertapenem ? Tigesiklin ? Kolistin?				

Hastanede “sorunlu” antibiyoterapi

- **Kinolonlar:**

  Pnömoni, CAİ, NÜSİ (?)

  Kombinasyonlarda kullanım

  ?Tedavi sürecinde direnç gelişimi

  ?? Diğer gruplara direnç gelişimi

  ??? MRSA artışı

Karbapenem !!!

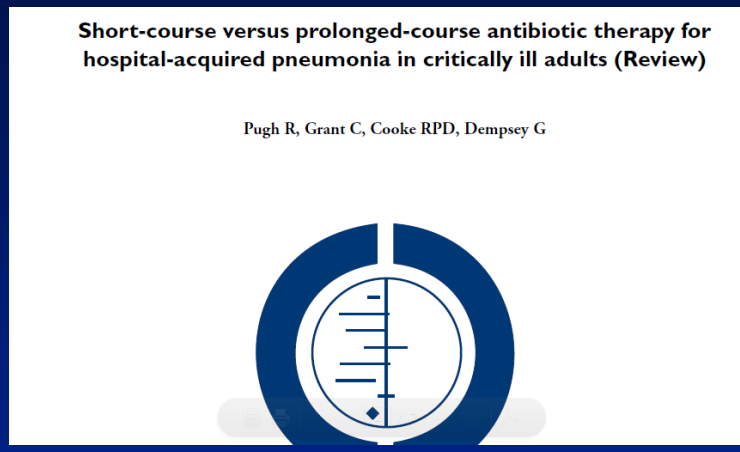
- GSBL = Karbapenem ?
- Ertapenem daha uygun bir karbapenem ?

- Karın içi, Cilt YD infeksiyonlarında Tigesiklin !?

Ampirik karbapenem için kriterler !

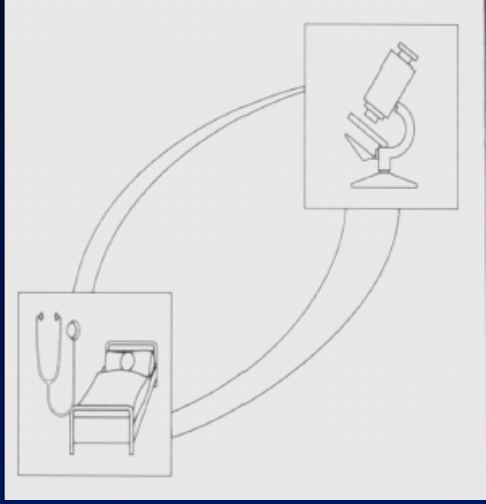
Antimikrobiyal tedaviyi kes(ebil) !!!

- Rehberler
- Prokalsitonin rehberliği(?)



- VAP (7 gün !)
- Karın içi sepsis (1-5 gün)

Laboratuvar !!!



Acil Gram !

Bakteri tür düzeyinde tanımlanmalı

Beta-laktamaz,Karbapenamaz

Mekanizma ?

MİK desteği

Sinerji testi ???

DOZ
(NP tedavi önerileri-IDSA)

Antibiyotik	Uygulama Önerisi
Sefepim	8-12 saatte bir 1-2 g
Seftazidim	8 saatte bir 2 g
İmipenem	6 saatte bir 500mg ya da 8 saatte bir 1g
Meropenem	8 saatte bir 1g
Piperasilin/Tazobaktam	6 saatte bir 4.5 g
Sefoperazon/Sulbaktam	12 saatte bir 2 g
Gentamisin*	7 mg/kg/gün (tek doz)
Tobramisin*	7 mg/kg/gün (tek doz)
Netilmisin*	7 mg/kg/gün (tek doz)
Amikasin*	20 mg/kg/gün (tek doz)
Levofloksasin	750 mg /gün
Siprofloksasin	8 saatte bir 400 mg
Vankomisin*	15 mg/kg her 12 saatte bir
Linezolid	12 saatte bir 600 mg

* Etkinlik ve yan etki yönünden serum düzeyleri ile izlenmesi önerilmektedir.

Farmakokinetik

Table 1
Summary of design and results for clinical studies of prolonged infusion (PI) of β-lactams.

Reference	Study design	Patients	Infection	Dosing regimen	PI findings
Arnold et al., 2013 [36]	Retrospective, single centre	503, ICU	Gram-negative bacteria	FEP or TZP or MEM 3-h inf. vs. FEP or TZP or MEM 30-min inf.	No difference in treatment success rates or mortality
Bauer et al., 2013 [37]	Retrospective, single centre	87, bacteraemia or pneumonia	*Pseudomonas aeruginosa*	FEP 2 g q8h 4-h inf. vs. FEP 2 g q8h 30-min inf.	Significantly lower mortality (20% vs. 3%)
Chastre et al., 2008 [20]	Prospective, multicentre, randomised	531, VAP	Gram-positive and -negative bacteria	DOR 500 mg q8h 4-h inf. vs. IMI 500 mg q6h 30-min inf. or IMI 1 g q8h 1-h inf.	Comparable clinical (68.3% vs. 64.8%) and microbiological (73.3% vs. 67.3%) cure rates; no difference in mortality (10.8% vs. 9.5%)
Dow et al., 2011 [29]	Retrospective, single centre	121, ICU	Gram-negative bacteria	TZP 3.375 g q8h or MEM 500 mg q6h 3- or 4-h inf. vs. TZP 3.375 g q6h or MEM 500 mg q6h 30-min inf.	No difference in mortality (12.4% vs. 20.7%)
Esterly et al., 2012 [32]	Retrospective, single centre	71, bacteraemia	*Acinetobacter baumannii*, *P. aeruginosa*, Enterobacteriaceae	IMI or MEM 3-h inf. vs. IMI or MEM 30-min inf.	No difference in mortality (28.6% vs. 24.1%)
Falagas et al., 2013 [38]	Meta-analysis, multicentre	1229, mixed infections	Gram-positive and -negative bacteria	TZP or IMI or MEM CI or EI vs. TZP or IMI or MEM 20–60-min inf.	Significantly lower mortality (RR = 0.59)
Itabashi, 2007 [28]	Prospective, single centre	42, severe pneumonia	Gram-positive and -negative bacteria	MEM 500 mg q12h 4-h inf. vs. MEM 500 mg q12h 1-h inf.	Significantly lower mortality (5.6% vs. 37.5%)
[illegible]	[illegible]	[illegible]	[illegible] ria	DOR 1 g q8h 4-h inf. × 7 days vs. IMI 1 g q8h 1-h inf. × 10 days	Clinical cure (45.6% vs. 56.8%) numerically lower and 28-day mortality numerically higher (21.5% vs. 14.8%) in DOR treatment arm
[illegible]	[illegible]	[illegible]	[illegible] ria	TZP 3.375 g q8h 4-h inf. vs. TZP 2.25–4.5 g q6–8 h 30-min inf.	Significantly lower 30-day mortality (19% vs. 38%)
[illegible]	[illegible]	[illegible]	[illegible]	TZP 3.375 g q8h 4-h inf. vs. TZP 3.375 g q4h or q6h 30-min inf.	Significantly lower mortality (12.2% vs. 31.6%) in severely ill

