Antibakteriyel Direncin Önlenmesinde Stratejik Yaklaşımlar

Dr. Oral ÖNCÜL
İstanbul Tıp Fakültesi
İnf. Hst. ve Kl. Mik. ABD

Sunum Planı

- Çoklu Antibakteriyel direnç
- Epidemiyolojik veriler
- Tedavi yaklaşımları
- Yeni arayışlar
- Yeni yaklaşımlar..

Antibakteriyel Direnç Sorunu Sanılandan Daha mı Fazla Abartılıyor?

Evet

Yüksek direnç oranlarına sahip ülkelerde sorun.

- Bu kadar büyütülec boyutlarda değil..

- Güçlü sağlık politikaları ile eritilebilir..

_ Yeni antibiyotikler ve sistemleri önemli..

?

Hayır

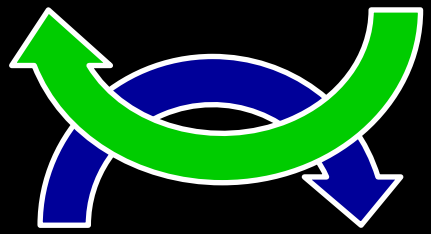
- Sağlık politikalarının güçlü belirleyicisi..

- Mortalite, morbidite ve maliyet artışı..

- Şu ana kadar uygulanan politikalar yetersiz..

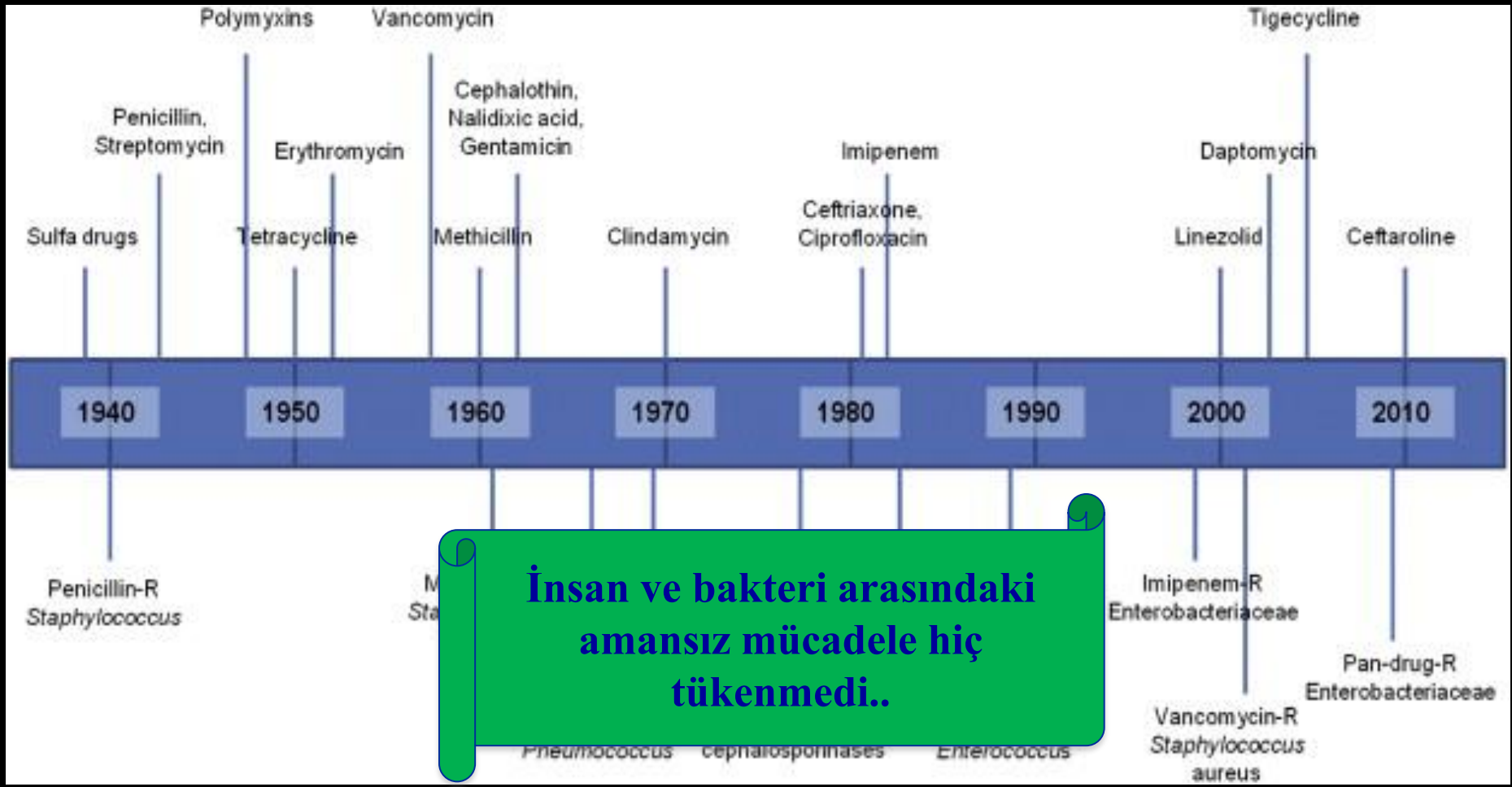
Cevap Arayan Sorular

Sağlık politikalarını antibiyotik direnci mi belirler?



Antibiyotik direncini sağlık politikaları belirler?

Antiyotik ve Direnç Gelişimi Arasındaki Amansız Takip..




AMX
TIC
PIP
MOX
TZP
CF
CAZ
AMC
CXM
IMP
CTX
TCC
FOX
CPO
FEP
ATM

MDR Bakteri Prevalansı

Bakteri	1999 Prevalansı (%)	2007 Prevalansı (%)
Vankomisin Dirençli Enterokok	24.7	33.3
Metisiline Dirençli *S.aureus*	53.5	56.2
P.aeruginosa (Karbapenem dirençli)	16.4	25.3
A.baumannii (Karbapenem dirençli)	11	30
Enterobacteriaceae (3.kuşak SS dirençli)		25.0
Enterobacteriaceae (Karbapenem dirençli)	0	8

Karbapeneme Dirençli *K.pneumoniae* %18 2015 (CDC)

NIH CDC, 2008

MDR İnfeksiyonları Önemli Sonuçlar Doğuruyor..

Değişken	S-KP (n=85)	ESBL-KP (n=65)	CRKP (n=42)	P
Hastane mortalitesi (%)	20 (24)	25 (39)	29 (69)	<0.001
İnfeksiyonla ilişkili mortalite (%)	14 (17)	14 (22)	20 (48)	0.001
İnf.sonrası hastanede yatış süresi, median gün (OR)	9 (16)	16 (34)	8 (22)	0.003
Total hastanede yatış süresi, median gün (OR)	21 (36)	36 (70)	37 (31)	0.001

S-KP: Duyarlı *K.pneumoniae*, ESBL-KP: ESBL (+) *K.pneumoniae*, CRKP: Karbapeneme Dirençli *K.pneumoniae*

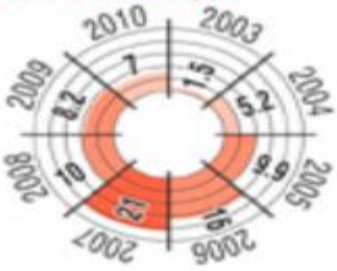
Ben-David D. CMI 2011

ABD Askeri Personeli ve MDR *Acinetobacter spp.*

- Mart 2003'de ilk olgu
- Landstuhl Regional Medical Center (Almanya)
- Walter Reed Army Medical Center (ABD)
- İnfeksiyonlar kabul edildiğinde ya da sonradan ortaya çıktı.

İŞGALİN BİLANÇOSU

Günde bombalardan ölen insan sayısı



Günde çatışmada ve idamdan ölen insan sayısı

Risk Haritası

Yüksek

Alçak ris

ABD Savaşın direkt maliyeti
797 Milyar $
Dolaylı maliyeti 4 Trilyon $
> 32.000 Yaralı asker

Sivil Ölüm Oranı

1 Mart 2003 — 21 Mart 2003

Mülteciler

1.683.579
Ürdün, Suriye gibi ülkelere sığınan Iraklı mültecilerin sayısı. (UNHCR)

264.285.225 $
2010 yılında UNHCR'ın Irak için ayırdığı bütçesi

1.5 milyon
Irak sınırları içerisinde geldiği yeri terk edip başka bir kente zorunlu göç eden insan sayısı. Bunların 500 bini evsiz kaldıkları için kötü durumlarda olan mülteci kamplarına yerleştirildi.

900 bin
Eşlerini savaşta kaybeden dul kadınların sayısı.

Hizmetler

%24
Yaklaşık dört Iraklıdan birinin temiz, sağlıklı suya erişimi yok.

%26
Irmak ya da nehirleri su ihtiyaçlarını gidermek için kullanan kırsal kesimdeki insan oranı.

%17
Temizlenen kanalizasyon suyunun oranı.

%83
Irmak ve nehirlere akıtılan kanalizasyon suyunun oranı.