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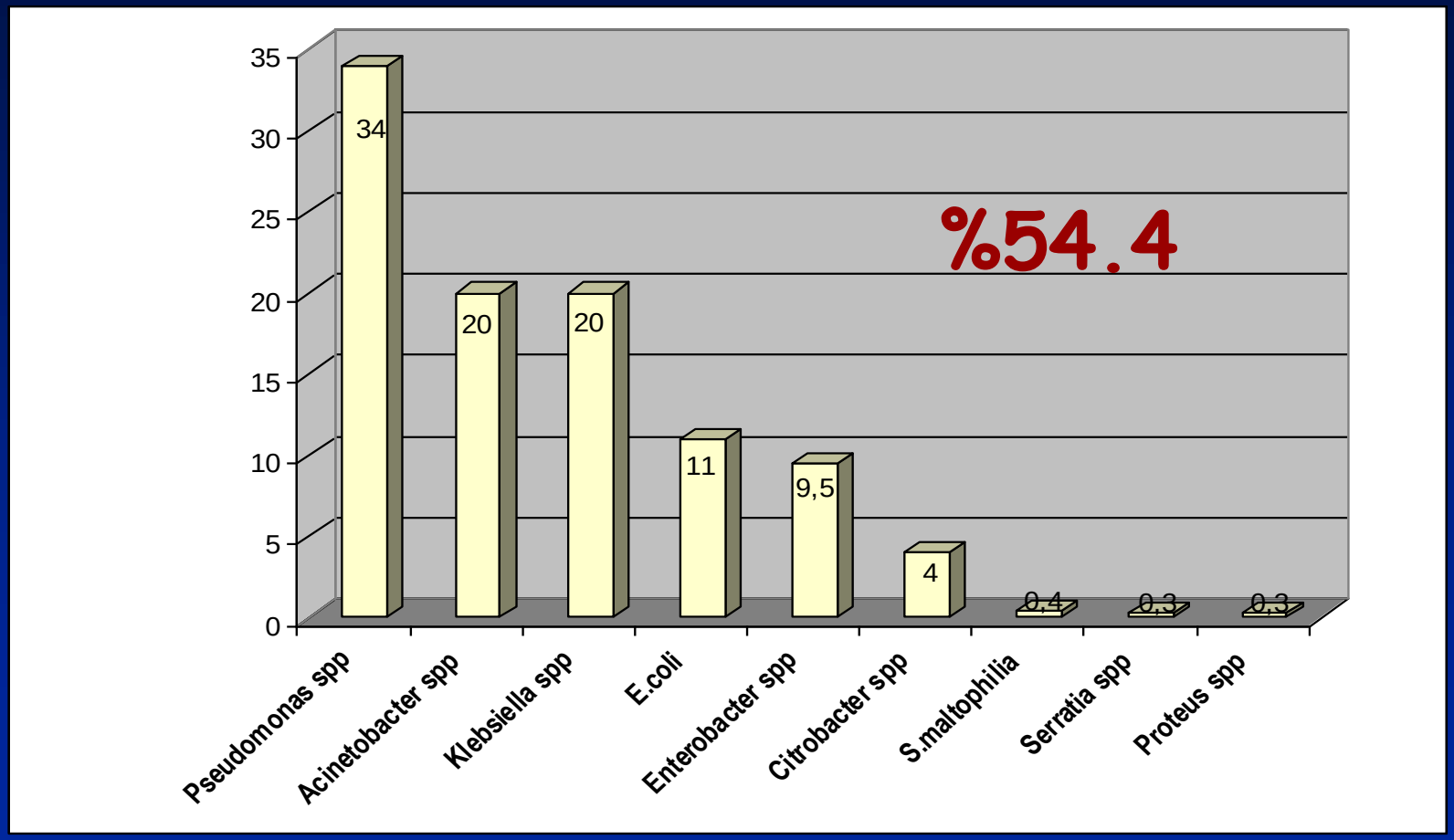
Review

Prolonging β-lactam infusion: A review of the rationale and evidence, and guidance for implementation

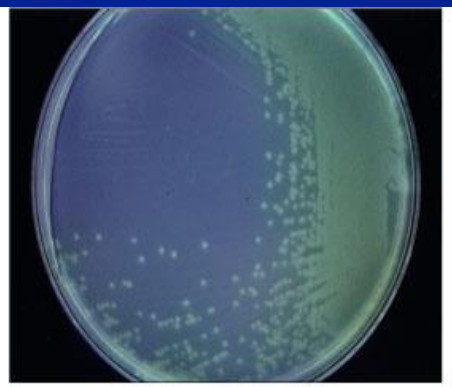
Shawn H. MacVane[a], Joseph L. Kuti[a], David P. Nicolau[a,b,*]

NFGNB'ler ve Ülkemiz YBÜ'lerinde Etkenlerin Dağılımı



Sorunlu mikroorganizmalar- Pseudomonas aeruginosa

- Çevre şartlara ve dezenfeksiyona dirençli
- Pnömoni, yara inf, ÜSİ,...
- Lavabolar, dezenfektanlar, kravat vb. giyecekler ile oluşan salgınlar olası
- Antibiyotik direnci önemli. Tedavi sırasında direnç gelişimi riski var.



© Elsevier 2004. Infectious Diseases 2e - www.idreference.com

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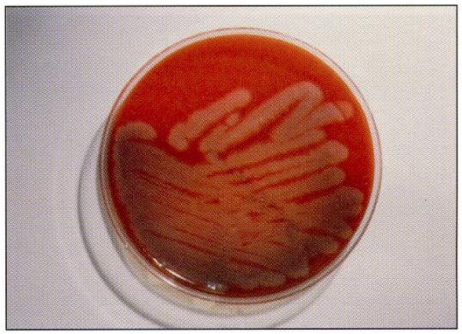


Plate 41 *Pseudomonas aeruginosa* on sheep blood agar with its typical large, dull, gray colonies that are beta hemolytic. Colonies typically have a "feathery edge" and may resemble ground glass.

P.aeruginosa direnç !

- Beta-laktamazlar(OXA-11,14,16, VİM-5,PER-1,OXA-10)

VIM, IMP-1
Özgümüş OB et al.
Microb Drug Resist 2007

VIM-2
Yakupoğulları Y et al.
J Antimicrob Chemother 2007

VIM-5
Bahar G et al.
J Antimicrob Chemother 2004

Table 1. Mutational resistances in *Pseudomonas aeruginosa*.

		Effect on strain, according to antipseudomonal drug								
Mechanism	Mutation site	Fq	Carb-Tic	Pip-Azl	Czid-Atm	Cpm-Cpr	Imi	Mero	Agl	Pm
Reduced affinity										
Of topoisomerase II	*gyrA*	r/R	—	—	—	—	—	—	—	—
Of topoisomerase IV	*parC*	r/R	—	—	—	—	—	—	—	—
Derepression of AmpC										
Partial	*ampD*	—	R	R	R	r	—	—	—	—
Total	*ampD* + other	—	R	R	R	R	—	—	—	—
Up-regulation										
Of MexAB-OprM	*nalB* at *mexR*; *nalC* at other	R/R	R	r/R	r/R	r/R	—	r	—	—
Of MexCD-OprJ	*nfxB*	r/R	r/R	r/R	r/R	R	—	r	—	—
Of MexEF-OprN	*nfxC* at *mexT*	r/R	r/R	r/R	r/R	r/R	r	r	—	—
Of MexXY-OprM		r/R	r/R	r/R	r/R	r/R	—	r	r/R	—
Reduced aminoglycoside transport		—	—	—	—	—	—	—	r/R	—
Loss of OprD	*oprD*; *nfxC* at *mexT*	—	—	—	—	—	R	r	—	—
Membrane changes		—	—	—	—	—	—	—	—	R

NOTE. Agl, aminoglycosides; Azl, azlocillin; Atm, aztreonam; Carb, carbenicillin, Czid, ceftazidime, Cpm, cefepime; Cpr, cefpirome; Fq, fluoroquinolone; Imi, imipenem; Mero, meropenem; Pip, piperacillin; Pm, polymyxin; r, reduced susceptibility; R, frank resistance, which may vary in its distinction from "r," according to the breakpoints adopted; Tic, ticarcillin.

Meta Analiz: Kombine Tedavi

- 64 çalışma, 7586 hasta
- Mortalite sıklıkları her iki grupta benzer
- Gram negatif ve P. aeruginosa'ya bağlı infeksiyonlarda kombine tedavinin üstünlüğü yok
- Direnç gelişimi açısından her iki grup arasında fark yok
- Klinik başarısızlık ve nefrotoksisite kombine tedavide daha fazla

Paul M. et al. BMJ 2004;328:668-772

Does combination antimicrobial therapy reduce mortality in Gram-negative bacteraemia? A meta-analysis

Nasia Safdar, Jo Handelsman, and Dennis G Maki

alone and in combination. The summary odds ratio was 0·96 (95% CI 0·70–1·32), indicating no mortality benefit with combination therapy. Subgroup analyses adjusting for year of publication, study design, and severity of illness did not change the results. Considerable heterogeneity was present in the main analyses. Analysis of only *Pseudomonas aeruginosa* bacteraemias showed a significant mortality benefit (OR 0·50, 95% CI 0·30–0·79). Our analysis does not support the routine use of combination antimicrobial therapy for Gram-negative bacteraemia, beyond settings where infection by *P aeruginosa* is strongly suspected or more than one drug would be desirable to assure in-vitro efficacy.

Lancet Infect Dis 2004; **4:** 519–27

P.aeruginosa Enfeksiyonlarında Tedavi

- **Ciddi enfeksiyonlar**
  Beta-laktam + Aminoglikozid veya Kinolon

- **Komplike Olmayan ÜSE**
  Monoterapi

P.aeruginosa

- İmipenem …..Duyarlı / Dirençli
  Meropenem …Dirençli/ Duyarlı

Porin defekti ?

Pompa sistemleri ?

Tedavi : Duyarlı bulunan (+)???

Acinetobacter

- Oportunistik patojen
- Virülansı düşük
- VİP ve kateter kolonizasyonu
- Dış membran geçirgenliği, PBP değişikliği, Beta-laktamazlar
- Çoklu AB direnci problemi
- Çevre kolonizasyonu !!!

A.baumannii - Direnç Mekanizmaları

- Beta-laktamazlar
  -Kromozomal sefalosporinazlar(AmpC)
  -PER-1, VEB-1
- Karbapenem direnci
  -Dış membran proteinlerinde azalma
  -PBP'lerde değişme
  -A,B ve D sınıfı karbapenemazlar
  IMP, VIM
  OXA-23,24,25,26,27,40
  Van Looveren M et al. Clin Microbiol Infect 2004
  Vahaboğlu H et al. Antimicrob Agents Chemother 1997

OXA-58, OXA-23
Gür D et al. J Med Microbiol 2008

- OXA-51, OXA-58
  Vahaboğlu H et al. J Antimicrob Chemother 2006

Acinetobacter

- Tedavi sürecinde direnç yok

- Sulbaktam etkili

  SCF? SAM?

  Laboratuvarda ne yapılmalı?

A.baumannii : SCF duyarlı ??

A.baumannii - Tedavi

- **Etkili antibiyotikler :**
  -Karbapenemler
  -Ampisilin/sulbaktam
  -Sefoperazon/sulbaktam
  -Polimiksin B
  -Polimiksin E (KOLİSTİN)
  -Amikasin, tobramisin
  -Seftazidim
  -Siprofloksasin, Levofloksasin, Ofloksasin

Urban C et al. Clin Infect Dis 2003
Van Looveren M et al. Clin Microbiol Infect 2004

A.baumannii - Tedavi

- Monoterapi ile kombinasyonu karşılaştıran klinik çalışma yok

  Cisneros JM et al. Clin Microbiol Infect 2002

- Ciddi enfeksiyonlarda ve/veya altta yatan hastalığı olan hastada Karbapenem direncinde kombinasyon tedavisi öneriliyor ?

  HETEROREZİSTANS !

  Urban C et al. Clin Infect Dis 2003
  ATS Guideline. Am J Respir Crit Care Med 2005
  Murray CK et al. Curr Opin Infect Dis 2005

- Bakteriyemilerde imipenem veya ampisilin/sulbaktam monoterapisi etkili

  Jellison TK et al. Pharmacotherapy 2001

- İmipenem dirençli *A.baumannii* infeksiyonu - Ampisilin/Sulbaktam %67.5 klinik yanıt

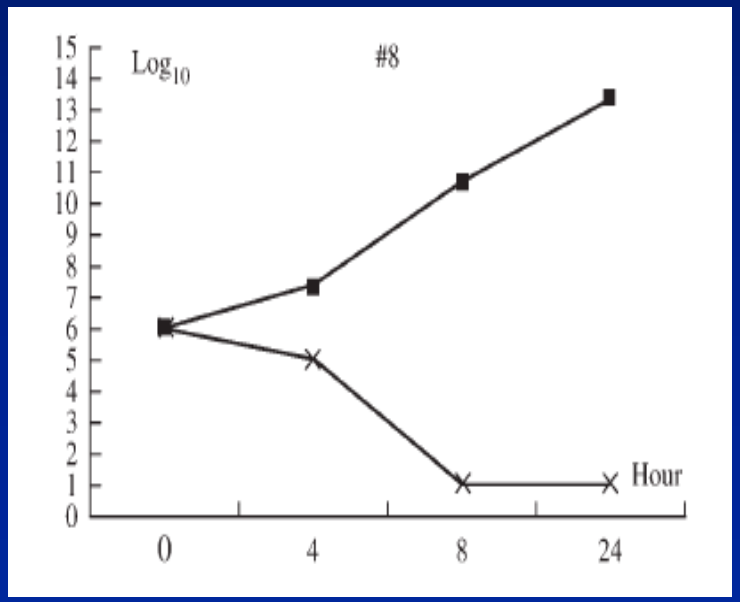
  Levin AS et al. Int J Antimicrob Agents 2003

- Yüksek doz Ampisilin/Sulbaktam, Kolistin kadar etkili

  Betrosian AP et al. J Infection 2008

Sulbaktam ile kombinasyon

- **Karbapenem + Sulbaktam in vitro etkili fakat klinik olarak yeterli yanıt yok**
  Lee CM et al. Scand J Infect Dis 2005



Song JY et al. J Antimicrob Chemother 2007

Sulbaktam + Kolistin

- **Meropenem ve sulbaktam dirençli *A. baumannii* menenjitinde tedaviye kolistin eklenmesi serum ve BOS bakterisidal aktivitesini artırmış**

- ***A. baumannii* : Kolistin + Sulbaktam, tek başına kolistine ve diğer kombinasyonlara göre daha etkili**

Lee CH et al. Microb Drug Resist 2008

Acinetobacter için kombinasyon sonuçları

Sinerji veya aditif etki

- A/S + DOR / IMP (44%)
- IMP + COL (38%)
- DOR + COL (31%)
- RIF + A/S (44%)

COL + TGC ve COL + RIF sinerjistik değil ?

- Kolistin + rifampisin
- Kolistin + amikasin
- Kolistin + imipenem
- Kolistin + doksisiklin

sinerjik…

Shields RK et al. ICAAC 2009 E-1458

Giamarellos-Bourboulis E et al. Diagn Microbiol Infect Dis 2001

Timurkaynak F et al. Int J Antimicrob Agents 2006

Haddad FA et al. Eur J Clin Microbiol Infect Dis 2005

Bratu S et al. Eur J Clin Microbiol Infect Dis 2005

YBÜ Acinetobacter CTF deneyimi

- 48 A.baumannii infeksiyonunda SCF kullanılmış (+ netilmisin, amikasin)

  19 bakteriyemi..... 6/19 başarı(% 31.5)

  26 pnömoni.....23/26 başarı(% 88.4)