Health services in Iraq

Thamer Kadum Al Hilfi, Riyadh Lafta, Gilbert Burnham

After decades of war, sanctions, and occupation, Iraq's health services are struggling to regain lost momentum. Many skilled health workers have moved to other countries, and young graduates continue to leave. In spite of much rebuilding, health infrastructure is not fully restored. National development plans call for a realignment of the health system with primary health care as the basis. Yet the health-care system continues to be centralised and focused on hospitals. These development plans also call for the introduction of private health care as a major force in the health sector, but much needs to be done before policies to support this change are in place. New init... include an active programme to match access to health services with the location and needs of the population

Lancet 2013; 381: 939–48

See **Editorial** page 875

See **Comment** page 877

Department of Community Medicine, Al Kindy College of Medicine, Baghdad, Iraq (Prof T K Al Hilfi MBChB); **Department of Community Medicine, Al Munstansiriya University, Baghdad, Iraq** (Prof R Lafta MBChB); **and Department of International Health, The Johns Hopkins Bloomberg School of Public Health, Baltimore, MD, USA** (Prof G Burnham MD)

Correspondence to:
Prof Gilbert Burnham,
Department of International Health, Johns Hopkins School of Public Health, Baltimore, MD 21205, USA
gburnham@jhsph.edu

Introduction

In this Review, we aim to provide an appreciation ... health status of Iraqis, the function ... the rapid changes occurri... need for improved policies ...

During the 1970s and ... medical education were ... region.[1] The country boa... 172 hospitals and 1200 pr... Iraqi medical graduates wo... training and certification in t... the late 1980s until 2004, mos... barred from leaving Iraq.

After Saddam Hussein cam... power, funds were diverted from the health sector ... 1980–88 Iran–Iraq War killed perhaps half a million people on both sides,

was ... tors and nurses ... Prime Minister ... last US forces ... e and political ... g to much of ... ering health ... th system.[16–18]

... decades a rapid demographic and ... ological transition has occurred in Iraq (figure 1,[19] panel[20–23]). The accompanying Review by Barry Levy and Victor Sidel[24] includes a further summary of key health and demographic indicators. The population of Iraq is estimated to be 32·2 million with annual growth of

Kişi başı sağlık harcamalarında
-186 USD sağlık sigortası
-İlaç giderlerine %28 ek yük
-Toplamda %36.8 sağlık gider artışı..

Iraq: putting people first

As recently as the 1970s, Iraq enjoyed a strong health-care system and universal access to health care for its citizens—written into the country's constitution and the envy of many countries worldwide. Fast forward to today. Iraq, having suffered three shattering conflicts in the past 35 years—the war with Iran, the 1991 Gulf War, and the 2003 US-led military invasion—is a wounded nation.

Yet in the north of the country—previously the target of Saddam Hussein's genocide against the Kurdish population—today is better than yesterday. Many of the region's people and their skills have been repatriated, with a reinvestment in infrastructure and strong commercial leadership helping the region to grow and flourish, a tantalising glimpse of what the rest of Iraq could achieve.

This themed issue of *The Lancet* aims to crystallise Iraq's current health situation, to clarify its most pressing health problems, and to offer a prognosis for the future health of the country. A comprehensive review of the current health situation is provided by Thamer Al Hilfi

and associated sanitation problems, means that communicable diseases (eg, tuberculosis, schistosomiasis, and measles) can prevail. Cholera outbreaks have recently been reported. Most experts believe t newest threat to Iraq's future health is a burgeoning emic of non-communicable diseases. A non-existe lic health system probably explains why 40% of ke, and why tw ental health (s, but ove similar cancers an afford i ancer hospital in Basra stands half built.

Meanwhile, Iraq is slowly overha its health system away from centralised hospita sed care to a network of primary health facilities, j ned to regional centres. However, an explosion in Iraq's birth rate, and too few health workers in Iraq's health system,

'Irak halkı yavaş yavaş yaralarını sarıyor. Bakalım derin yaralarımızı biz nasıl saracağız?'

See **Comment** page 879
See **Special Report** page 891
See **Perspectives** page 897
See **Review** pages 939 and 949
See **Viewpoint** page 959

Obama Signs Health Care Overhaul Bill, With a Flourish

By SHERYL GAY STOLBERG and ROBERT PEAR MARCH 23, 2010

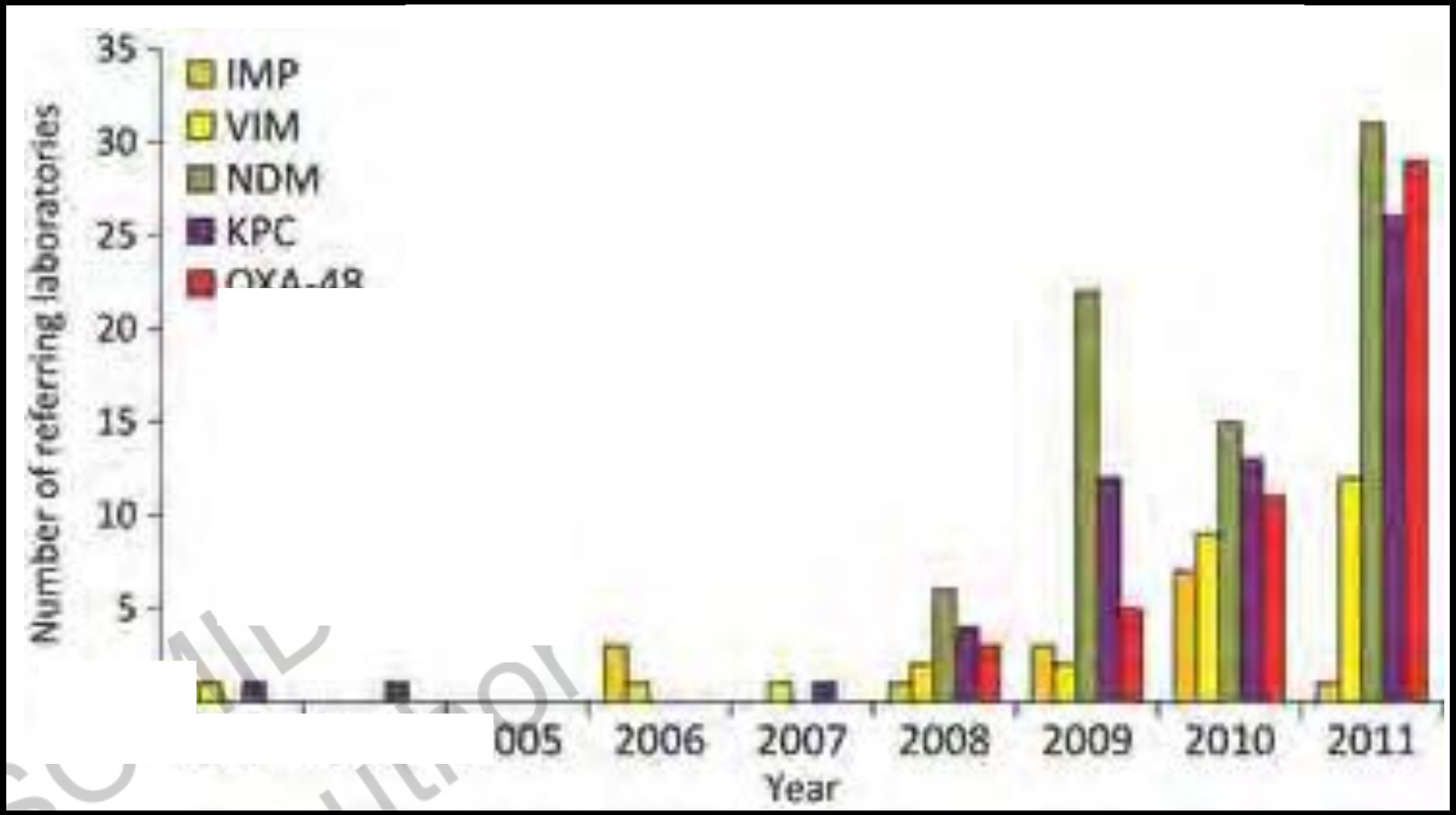
President Obama signed major health care legislation into law on Tuesday. Doug Mills/The New York Times

- Aynı dönemlerde ABD'de Ulusal Sağlık Reformu adımları atılıyordu..