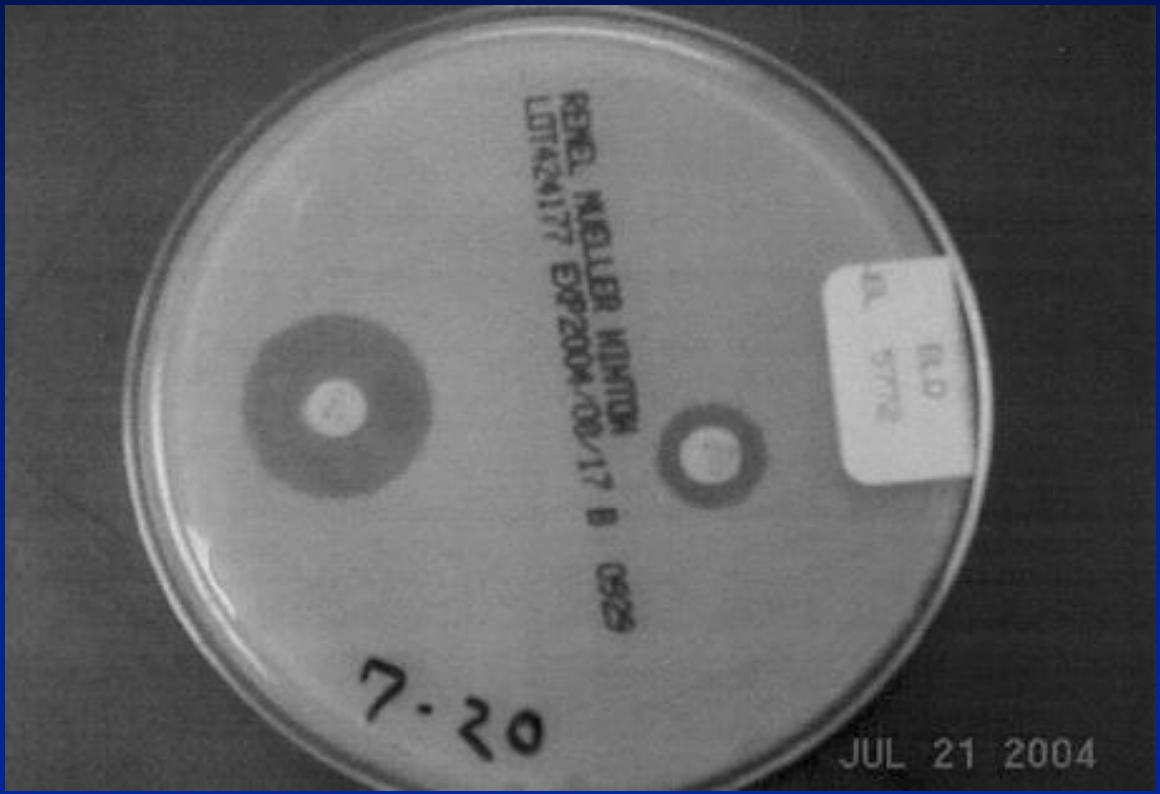
  3 CAİ..... 3/3 başarı (%100)

- 23 A.baumannii infeksiyonunda karbapenem (yarısı monoterapi)

  17 bakteriyemi..6/17 başarı (%35.2)

  6 pnömoni.....4/6 başarı (% 66.6)

Fatal *Acinetobacter baumannii* Infection with Discordant Carbapenem Susceptibility



Stenotrophomonas maltophilia

- **TMP/SMX tedavisi (15 mg/kg TMP)**
- **TMP/SXT dışı tedaviler:**

Siprofloksasin monoterapisi ya da kombinasyonu %90

Seftriakson ya da seftazidim kombinasyonu %75

Falagas ME et al. J Antimicrob Chemother 2008

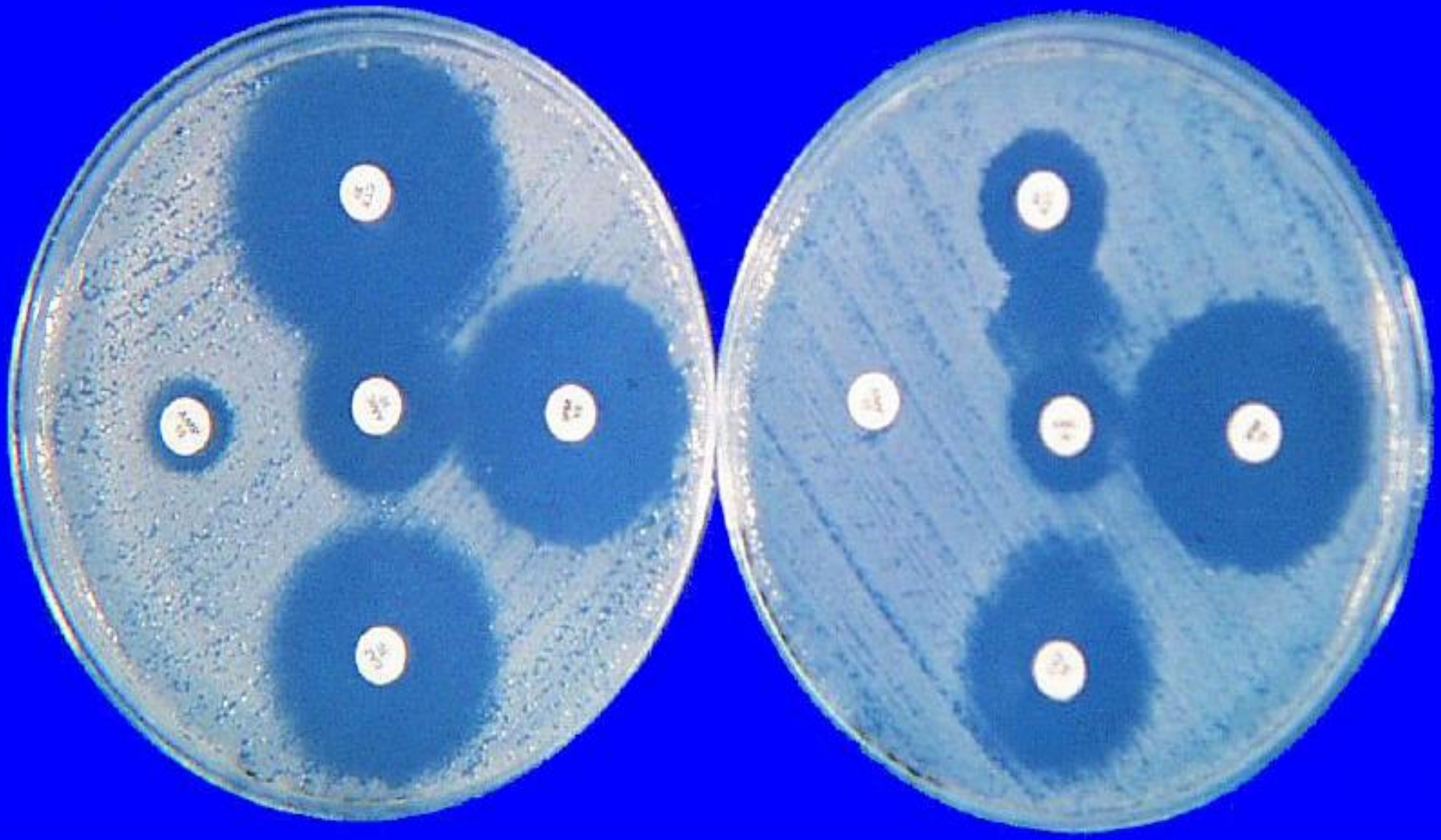
- **Ciddi enfeksiyonlar**

TMP/SMX + Tik/Klav,

TMP/SMX + Florokinolon

Polimiksin + Rifampin

Nyc O. Folia Microbiol 2010



K. pneumoniae

K. pneumoniae
ESBL (+)

GSBL: “Sonun Başlangıcı”

JOURNAL OF CLINICAL MICROBIOLOGY, June 2001, p. 2206–2212 Vol. 39, No. 6
0095-1137/01/$04.00+0 DOI: 10.1128/JCM.39.6.2206–2212.2001
Copyright © 2001, American Society for Microbiology. All Rights Reserved.

Outcome of Cephalosporin Treatment for Serious Infections Due to Apparently Susceptible Organisms Producing Extended-Spectrum β-Lactamases: Implications for the Clinical Microbiology Laboratory

DAVID L. PATERSON,[1,2] WEN-CHIEN KO,[3] ANNE VON GOTTBERG,[4] JOSE MARIA CASELLAS,[5] LUTFIYE MULAZIMOGLU,[6] KEITH P. KLUGMAN,[4] ROBERT A. BONOMO,[7] LOUIS B. RICE,[7] JOSEPH G. McCORMACK,[2] AND VICTOR L. YU[1]*

Infectious Disease Division, University of Pittsburgh Medical Center, Pittsburgh, Pennsylvania[1]; Department of Medicine, University of Queensland, Brisbane, Australia[2]; Department of Medicine, National Cheng Kung University Medical College, Tainan, Taiwan[3]; South African Institute of Medical Research, Johannesburg, South Africa[4]; Departmento de Infectologia y Microbiologia, Sanatorio San Lucas, Buenos Aires, Argentina[5]; Department of Microbiology, Marmara University, Istanbul, Turkey[6]; and Infectious Disease Section, VA Medical Center, Cleveland, Ohio[7]

TABLE 4. Outcome of serious infections due to ESBL-producing organisms is inferior when the MIC of antibiotics is 2 to 8 μg/ml

MIC (μg/ml)	% (no./total) of patients who:	
	Experienced failure of cephalosporin therapy	Died within 14 days of bacteremia
8	100 (6/6)	33 (2/6)
4	67 (2/3)	0 (0/3)
2	33 (1/3)	0 (0/3)
≤1	27 (3/11)	18 (2/11)
Total[a]	54 (15/28)	

[a] Includes five patients with whose isolates for which MICs were recorded simply as 0.5 to 4 mg/liter.