Email

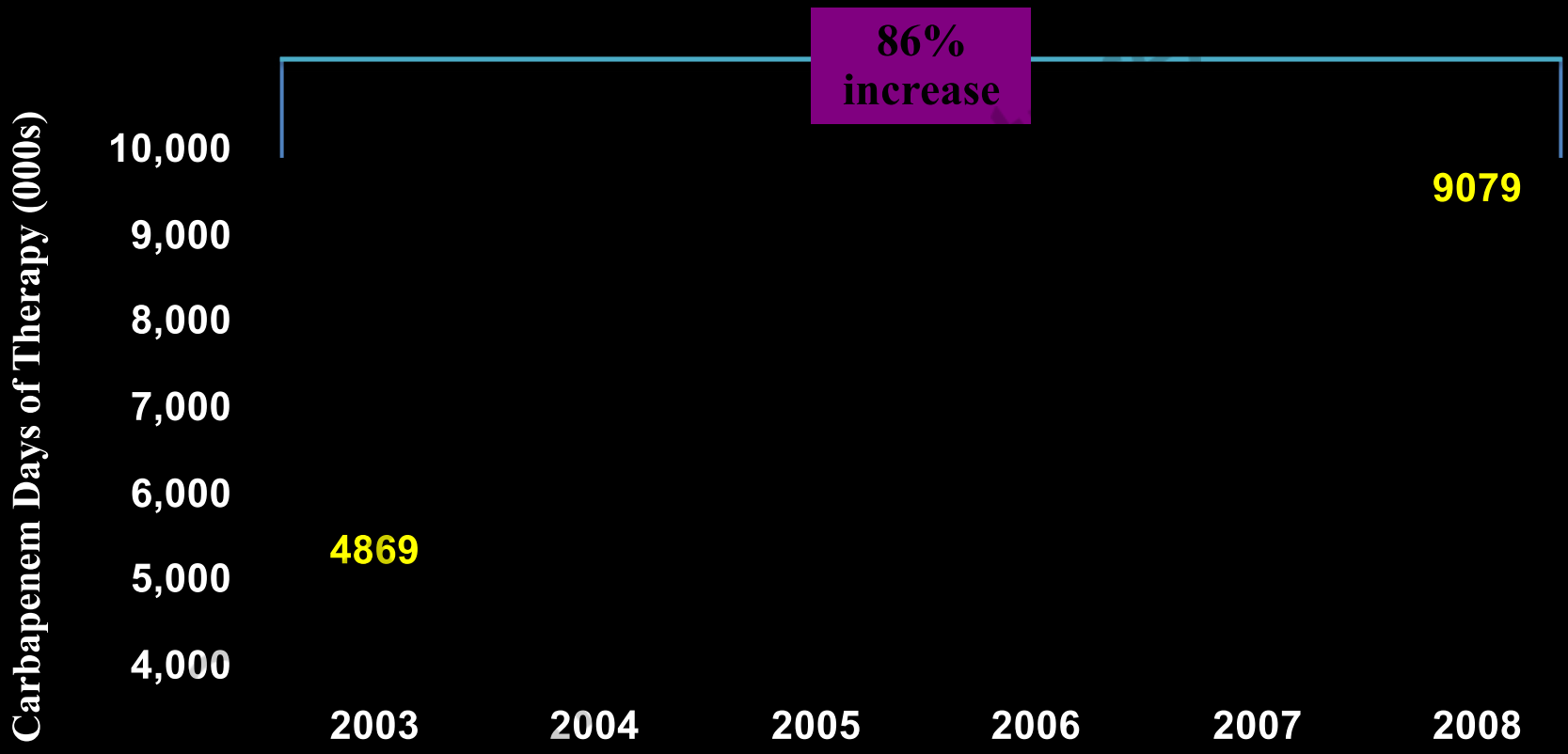
WASHINGTON — With the strokes of 22 pens, President Obama signed his landmark health care overhaul — the most expansive social legislation

Global Bir Sorun: Gram Negatiflerde Çoklu Antibiyotik Direnci



Clinical Microiology and Infection, Vol:18, 413-438

Karbapenem Kullanımı Giderek Artıyor



National Sales Perspective (NSP) Audit US data. IMS. December 2008.

Gram Negatif Bakterilerde Direnç Tanımı

Çoklu Direnç (Multidrug Resistant)

- ≥ 3 Sınıf Antibiyotik Direnci

- Kinolonlar
- Sefalosporinler
- Karbapenemler

Panresistant

- Tüm standart antibiyotiklere direnç

- Kolistin hariç..

Paterson DI, Clin Infect Dis, 2006

Multidrug-resistant, extensively drug-resistant and pandrug-resistant bacteria: an interna[illegible]onal expert proposal for interim stand[illegible]rd [illegible]efinitions [illegible] ac[illegible]ed [illegible]sistance

A.-P. [illegible] [illegible] Carmeli[3], M. E. Fa[illegible], [illegible], G. K[illegible] [illegible] B. Rice[12], J. Stelling[illegible] [illegible]r[2] and D. L[illegible]

1) E[illegible] [illegible]ockholm, Sweden, 2) Off[illegible] of Infectious [illegible] [illegible]h an[illegible] [illegible]n Services, Centers for Disea[illegible] [illegible]reve[illegible] [illegible]lanta, GA, [illegible], 3) [illegible]vision of Epi[illegible]logy, Tel Avi[illegible] Sourasky [illegible]l Cente[illegible] Aviv, Israel, 4) [illegible]lfa Institute of Biomedical Sc[illegible]nces (AIB[illegible]nens, Gre[illegible]rtment [illegible]ine, [illegible] [illegible] of Medicin[illegible]oston, MA, U[illegible], 6) Department of Clinical Microbiology, Karolinska Uni[illegible]sity Hospital, Stockh[illegible]e, University of Geneva Hospitals, Geneva, Switzerland, 8) Department of Pathology and Laborato[illegible] [illegible] Angeles, CA, USA, 9) Department of Clinical Microbiology, Central Hospital, Växjö, 10) [illegible] [illegible]us Disease Control, Solna, Sweden, 11) The University of Queensland Centre for Clinical Research, Royal Br[illegible] [illegible]12) Warren Alpert Medical School of Brown University, Providence, RI, 13) Departmen[illegible] [illegible]n, MA, USA and 14) Department of Microbiology, National School of Public Health, Athen[illegible]

MDR
≥3 Grup AB direnci

PDR
Tüm AB gruplarına
Karşı direnç..

XDR
Bir ya da iki AB grubu
Dışında tümüne direnç

Clin[illegible]l Mic[illegible]biology and Infection
Volume 18, Issue 3, March 2012, Pages 268–281

Abstract

ELSEVIER

SUPPLEMENT ARTICLE

Appraising Contemporary Strategies to Combat Multidrug Resistant Gram-Negative Bacterial Infections–Proceedings and Data From the Gram-Negative Resistance Summit

Marin H. Kollef,[1] Yoav Golan,[2] Scott T. Micek,[3] Andrew F. Shorr,[4,5] and Marcos I. Restrepo[6,7]

[1]Washington University School of Medicine, St Louis, Missouri; [2]Tufts University School of Medicine, Boston, Massachusetts; [3]Barnes-Jewish Hospital, St Louis, Missouri; [4]Georgetown University, Washington, D.C.; [5]Pulmonary and Critical Care Medicine, Washington Hospital Center, Washington, D.C.; [6]University of Texas Health Science Center, [7]Department of Medicine, Division of Pulmonary and Critical Care Medicine, Audie L. Murphy Veterans Hospital, San Antonio, Texas

The emerging problem of antibiotic resistance, especially among Gram-negative bacteria (GNB), has become a serious threat to global public health. Very few new antibacterial classes with activity against antibiotic-resistant GNB have been brought to market. Renewed and growing attention to the development of novel compounds targeting antibiotic-resistant GNB, as well as a better understanding of strategies aimed at preventing the spread of resistant bacterial strains and preserving the efficacy of existing antibiotic agents, has occurred. The Gram-Negative Resistance Summit convened national opinion leaders for the purpose of analyzing current literature, epidemiologic trends, clinical trial data, therapeutic options, and treatment guidelines related to the management of antibiotic-resistant GNB infections. After an in-depth analysis, the Summit investigators were surveyed with regard to 4 clinical practice statements. The results then were compared with the same

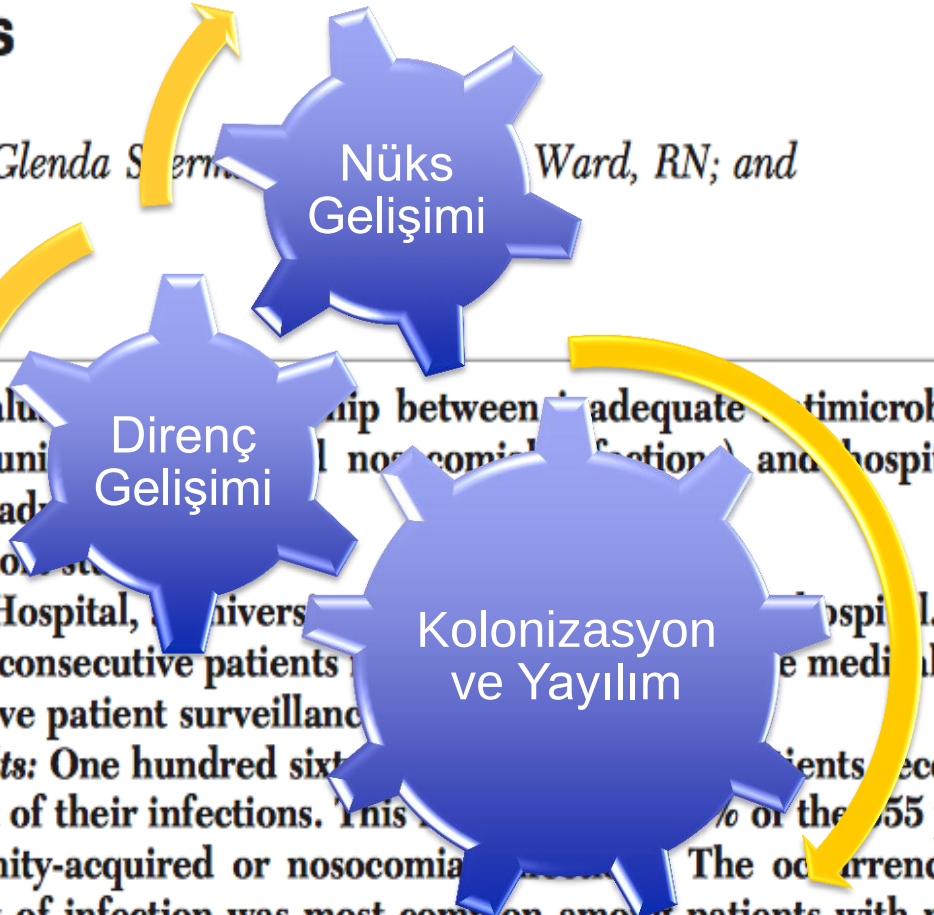
GNB İnfeksiyonları Tedavi Zirvesinin Yaklaşımı