CLINICAL MICROBIOLOGY REVIEWS, Oct. 2005, p. 657–686 Vol. 18, No. 4
0893-8512/05/$08.00+0 doi:10.1128/CMR.18.4.657–686.2005
Copyright © 2005, American Society for Microbiology. All Rights Reserved.

Extended-Spectrum β-Lactamases: a Clinical Update

David L. Paterson[1]* and Robert A. Bonomo[2]

Infectious Disease Division, University of Pittsburgh Medical Center, Pittsburgh, Pennsylvania,[1] and Infectious Disease Division, Louis Stokes VA Medical Center, Cleveland, Ohio[2]

TABLE 3. Recommended treatment for infections with ESBL-producing organisms

Infection type	Therapy of choice	Second-line therapy
Urinary tract infection	Quinolone[a]	Amoxicillin/clavualante
Bacteremia	Carbapenem	Quinolone[a]
Hospital-acquired pneumonia	Carbapenem	Quinolone[a]
Intra-abdominal infection	Carbapenem	Quinolone[a] (plus metronidazole)
Meningitis	Meropenem	Intrathecal polymyxin B

[a] If the organism is quinolone susceptible.

GSBL CLSI 2010…

- CTX: >25mm
- CRO: > 23 mm
- CAZ: >20 mm
- FEP: > 17 mm

Duyarlı bildirin !!!

- Duyarlı ise MİK sonuçları uygunsa sefalosporin veririm!
- Karbapenem kullanımında bu grupta ETP daha uygun ?
- Tigesiklin !

Enterobacter cloacae

İBL (+) (CLSI)

- Enterobacter spp
- Citrobacter spp
- Serratia spp

lll.kuşak sefalosporinlere tedavi sırasında cevap geliştirebilir!

- P.aeruginosa uzun süreli tedavide tüm antibiyotiklere direnç geliştirebilir !

İBL (+) enterik bakteriler

- Ciddi infeksiyonlarda 3.kuşak sefalosporin kullanılmamalıdır !?
- Beta-laktamaz inhibitörleri güvenilmez !!
- Sefepim seçilebilir !!!

  MİK 4-8 mg/L ise dikkat
- ESBL varlığı atlanabilir ?!

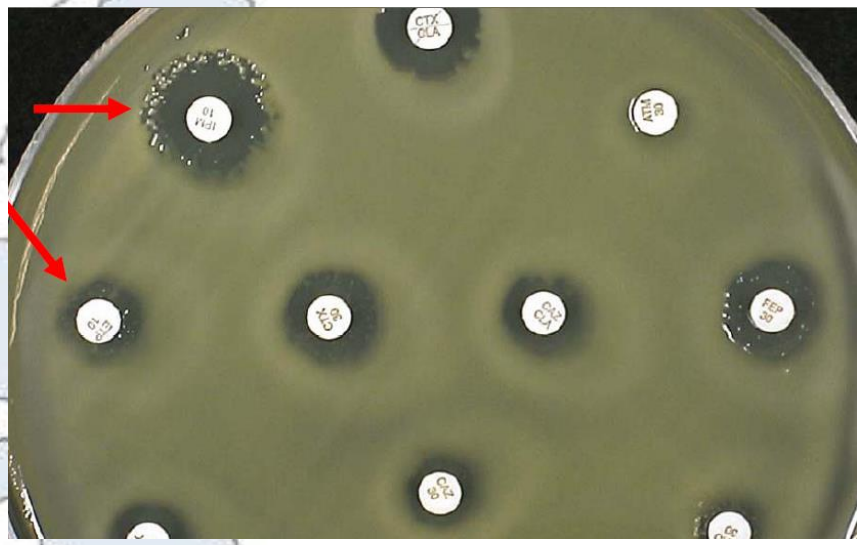
KARBAPENEM sıklıkla tercih ediliyor !

Proportion of carbapenem-resistant *Klebsiella pneumoniae* isolates in EARSS participating countries, 2006.

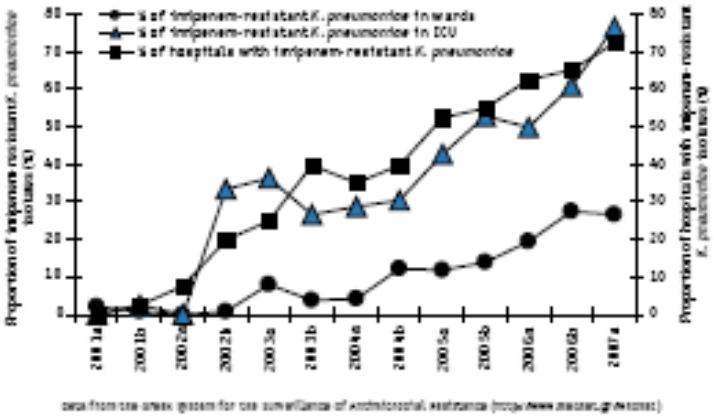
legend

- No Data
- < 1%
- 1-5 %
- 5-10%
- 10-25%
- 25-50%

Israel



Trends in proportion of imipenem-resistant *Klebsiella pneumoniae* isolates in hospitals in Greece, 2000-2006



Surveillance System (EARSS), http://www.rivm.nl/earss/database/

Karbapenemaz !

- Metallo beta laktamazlar (VIM, IPM, NDM-1,…)
- KPC enzimleri

(K.pneumoniae …ABD)

- TEM, SHV ya da ampC enzimler +

  OMP defektleri
- OXA + OMP defektleri
- ???

Country	Types of detected carbapenemase			
Author/year	OXA	VIM	KPC	NDM-1
Lebanon				
Matar et al./2008	48			
Matar et al./2010	48			
El-Herte et al./2012	48			+
Turkey				
Poirel et al./2004	+1,47,48			
Gaçar et al./2005		5		
Aktaş et al./2008	48			
Gülmez et al./2008	48			
Carrer et al./2008	48			
Carrer et al./2010	48			
Egypt				
Cuzon et al./2009	48			
Kuwait				
Jamal et al./2011				+
Oman				
Poirel et al./2010				+
Saudi Arabia				
Guerin et al./2005	48			
Israel				
Navon-Venezia et al./2006			2	
Leavitt et al./2007			3	
Lopez et al./2010			3	
Greece				
Giakkoupi et al./2003		1		
Loli et al./2006		1		
Ikonomidis et al./2007		4		
Ikonomidis et al./2007		+1/+2		
		12		
Psichogiou et al./2008		1		
Tsakris et al./2008			2	
Tokatlidou et al./2008		12		
Giakkoupi et al./2009		1	2	
Giakkoupi et al./209			2	
Pournaras et al./2009			2	
Hawser et al./2009			KPC not subtyped	
Pournaras et al./2010		19	2	
Kontopoulou et al./2010			2	
Zioga et al./2010		1	2	

Karbapenem direnci

Karbapenemaz ?

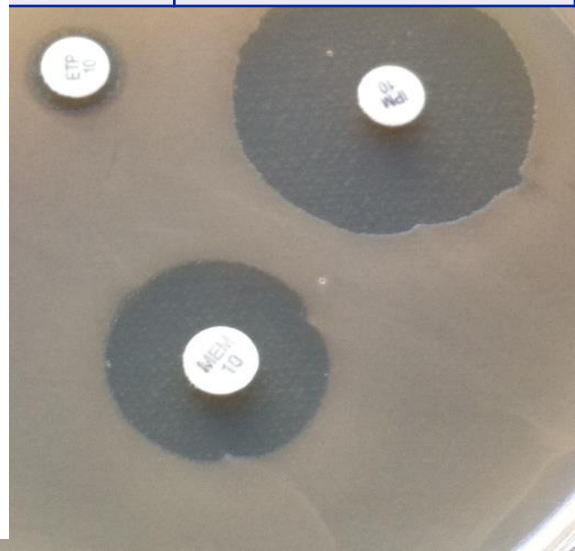
- Hodge testi ? Gereksiz !
- IMP, MEM MİK değeri
- ETP ? MEM ? İle tarama !
- Duyarlı olan verilebilir ?