- Karbapenem ya da diğer antibiyotiklerden oluşan tedavi kombinasyonları ilk seçenek olarak tercih edilmelidir (Author: Y. G.)
- Gram negatif aktiviteli antibiyotiklerin PK/PD özelliklerinin iyi değerlendirilmesi, direnç sorununun üstesinden gelmek için yeterlidir. (Author: S. T. M.)
- Antibiyotiklere maruz kalma süresinin kısaltılması GNB'lerde direnç gelişim sorununu azaltan önemli bir stratejidir (Author: A. F. S.)
- MDR GNB'lli hastaların izolasyonu ve aktif sürveyans yöntemleri MDR yayılımını önleyici demetler arasında yer alır (Author: M.I.R)

Inadequate Antimicrobial Treatment of Infections

A Risk Factor for Hospital Mortality Among Critically Ill Patients

Marin H. Kollef, MD, FCCP; Glenda S[illegible] Ward, RN; and Victoria J. Fraser, MD



Study objective: To [illegible] between inadequate [illegible]timicrobial treatment of infections (both co[illegible]muni[illegible] nos[illegible]ction) and hospital mortality for patients requiring ICU ad[illegible]
Design: Prospective coho[illegible]
Setting: Barnes-Jewish Hospital, [illegible]nivers[illegible]ospi[illegible]l.
Patients: Two thousand consecutive patients [illegible]e medi[illegible]l or surgical ICU.
Interventions: Prospective patient surveillanc[illegible]
Measurements and results: One hundred six[illegible]ients [illegible]eceived inadequate antimicrobial treatment of their infections. This [illegible]% of the [illegible]55 patients assessed to have either community-acquired or nosocomia[illegible] The oc[illegible]rrence of inadequate antimicrobial treatment of infection was most common among patients with nosocomial infections, which developed after treatment of a community-acquired infection (45.2%), followed by patients with nosocomial infections alone (34.3%) and patients with community-acquired infections alone (17.1%) ($p < 0.001$). Multiple logistic regression analysis, using only the cohort of

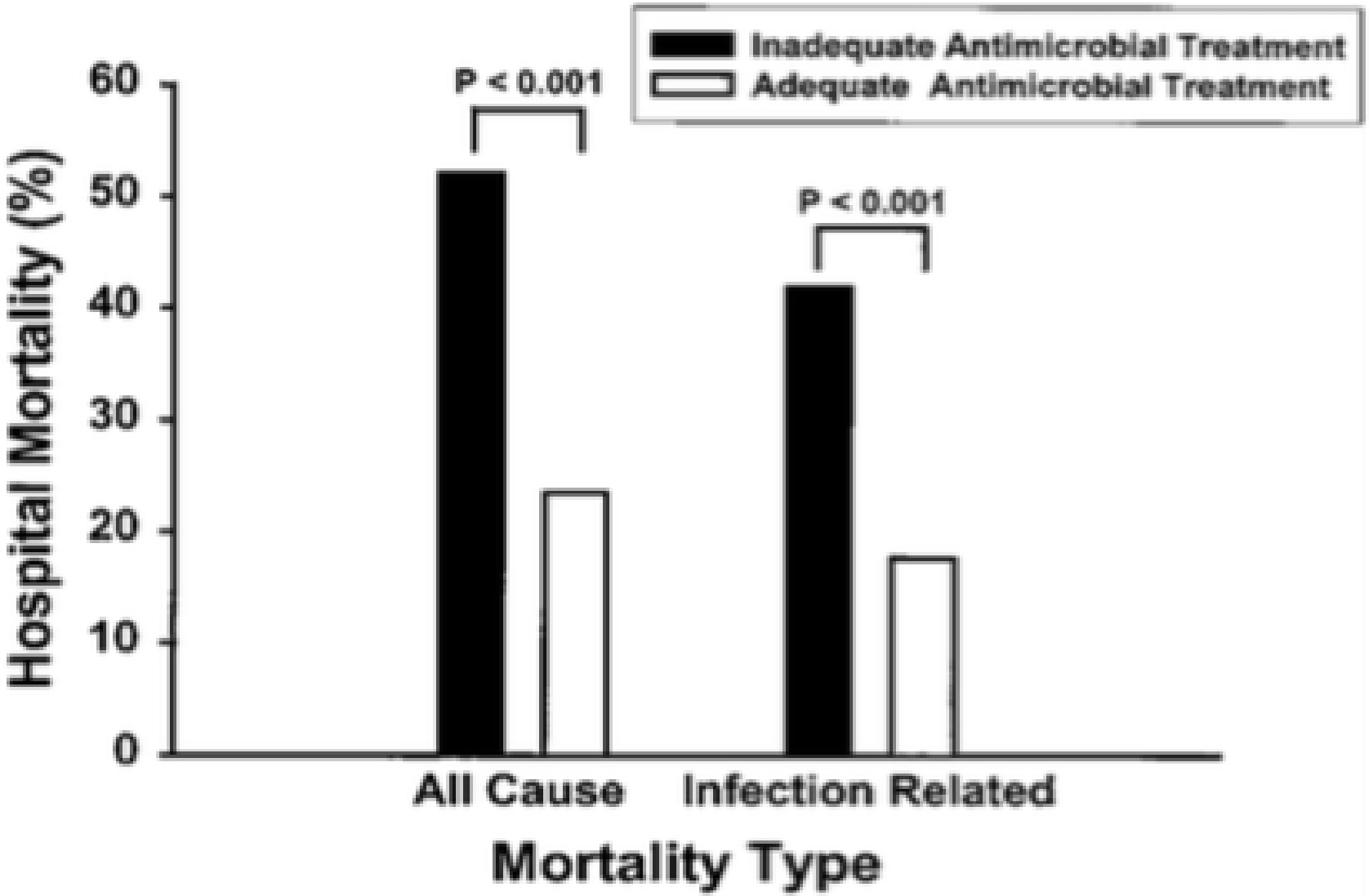


FIGURE 2. Hospital mortality and infection related mortality rates for infected patients from all causes (n = 655) receiving either initially inadequate or adequate antimicrobial treatment.

Table 7—*Independent Risk Factors for Hospital Mortality

Risk Factor	AOR†	95% CI	p Value
Inadequate antimicrobial therapy	4.26	3.35–5.44	< 0.001
Acquired organ system derangements (one-organ increments)	3.25	2.98–3.54	< 0.001
Use of vasopressors	2.20	1.81–2.66	< 0.001
Underlying malignancy	1.81	1.44–2.27	0.009
APACHE II score (one-point increments)	1.05	1.04–1.07	< 0.001
Increasing age (1-yr increments)	1.02	1.01–1.03	< 0.001
Surgical patient	0.40	0.33–0.49	< 0.001
Intercept	0.0013	0.0008–0.0021	

*Includes logistic regression model, where hospital mortality is the dependent outcome variable and the study population was the entire patient cohort (n = 2,000).

†AOR = adjusted odds ratio.

Karbapenemler (Meropenem)

Hafif Orta

500 mg 3x1 (3 h)

1000 mg 3x1 (30 dak)

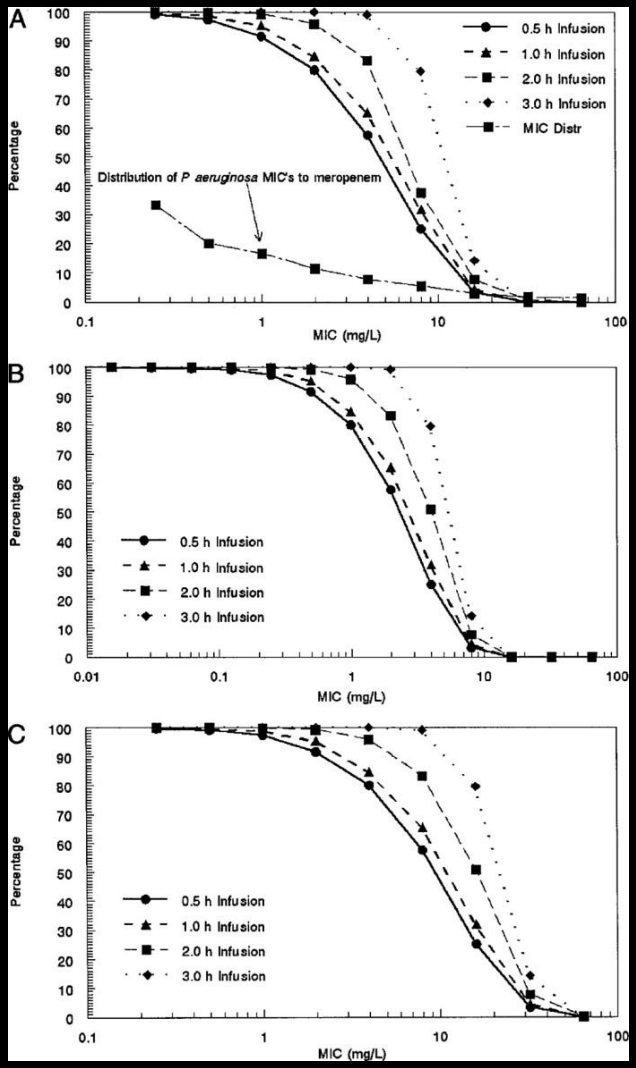
Ciddi Enf.