Antibiyotik	Sonuç
Sefotaksim	R
Seftazidim	R
İmipenem	S
Ertapenem	R
Amikasin	S
Sefepim	R
Kolistin	S ?
Tigesiklin	S ?

Table 1. Clinical breakpoints and screening cut-off values for carbapenemase-producing Enterobacteriaceae (according to EUCAST methodology).

Carbapenem	MIC (mg/L)		Disk diffusion zone diameter (mm) with 10 µg disks	
	S/I breakpoint	Screening cut-off	S/I breakpoint	Screening cut-off
Meropenem[1]	≤2	>0.12	≥22	<25[2]
Imipenem[3]	≤2	>1	≥22	<23
Ertapenem[4]	≤0.5	>0.12	≥25	<25

[1]Best balance of sensitivity and specificity



Clinical Microbiology Reviews

Carbapenemases in Klebsiella pneumoniae and Other Enterobacteriaceae: an Evolving Crisis of Global Dimensions

L. S. Tzouvelekis, A. Markogiannakis, M. Psichogiou, P. T. Tassios and G. L. Daikos

Clin. Microbiol. Rev. 2012, 25(4):682. DOI: 10.1128/CMR.05035-11.

TABLE 5 Results of carbapenem monotherapy in 50 CPE-infected patients from 15 studies[a]

MIC of carbapenem (μg/ml)	No. of patients	No. of successes	No. of failures	% Failure
≤1	17	12	5	29.4
2	12	9	3	25.0
4	7	5	2	28.6
8	6	4	2	33.3
Subtotal	42	30	12	28.6[b]
>8	8	2	6	75.0[b]
Total	50	32	18	36

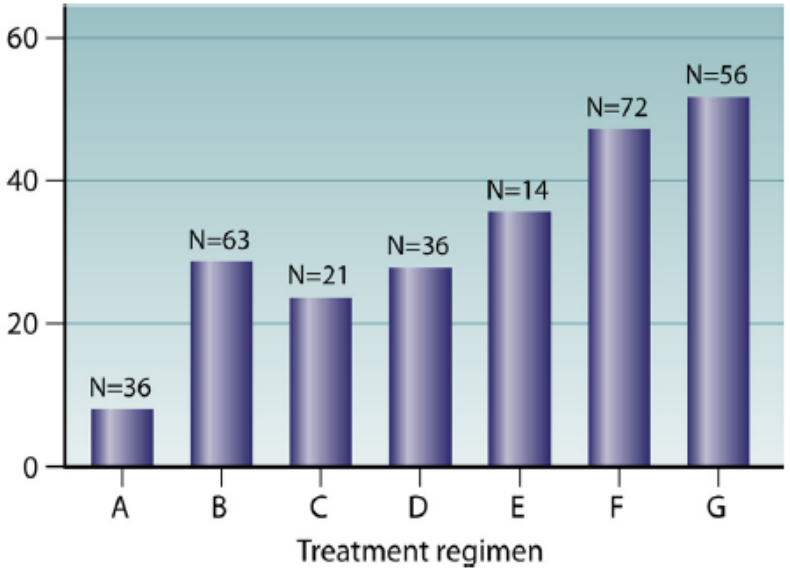


FIG 2 Outcomes of infections caused by carbapenemase-producing *Klebsiell pneumoniae*, according to treatment regimen. Regimen A, combination ther apy with ≥2 active drugs, one of which was a carbapenem; regimen B, combi nation therapy with ≥2 active drugs, not including a carbapenem; regimen C monotherapy with an aminoglycoside; regimen D, monotherapy with a car bapenem; regimen E, monotherapy with tigecycline; regimen F, monotherap

Tigesiklin

- Endikasyonlarında kullanalım (İntraabdominal, Deri Yumuşak doku)
- Kolistin + Tigesiklin kombinasyonları genellikle sinerjik değil
- Özellikle Ab için olumsuz deneyimler !
- Tigesikline direnç gelişimi hızlı
- Üçlü kombinasyonlarda yer alabilir?

KPC(+) *K. pneumoniae* -Tedavi

- 41 bakteriyemi
- 28 günlük mortalite %39
- Kombinasyon – mortalite 2/15(%13.3)
- Monoterapi – mortalite 11/19(%57.8), p=0.01

- En sık kombinasyon
  -Karbapenem + Kolistin
  -Karbapenem + Tigesiklin

- Kombinasyon tedavisi(kesin tedavi olarak) yaşamın devamı açısından bağımsız koruyucu faktör (OR 0.07, p=0.02)

Qureshi Z et al. Antimicrob Agents Chemother 2010

Kolistin (Özet)

- Karbapenem direncinde KOLİSTİN bir seçenek (tek seçenek)
- Klinik olarak olumlu veri var
- Dozun yüksek olması ve üç dozda verilmesi direnç gelişmesi açısından daha az riskli !
- Heterorezistans nedeniyle monoterapi ?
  (özellikle Ab için veri çok)

- Kolistin + Karbapenem(en sık kullanılan)
- Kolistin + Sulbaktam
- Kolistin + Sefepim veya Beta-laktam olumlu veriler !!!

- Kolistin + Rifampisin
  -Nefrotoksisite
- Kolistin + Aminoglikozid
  -AG: Akciğerlere geçişi zayıf?
  -Nefrotoksisite

Kolistin (Özet)

- Pnömonilerde inhalasyon tedavisi (?)
- Menenjitlerde intraventriküler/intratekal tedavi etkili
- Karaciğer yetmezliğinde doz ayarlamasına gerek yok
- Böbrek yetmezliğinde dozu ayarla
- Toksisite riski var!

Nefrotoksik ve nörotoksik !!!

Yükleme ve Yüksek Doz: Klinik Sonuç

- 300 mg yükleme – 2x150 mg idame
- 28 atak, 18 KDE ve 10 VİP
- *A.baumannii(*13), *K.pneumoniae*(13), *P.aeruginosa*(2)
- 14 monoterapi, 14 kombinasyon

  (AG veya Karbapenem)
- Klinik kür: %82.1
- Akut böbrek hasarı %17.8

Dalfino L et al. Clin Infect Dis 2012

Multidrug-resistant bacteria: what is the threat?

Matteo Bassetti[1] and Elda Righi[1]

[1]*Infectious Diseases Division, Santa Maria Misericordia University Hospital, Udine, Italy*

Table 3. Modification of the initial therapy due to colonization/previous infection with resistant bacteria

Resistant bacteria	Primary choice	Secondary choice
MRSA	Daptomycin or linezolid	Vancomycin
VRE	Daptomycin or linezolid	Tigecycline
ESBL	Meropenem	Ertapenem
Carbapenemase-producing Enterobacteriaceae	High-dose meropenem (6 g/d) + tigecycline + colistin	Tigecycline + gentamicin + colistin
MDR *P aeruginosa*	Piperacillin-tazobactam + amikacin	Piperacillin-tazobactam + colistin
MDR *Acinetobacter baumannii*	Colistin + rifampin	Tigecycline + colistin
Stenotrophomonas maltophilia	Trimetoprim-sulfamethoxazole	Quinolone or tigecycline

Clinical Experience of Colistin-Glycopeptide Combination in Critically Ill Patients Infected with Gram-Negative Bacteria

Nicola Petrosillo,[a] Maddalena Giannella,[a] Massimo Antonelli,[b] Mario Antonini,[c] Bruno Barsic,[d] Laura Belancic,[d] Cagkan Inkaya A.,[e] Gennaro De Pascale,[b] Elisabetta Grilli,[a] Mario Tumbarello,[f] Murat Akova[e]

2nd Division of Infectious Diseases[a] and Department of Intensive Care Unit and Anaesthesia,[c] National Institute for Infectious Diseases Lazzaro Spallanzani, Rome, Italy; Department of Intensive Care and Anesthesiology[b] and Institute of Infectious Diseases,[f] Università Cattolica del Sacro Cuore, Rome, Italy; School of Medicine, University of Zagreb, Hospital for Infectious Diseases, Zagreb, Croatia[d]; Department of Medicine, Section of Infectious Diseases, Hacettepe University School of Medicine, Ankara, Turkey[e]

A colistin-glycopeptide combination (CGC) has been shown *in vitro* to be synergistic against multidrug-resistant Gram-negative bacteria (MDR GNB), especially *Acinetobacter baumannii*, and to prevent further resistance. However, clinical data are lacking. We carried out a retrospective multicenter study of patients hospitalized in intensive care units (ICUs) who received colistin for GNB infection over a 1-year period, to assess the rates of nephrotoxicity and 30-day mortality after treatment onset among patients treated with and without CGC for ≥48 h. Of the 184 patients treated with colistin, GNB infection was documented for 166. The main causative agents were MDR *A. baumannii* (59.6%), MDR *Pseudomonas aeruginosa* (18.7%), and carbapenem-resistant *Klebsiella pneumoniae* (14.5%); in 16.9% of patients, a Gram-positive bacterium (GPB) coinfection was documented. Overall, 68 patients (40.9%) received CGC. Comparison of patients treated with and without CGC showed significant differences for respiratory failure (39.7% versus 58.2%), ventilator-associated pneumonia (54.4% versus 71.4%), MDR *A. baumannii* infection (70.6% versus 52%), and GPB coinfection (41.2% versus 0%); there were no differences for nephrotoxicity (11.8% versus 13.3%) and 30-day mortality (33.8% versus 29.6%). Cox analysis performed on patients who survived for ≥5 days after treatment onset showed that the Charlson index (hazard ratio [HR], 1.26; 95% confidence interval [CI], 1.01 to 1.44; $P = 0.001$) and MDR *A. baumannii* infection (HR, 2.51; 95% CI, 1.23 to 5.12; $P = 0.01$) were independent predictors of 30-day mortality, whereas receiving CGC for ≥5 days was a protective factor (HR, 0.42; 95% CI, 0.19 to 0.93; $P = 0.03$). We found that CGC was not associated with higher nephrotoxicity and was a protective factor for mortality if administered for ≥5 days.

- February 2014 Antimicrobial Agents and Chemotherapy p. 851–858

Kolistini çok kullanmak?

NEFROTOKSİSİTE

Eski çalışmalar(1962-1977)
Genellikle IM verilmi
Yüksek dozlar

%10.5-50(%20.2-%36)

- Yeni çalışmalar
- Nefrotoksisite tanımında farklılıklar
  Kolistin %14-18.6
- Doza bağımlı, membran permeabilite artışı, akut tübüler nekroz

- NÖROTOKSİSİTE
- Eski çalışmalar

  Parestezi %7.3-27

  Apne

  Nöromuskuler blok

- Yeni çalışmalar

Nörotoksisite yok ???

Falagas ME et al. Critical Care 2006

Kolistine Dirençli Bakteriler

- *Serratia* spp.
- *Proteus* spp.
- *Providencia* spp.
- *Burkholderia cepacia*
- *Morganella* spp.
- *Moraxella catarrhalis*

- Kolistine direnç !
- Heterorezistans A.baumannii (+)

Infection due to colistin-resistant *Enterobacteriacae* in critically-ill patients

Musa Abubakar Garbati[1], Aref Bin Abdulhak[2], Kamaldeen Baba[3], Hussam Sakkijha[4]

[1]*Section of Infectious Diseases, Department of Medicine, King Fahad Medical City, Riyadh, Saudi Arabia*
[2]*Internal Medicine Department,School of Medicine, University of Missouri-Kansas City, Kansas City, MO, USA.*
[3]*Department of Clinical Microbiology, King Fahad Medical City, Riyadh, Saudi Arabia*
[4]*Department of Pulmonary and Critical Care Medicine, King Fahad Medical City, Riyadh, Saudi Arabia*

J Infect Dev Ctries 2013; 7(10):713-719.doi:10.3855/jidc.2851

Eski/yeni çözüm?

Could chloramphenicol be used against ESKAPE pathogens? A review of *in vitro* data in the literature from the 21st century

February 2014, Vol. 12, No. 2 , Pages 249-264 (doi:10.1586/14787210.2014.878647)

The widespread use of antibiotics has been associated with the emergence of antimicrobial resistance among bacteria. 'ESKAPE' (*Enterococcus faecium, Staphylococcus aureus, Klebsiella pneumoniae, Acintobacter baumannii, Pseudomonas aeruginosa* and *Enterobacter* spp.) pathogens play a major role in the rapidly changing scenario of antimicrobial resistance in the 21st century. Chloramphenicol is a broad spectrum antibiotic that was abandoned in developed countries due to its association with fatal aplastic anemia. However, it is still widely used in the developing world. In light of the emerging problem of multi-drug resistant pathogens, its role should be reassessed. Our paper reviews *in vitro* data on the activity of chloramphenicol against ESKAPE pathogens. Susceptibility patterns for Gram-positives were good, although less favorable for Gram-negatives. However, in combination with colistin, chloramphenicol was found to have synergistic activity. The risk-benefit related to chloramphenicol toxicity has not been analyzed. Therefore, extra precautions should be taken when prescribing this agent.

FOSFOMİSİN (IV)

31 çalışmanın gözden geçirilmesi…

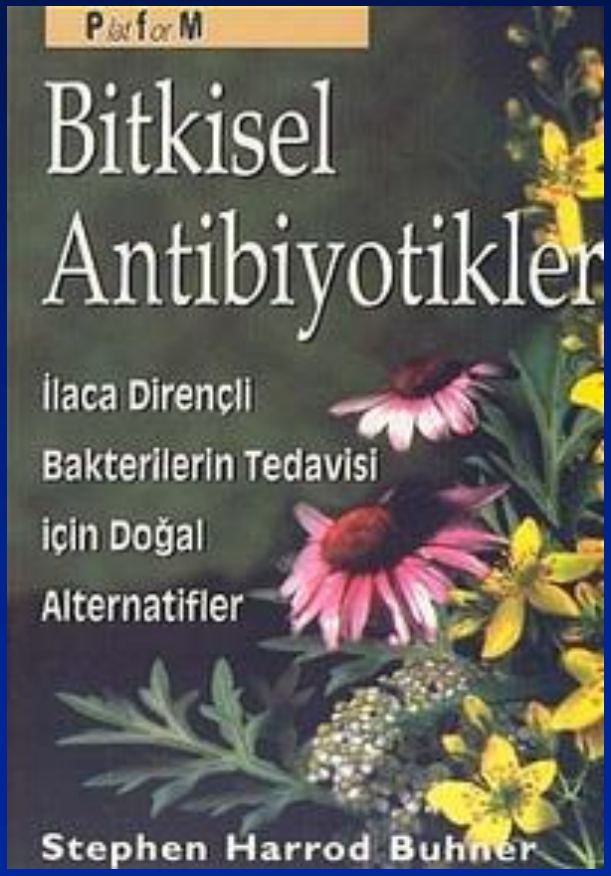
- Günlük doz 2-24 g/gün, 6-8 saatte bir
- 5-21 gün
- Tek başına veya kombinasyon
- Klinik başarı %81.2

Falagas ME et al. Clin Infect Dis 2008

Parezistan Ab

? ? ?

? ?



Gelecek Çözüm-1

- Yeni antibiyotikler ???