500 mg 3x1 (3h)

500 mg 4x1 (30 dak)

1000 mg 3x1 (30 dak)

EŞDEĞER..



Patel SJ. et al. AJIC, 2014

Resolution of Infectious Parameters after Antimicrobial Therapy in Patients with Ventilator-associated Pneumonia

PAUL J. W. DENNESEN, ANDRÉ J. A. M. van der VEN, ALPHONS G. H. KESSELS, GRAHAM RAMSAY, and MARC J. M. BONTEN

Departments of Medical Microbiology, Medical Technology Assessment and Surgery, University Hospital Maastricht, Maastricht, The Netherlands; and Department of Internal Medicine, Division of Infectious Diseases and AIDS, University Hospital Utrecht, Utrecht, The Netherlands

Although recommended durations of antimicrobial therapy for ventilator-associated pneumonia (VAP) range from 7 to 21 d, these are not based on prospective studies and little is known about the resolution of symptoms after start of antibiotics. Resolution of these symptoms was investigated in 27 patients. VAP was diagnosed on clinical, radiographic, and microbiological criteria, including quantitative cultures of bronchoalveolar lavage. All patients received appropriate antibiotic therapy. Highest temperatures, leukocyte counts, $Pa_{O_2}/F_{I_{O_2}}$ ratios, and semiquantitative cultures of endotracheal aspirates were recorded from start of therapy until Day 14. Resolution was defined as the first day that these parameters fulfilled the following definition: temperature ≤ 38°C, leukocytes ≤ 10×10^9/L, $Pa_{O_2}/F_{I_{O_2}}$ ratio ≥ 25 kPa, and no or +1 of bacterial growth of etiologic pathogens in cultures of endotracheal aspirate. VAP was caused by Enterobacteriaceae (n = 14), *P. aeruginosa* (n = 7), *S. aureus* (n = 6), *H. influenzae* (n = 3), and *S. pneumoniae* (n = 1). *H. influenzae* and *S. pneumoniae* were eradicated from tracheal aspirates, whereas Enterobacteriaceae, *S. aureus*, and *P. aeruginosa* persisted, despite *in vitro* susceptibility to antibiotics administered. Significant improvements were observed for all clinical parameters, most apparently within the first 6 d after start of antibiotics. Newly acquired colonization, especially with *P. aeruginosa* and Enterobacteriaceae, occurred in the second week of therapy. Six patients developed a recurrent episode of VAP, four of them with *P. aeruginosa*. Clinical responses to therapy for VAP occur within the first 6 d of therapy, endotracheal colonization with Gram-negative bacteria persists despite susceptibility to therapy, and acquired colonization usually occurs in the second week of therapy and frequently precedes a recurrent episode.

Tedavinin ikinci haftaya uzatılması dirençli yeni infeksiyon riskini artırıyor...

though the sensitivity of these criteria is high, specificity is low and antibiotics are frequently prescribed unnecessarily. The enormous use of antibiotics creates a constant threat for selection and induction of resistant pathogens and exposes patients to adverse effects. Therefore, reducing antibiotic use may have several beneficial aspects. Reductions in antibiotic use may be achieved by preventing the development of infections, optimizing the accuracy of diagnostic procedures (7), or reducing the length of treatment.

Little is known about the optimal duration of antibiotic therapy for VAP. According to guidelines from the American Thoracic Society, VAP due to *Haemophilus influenzae* and methicillin-sensitive *Staphylococcus aureus* should be treated for 7 to 10 d, whereas episodes caused by *Pseudomonas aeruginosa* and *Acinetobacter* spp. should be treated for at least 14 to 21 d (8). However, these recommendations are not based on the results of prospective studies. Furthermore, there is sparse information about resolution of infectious parameters associated with VAP after institution of appropriate antimicrobial therapy.

Garrard and A'Court described a gradual normalization of a combination of clinical, microbiological, and radiographic parameters after the institution of antibiotic therapy (9). And Montravers and coworkers demonstrated, with a second bronchoscopy 3 d after institution of antimicrobial therapy, that appropriate therapy results in a rapid bacteriological clearance of the distal airways. However, the effects on clinical parameters were less evident (10). The aims of the present study were to describe the clinical and microbiological response to appropriate antimicrobial therapy in patients with VAP.

GNB'lerde Direnç Gelişimini Önlemek İçin Tedavi Süresi Ne Olmalıdır?

Prospektif çalışmada 27 VİP Olgusu

Bronkoskopi ile doğrulanmış

Ortalama 13 gün uygun AB tedavisi almış..

6 (%22) olguda yeni infeksiyon gelişimi *(P.aeruginosa)*

Bunların %50'si PDR

İlk 6 günde ETA steril

> 6. günlerde ETA kolonizasyonu

> 6 günlerde PDR yeni infeksiyonlar

Resolution of Infectious Parameters after Antimicrobial Therapy in Patients with Ventilator-associated Pneumonia

PAUL J. W. DENNESEN, ANDRÉ J. A. M. van der VEN, ALPHONS G. H. KESSELS, GRAHAM RAMSAY, and MARC J. M. BONTEN

Departments of Medical Microbiology, Medical Technology Assessment and Surgery, University Hospital Maastricht, Maastricht, The Netherlands; and Department of Internal Medicine, Division of Infectious Diseases and AIDS, University Hospital Utrecht, Utrecht, The Netherlands

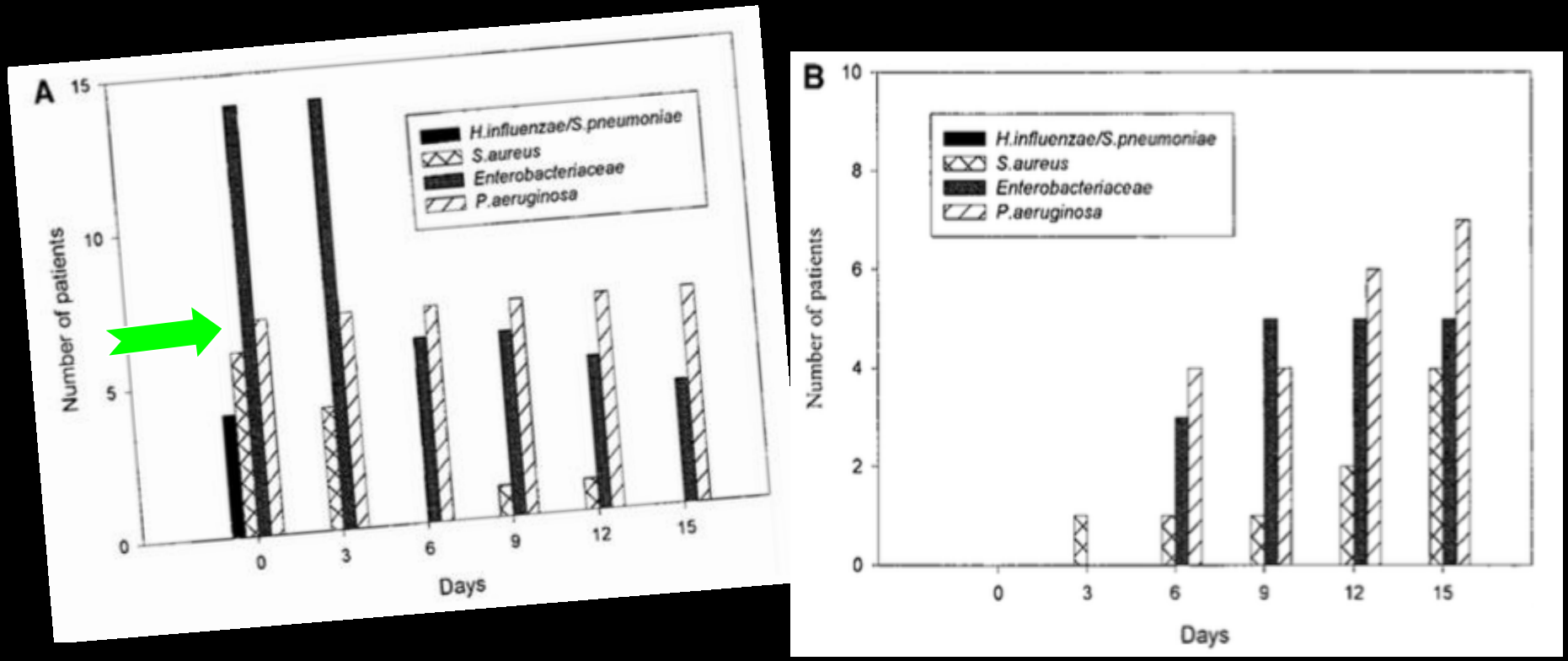


Figure 2. (*A*) Number of patients with initially isolated microorganisms from endotracheal aspirates collected in time after initiation of antibiotic treatment. (*B*) Number of patients with newly isolated microorganisms from endotracheal aspirates in time after initiation of antibiotic treatment.