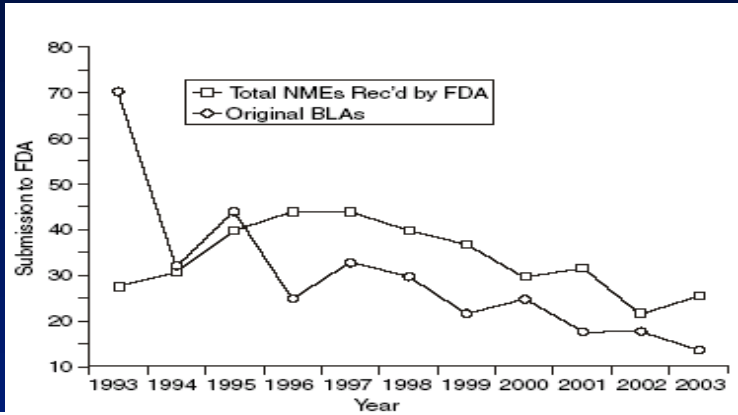


TABLE 8 Experimental β-lactamase inhibitors active against carbapenemases from *Enterobacteriaceae*

Inhibitor	Compound type	Inhibition spectrum (β-lactamase classes)	Susceptible carbapenemases[a]
BLI-489	Penem	A, C, D	KPC type
J-110,411 and J-111,225	1-β-Methyl carbapenem	A, C, B	IMP type
Mercaptomethyl sulfones	C-6-substituted penicillin sulfone	B	VIM and IMP types
2,3-(*S*,*S*)-Disubstituted succinic acids	Succinic acid	B	IMP type
Thiomandelic acids	Thiol	B	VIM and IMP types
Avibactam (NLX104)	Diazabicyclo-octanone	A, C, D	KPC type

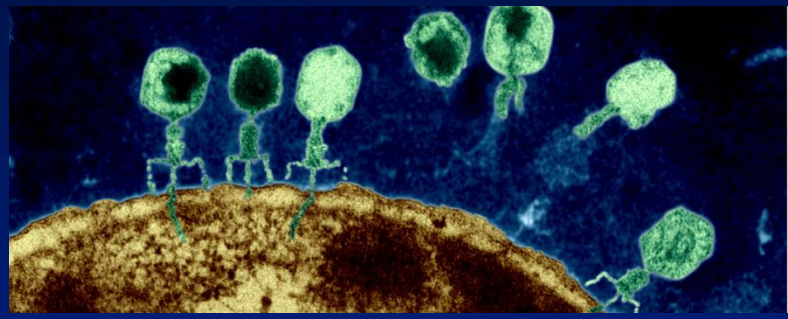
[a] Only carbapenemase types with documented susceptibility to the respective inhibitor are included.

TABLE 7 Experimental antimicrobial agents active against carbapenemase-producing *Enterobacteriaceae*

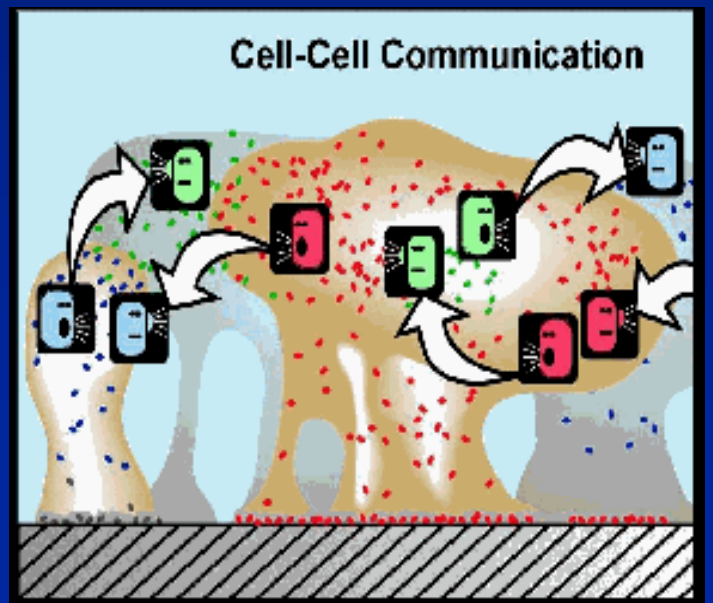
Drug	Compound type	Relevant target
BAL30072	Siderophore-containing sulfactam	*Enterobacteriaceae*, including MβL producers
Plazomicin (ACHN-490)	Sisomicin derivative	Gram-negative organisms, including carbapenemase producers
GSK2251052	Leucyl-tRNA synthetase inhibitor	Gram-negative organisms, including carbapenemase producers

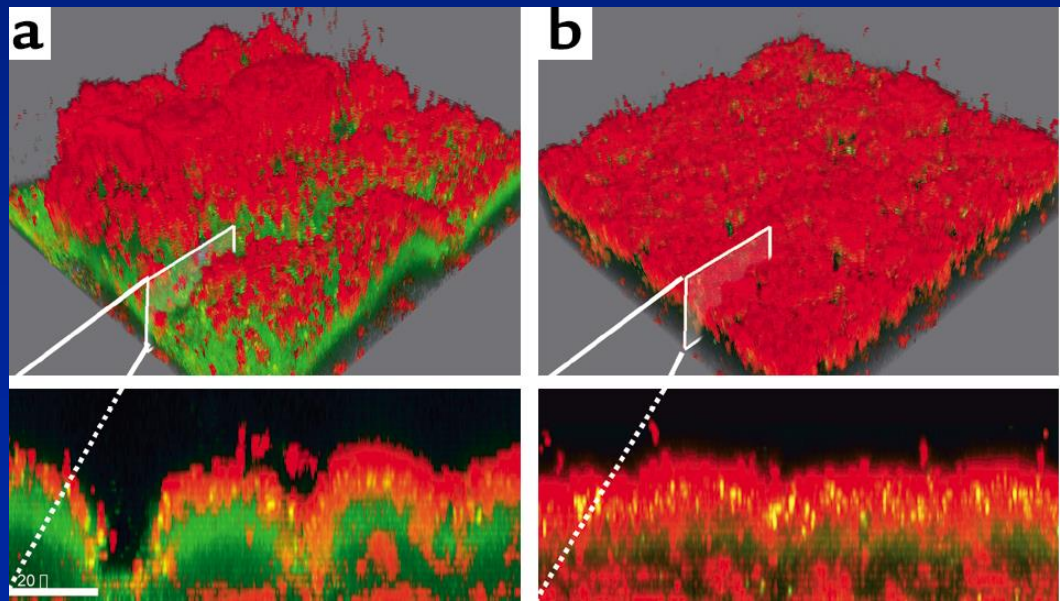
Gelecek çözüm-2

- Farklı tedavi yaklaşımları (FAJ ?)



- Mikroplarla “seviyeli ilişki” (iletişim)





Gelecek çözüm-3

- Aşı

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Vaccination and passive immunisation against *Staphylococcus aureus*☆

Adam C. Schaffer, Jean C. Lee*

REVIEW

Arch. Immunol. Ther. Exp., 2006, 54, 113–120
PL ISSN 0004-069X
DOI 10.1007/s00005-

Novel therapies of multidrug-resistant *Pseudomonas aeruginosa* and *Acinetobacter* spp. infections: the state of the art

Marta Wróblewska

Table 2. Novel approaches to vaccine development against *P. aeruginosa* (based on Ramsey and Wozniak [67])

Target	Vaccine
Adherence inhibition	flagellin-based chimeric exotoxin A-pilus protein outer membrane protein (e.g. OprF) O-polysaccharide-toxin A conjugate
Type III secretion-translocation system inhibition	V antigen
Mucoid exopolysaccharide (alginate) inhibition	mucoid exopolysaccharide-alginate conjugate vaccine

Gelecek çözüm-4

- Koruyucu mikroplar
- A- insanda

CHEST

Official publication of the American College of Chest Physicians

CHEST ONLINE

Probiotics for Preventing and Treating Nosocomial Infections*: Review of Current Evidence and Recommendations

Warren Isakow, Lee E. Morrow and Marin H. Kollef

Chest 2007;132;286-294
DOI 10.1378/chest.06-2156

- B-Çevrede

"... Some have talked about spraying hospital rooms with susceptible commensal organisms to replace and compete with the disease agents."

Levy, 1997

SONUÇ (bugün)

- İyi hastane hastane infeksiyonlarını önlemek için en çok uğraşan hastanedir
- İyi sağlık sistemi önleyici yaklaşımları en öncelikli olarak gören, önlemek için yapılanlara katkı sağlayan sistemdir.
- İnfeksiyon Hastalıkları Uzmanları “Önleyici” bir bakış açısının gelişmesinde öncelik etmelidir !

SORUN BAKTERİLERLE MÜCADELE ELİMİZDEDİR