Short-course Empiric Antibiotic Therapy for Patients with Pulmonary Infiltrates in the Intensive Care Unit

A Proposed Solution for Indiscriminate Antibiotic Prescription

NINA SINGH, PAUL ROGERS, CHARLES W. ATWOOD, MARILYN M. WAGENER, and VICTOR L. YU

Veterans Affairs Medical Center and University of Pittsburgh, Pittsburgh, Pennsylvania

Inappropriate antibiotic use for pulmonary infiltrates is common in the intensive care unit (ICU). We sought to devise an approach that would minimize unnecessary antibiotic use, recognizing that a gold standard for the diagnosis of nosocomial pneumonia does not exist. In a randomized trial, clinical pulmonary infection score (CPIS) (Pugin, J, R. Auckenthaler, N. ..., R. D. Low, and P. M. Suter. Diagno... by bacteriologic analysis o... noscopic "blind" bro... 1121–1129) was ... n-making regarding ... ng low likelihood ... ceive either stan-dard therapy (ch... at the discretion of physicians) ... ciprofloxacin ... apy with ... evaluation at 3 d; ciprofloxacin was discontinued if C... remained ≤ 6 at 3 d. Antibiotics were continued beyond 3 d in ...% (38 of 42) of the patients in the standard as therapy compared with 28% (11 of 39) in the ex-

for 49% ... all antibiotics prescribed in the ICU; 63% of the antibiotic ... were ... clinically suspected and ... (3). Other studies have do... ICU patients with pul-... ging from 34 to ...% ... biotic usage in the ICU h... ts.

... comial pneumonia is the fact tha... an reliably distin-guish pneu...nia from ... pulmonary infiltrates do not exist. Even invasive diagnostic procedures have numerous and serious limitations and have not met with total acceptance (7). Sampling techniques and threshold for positivity remain unstandardized. Routine performance of such invasive tests is neither feasible nor cost-effective.

A major factor contributing to the "spiraling empiricism" in

Kısa süreli tedaviler tedavide daha başarılı..

Kısa süreli tedaviler direnç gelişiminde daha az etkili..

Short-course Empiric Antibiotic Therapy for Patients with Pulmonary Infiltrates in the Intensive Care Unit

A Proposed Solution for Indiscriminate Antibiotic Prescription

NINA SINGH, PAUL ROGERS, CHARLES W. ATWOOD, MARILYN M. WAGENER, and VICTOR L. YU

Veterans Affairs Medical Center and University of Pittsburgh, Pittsburgh, Pennsylvania

Hastanede kalış süresi, mortalite ve klinik iyileşme kısa süreli tedavi grubunda daha iyi

TABLE 4

OUTCOME ENDPOINTS IN THE TWO STUDY GROUPS

Variable	Experimental	Standard Therapy	p Value
Length of ICU stay, d			
Mean/median	9.4/4	14.7/9	0.04
Range	1–47	1–91	
Mortality, d			
3	0% (0/39)	7% (3/42)	NS*
14	8% (3/39)	21% (9/42)	NS
30	13% (5/39)	31% (13/42)	NS (0.06)
Resolution of pulmonary infiltrate			NS
Complete resolution	41% (16/39)	21% (9/42)	
Partial resolution	18% (7/39)	14% (6/42)	
Unchanged	18% (7/39)	36% (15/42)	
Worsening	0/39	10% (4/42)	
No follow-up films	23% (9/39)	19% (8/42)	

* NS = not significant, $p > 0.05$.

BMC Infectious Diseases

BioMed Central

Research article

Open Access

Outcome of infections due to pandrug-resistant (PDR) Gram-negative bacteria

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This article is available from: http://www.biomedcentral.com/1471-2334/5/24

Abstract

Background: The increasing problem of infections due to multidrug-resistant Gram-negative bacteria has led to re-use of polymyxins in several countries. However, there are already clinical

PDR GNB İnfeksiyonları

Yazar ve Yıl	Olgu Sayısı	Tedavi Rejimi	Klinik Sonuç
Beno et al	9	Detay belirtilmemiş	4 ex
Falagas et al	7	Col + MEM + RIF/DOX	2 ex
Falagas et al	28	3 olgu (Col + TİG + RIF) 6 lolgu Col + TİG 19 olgu (Col +MEM/DOX/RIF/CIP)	12 ex
Tsioitis et al.	21	9 olgu Monoterapi 12 olgu (Col +MEM/DOX/RIF/CIP)	5 ex
Ghafur et al	9	1 olgu Col 1 olgu Col + MEM 1 olgu Col + MEM + TIG + RIF+ TEİC) 1 olgu Col + MEM + TEIC 1 olgu Col + TEIC + SEFEP 1 olgu CRO 1 olgu Col + TİG 2 olgu Col + TİG + RIF + DOX	3 ex

ELSEVIER

International Journal of Antimicrobial Agents 29 (2007) 630–636

INTERNATIONAL JOURNAL OF Antimicrobial Agents

www.ischemo.org

Review

Pandrug-resistant Gram-negative bacteria: the dawn of the post-antibiotic era?

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Journal of Antimicrobial Chemotherapy Advance Access published January 26, 2016

J Antimicrob Chemother
doi:10.1093/jac/dkv467

Journal of Antimicrobial Chemotherapy

Emergence of pan-resistance in KPC-2 carbapenemase-producing *Klebsiella pneumoniae* in Crete, Greece: a close call

E. Bathoorn[1]†, C. Tsioutis[2]†, J. M. da Silva Voorham[1], E. V. Scoulica[3], E. Ioannidou[4], K. Zhou[1], J. W. Rossen[1], A. Gikas[2], A. W. Friedrich[1]* and H. Grundmann[1]

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*Corresponding author. Tel: +31-(0)50-36[illegible]ich@umcg.nl

Received 8 September 2015; re[illegible] December 2015

Objectives: KPC-2-producing *Kleb[illegible]* expanding and is often associated with serious noso[illegible] tigecycline often remain the only treatment opti[illegible]olates in Crete, Greece.

Methods: We tested the antibiotic[illegible] patie[illegible]talized in 2010 and 2013–14. Whole-genome sequences[illegible] quired resist[illegible]e genes and gene mutations.

Results: All KPC-KP isolates belo[illegible] ST258 w[illegible] e[illegible] of one[illegible]7 isolate. From 2014, 26% of isolates were non-susceptible to[illegible] antibiotics, co[illegible]ed wi[illegible]11 isolates[illegible]m 2010. Colistin resistance was associated with mutations in *mgrB*, which was p[illegible]ent in 61[illegible]solates from 2014. Core-genome MLST analysis showed that pan-resistant isolates were closely related and [illegible]eared in two separate clusters.

Conclusions: KPC-KP is rapidly evolving to pan-resistance in Cr[illegible]e. We identified molecular resistance markers for pan-resistant isolates and showed that core-genome MLST is a promising tool for molecular fingerprinting of KPC-KP ST258.

Yunanistan'da
2010: % 10
2014: %26

International Journal of Infectious Diseases 33 (2015) e132–e134

Contents lists available at ScienceDirect

International Journal of Infectious Diseases

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

Case Report

Therapeutic strategy for pandrug-resistant *Klebsiella pneumoniae* severe infections: short-course treatment with colistin increases the in vivo and in vitro activity of double carbapenem regimen

Alessandra Oliva [a], Maria T. Mascellino [a], Alessia Cipolla [a], Alessandra D'Abramo [a], Annalisa De Rosa [a], Stefano Savinelli [a], Maria Rosa Ciardi [a], Claudio M. Mastroianni [a,b,*], Vincenzo Vullo [a]

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ARTICLE INFO

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Corresponding Editor: Eskild Petersen, Aarhus, Denmark

Keywords:

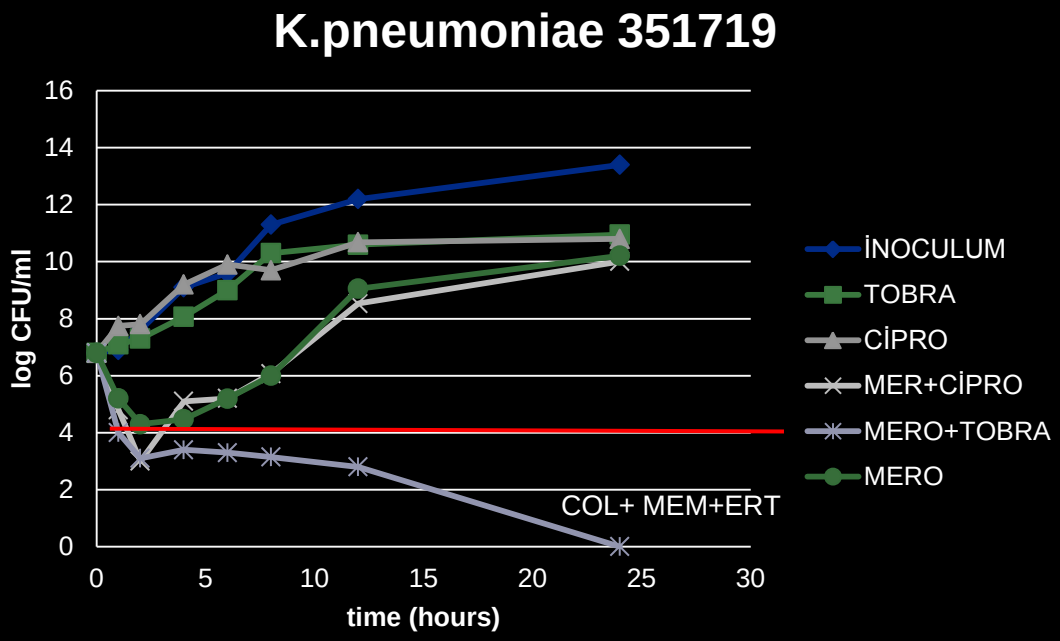
SUMMARY

Infections due to carbapenemase-producing *Klebsiella pneumoniae* represent an emerging threat due to the high mortality rate and lack of valid antimicrobial combinations, especially when the strain is colistin-resistant. We report a case of bloodstream infection due to pandrug-resistant *K. pneumoniae* treated successfully with an innovative regimen comprising a combination of colistin plus double carbapenem, along with an in vitro analysis showing the synergistic and bactericidal effect.

- Not olarak, ERT + MEM + COL kombinasyonu için;
  - ERT + MEM + COL (0.5 x MIK) ve
  - ERT + MEM + COL (1 x MIK)
- konsantrasyonlarının her ikisinde de 8. saatten sonra da sinerjistik ve bakterisidal aktivite (24 saate kadar)

Patel SJ. et al. AJIC, 2014

PDR K.pneumoniae İnfeksiyonları ve Tedavi Yaklaşımı



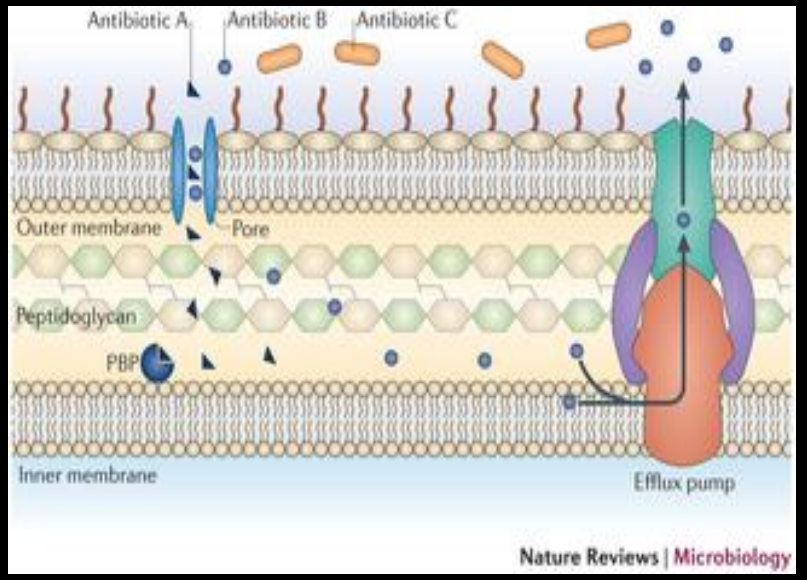
time	İNOCULUM	TOBRA	CİPRO	MER+CİPRO	MERO+TOBRA	MERO
0	6.8	6.8	6.8	6.8	6.8	6.8
1	6.9	7.1	7.746	4.8	4	5.2
2	7.6	7.3	7.804	3	3.1	4.3
4	9.1	8.07	9.2	5.1	3.4	4.47
6	9.6	9	9.9	5.2	3.3	5.195
8	11.3	10.3	9.7	6.07	3.146	6
12	12.2	10.6	10.681	8.53	2.8	9.055
24	13.4	10.95	10.799	10.01	0	10.209

Blood culture

	351719
AMPİCİLİN	>256 R
AMOX/CLAV	>256 R
PİPER/TAZO	>256 R
CEFOXİTİN	16 İ
CEFUROXİME	>256 R
CEFOTAXİM	>32 R
CEFOTAXİM/CTL	>16/>1
CEFTRİAXON	>256 R
CEFTAZİDİME	24 R
CEFTAZİDİME/TZL	>32/<0,64**
CEFOPERAZONE/SULB	32
MEROPENEM	1,5 İ
ERTAPENEM	>256 R
IMIPENEM	2 İ
IMIPENEM/IM+EDTA	>4/>1
LEVOFLOXACİN	>32 R
CİPROFLOXACİN	>32 R
OFLOXACİN*	>32 R
TOBRAMYCİN	12 İ
AMİKACİN	6 S
GENTAMYCİN	0,38 S
TİGECYCLİNE*	8 R
COLİSTİN*	0,19 S

İkili Karbapenem Bu Etkiyi Nasıl Sağlıyor?

- Ertapenem (karbapenemaz türü hidrolitik enzimlere bağlanır (Suisid İnhibitör Etki) diğer karbapenemin bakterisidal aktivitesine izin verir..
- Bu kombinasyonun sinerjistik etkisi, yüksek karbapenem direncinde bile gözlenmiş



J Antimicrob Chemother 2014
doi:10.1093/jac/dku027
Advance Access publication 11 February 2014

Synergistic activity and effectiveness of a double-carbapenem regimen in pandrug-resistant *Klebsiella pneumoniae* bloodstream infections

Alessandra Oliva[1]†, Alessandra D'Abramo[1]†, Claudia D'Agostino[1], Marco Iannetta[1], Maria T. Mascellino[1], Carmela Gallinelli[1], Claudio M. Mastroianni[1,2]* and Vincenzo Vullo[1]

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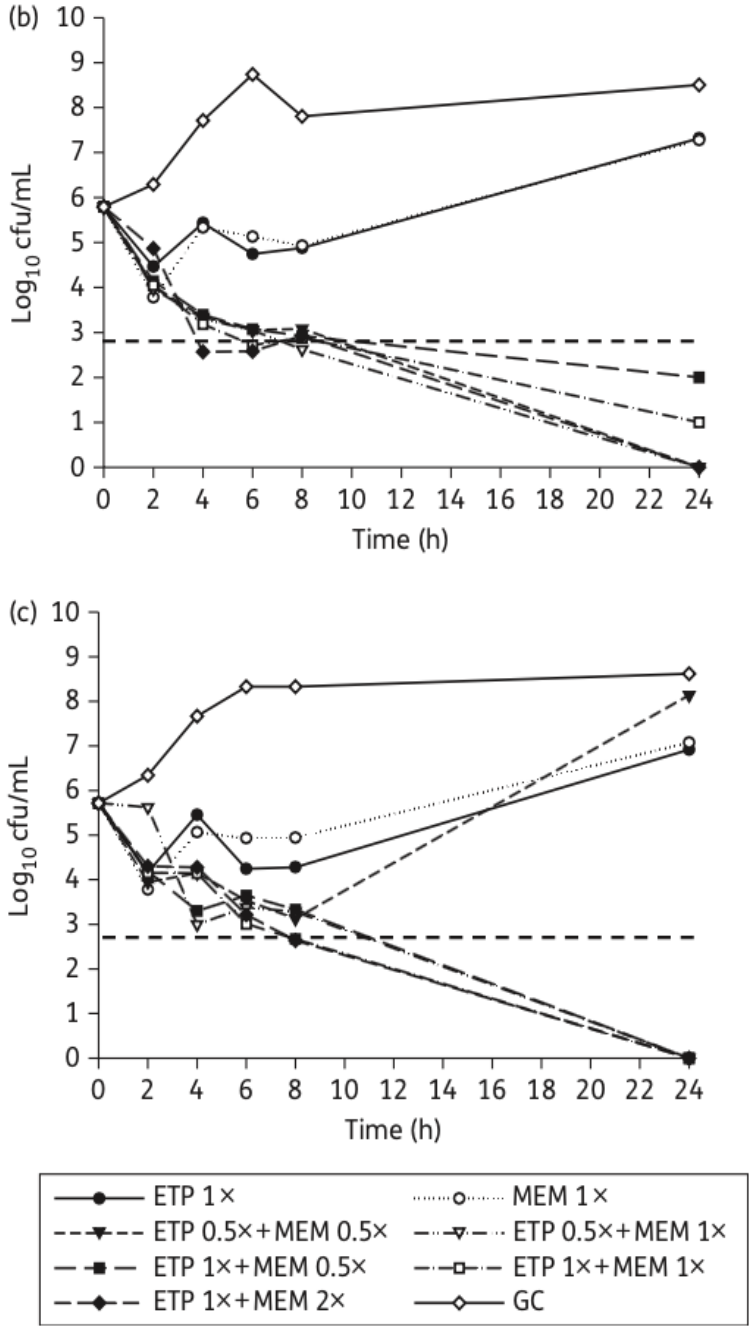
†Alessandra Oliva and Alessandra D'Abramo equally contributed to the manuscript.

Keywords: meropenem, ertapenem, KPC, bacteraemia, nosocomial infections

Sir,

Infections due to carbapenemase-producing *Klebsiella pneumoniae* (CP-Kp) are associated with a high mortality rate.[1,2] Therapeutic options are limited, especially when associated with colistin resistance.[3] In this setting, a double-carbapenem regimen has been shown to be effective and safe.[4,5]

Herein, we evaluated through antibiotic kill studies the *in vitro* synergistic activity of meropenem plus ertapenem against pandrug-resistant CP-Kp isolated from three patients with bacteraemia who were successfully treated with double-carbapenem therapy.



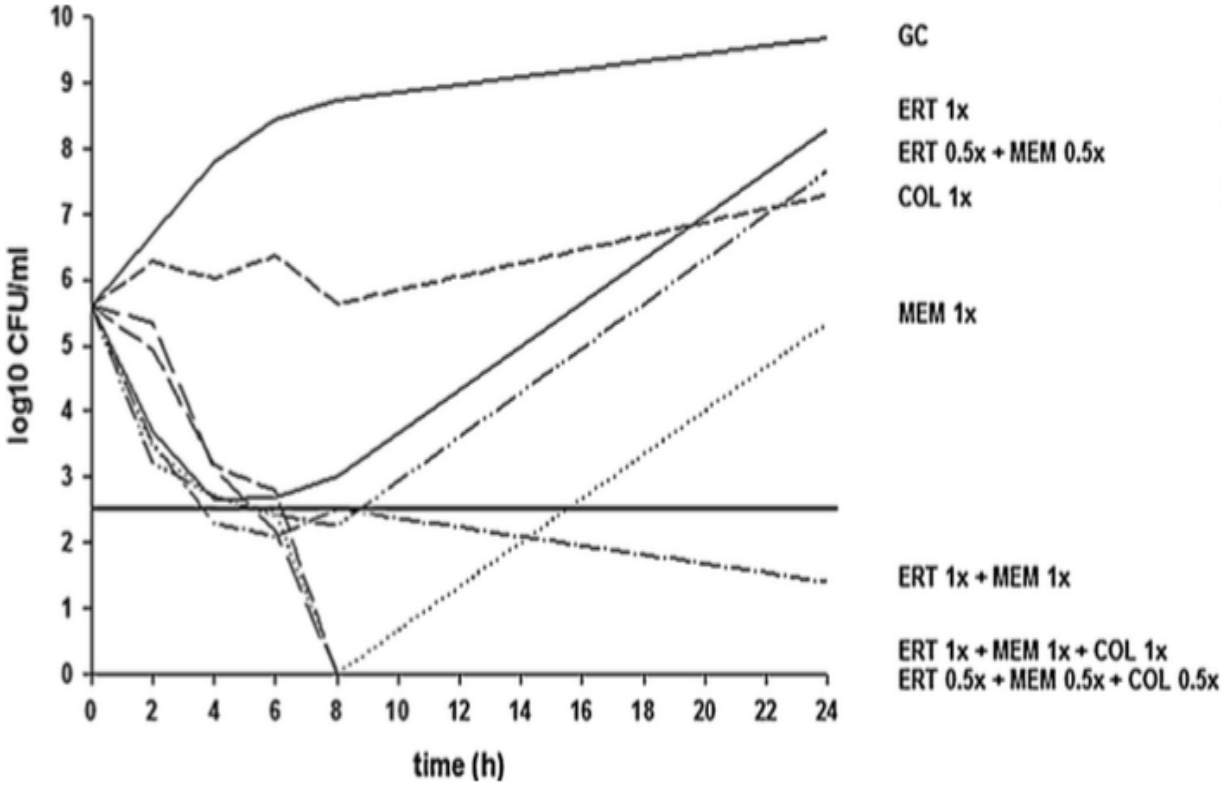
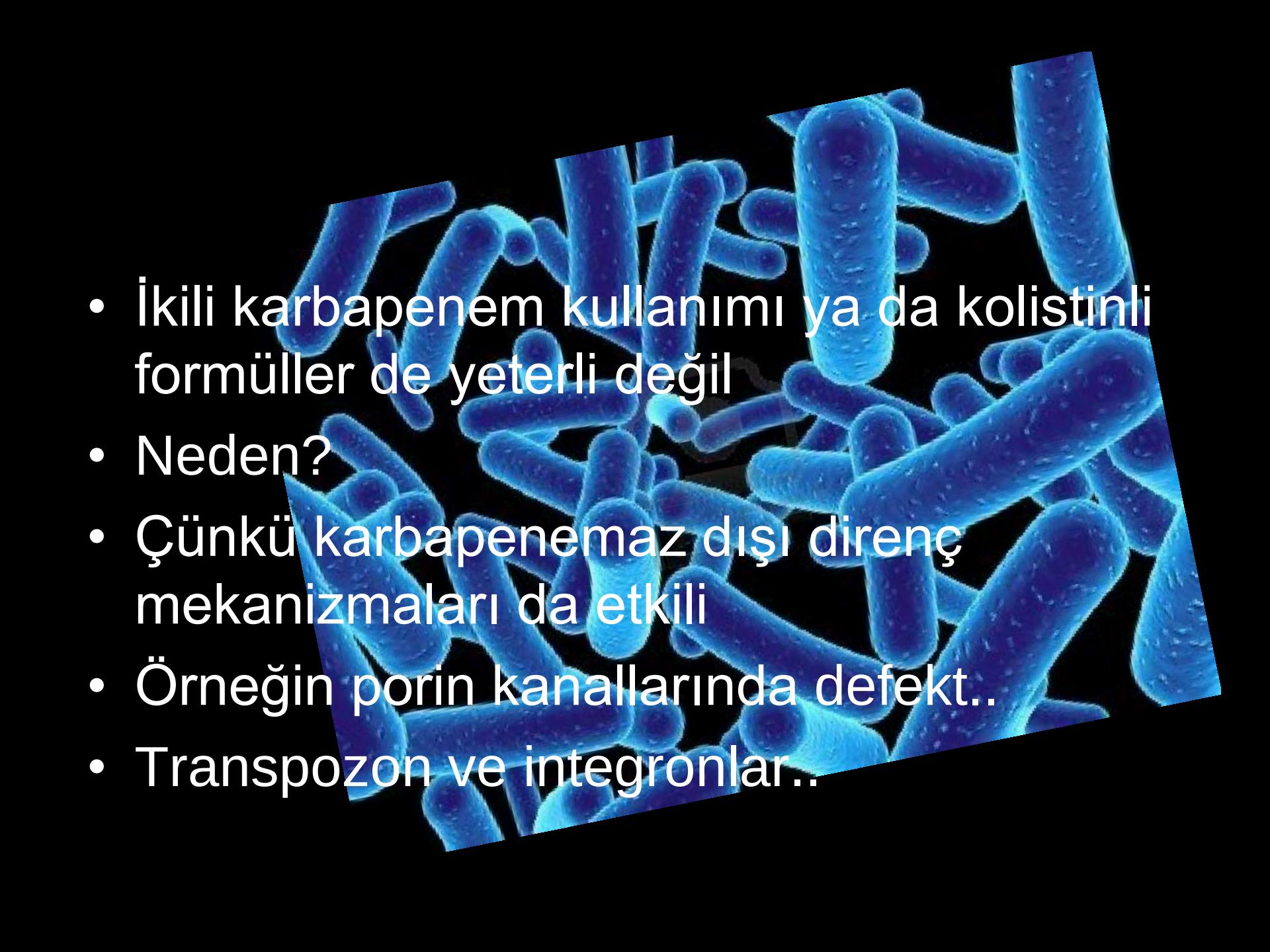


Figure 1. Time–kill studies for ertapenem, meropenem, colistin, ertapenem plus meropenem, and ertapenem plus meropenem plus colistin against pandrug-resistant *Klebsiella pneumoniae* isolated from a patient with a bloodstream infection. The horizontal line represents a reduction of 3 $\log_{10}$ CFU/ml compared with the initial bacterial count. GC, growth control; MEM, meropenem; ETP, ertapenem; COL: colistin.

- Kolistin + Meropenem + Ertapenem 0.5 ve 1 mcg/ml MİK düzeyinde etkili
- Diğer monotepapi ve ikili tedaviler ilk sekiz saat etkili, daha sonra etkisiz

Oliva A, IJID, 2015



- İkili karbapenem kullanımı ya da kolistinli formüller de yeterli değil
- Neden?
- Çünkü karbapenemaz dışı direnç mekanizmaları da etkili
- Örneğin porin kanallarında defekt..
- Transpozon ve integronlar..

Journal of Medical Microbiology (2012), **61**, 1417–1420 DOI 10.1099/jmm.0.038968-0

Transposons and integrons in colistin-resistant clones of *Klebsiella pneumoniae* and *Acinetobacter baumannii* with epidemic or sporadic behaviour

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[4]Laboratorio de Bacteri[illegible]a, Sanatorio de la Trinidad Mitre, Ciudad Autónoma de Buenos Aires, Argentina

[illegible]s and carbapenemases were found in *Klebsiella pneumoniae* [illegible]ll as a genomic resistance island of the AbaR type in *Acinetobacter* [illegible]ates from different hospitals from Buenos Aires City. PFGE [illegible]ssemination of antimicrobial resistance mechanisms among *K.* [illegible]olates, while in *A. baumannii* isolates the epidemic clone 1 from South America was found. Resistance determinants associated with horizontal gene transfer are contributing to the evolution to pandrug resistance in both epidemic and sporadic clones.

Received
Accepted [illegible] 2012

***K.Pneumoniae* ve *A.baumannii* suşlarında transpozon ve integron kaynaklı Kolistin direnci..**

AAC Journals.ASM.org

Successful Treatment of Carbapenemase-Producing Pandrug-Resistant *Klebsiella pneumoniae* Bacteremia

Jose F. Camargo,[a] Jacques Sim...s,[a] Thiago Beduschi,[b] Akin Tekin,[b] Laura Aragon,[c] Armando Pérez-Cardona,[d] Clara E. Prado,[e] Michele I. Morris,[a] Lilian M. Ab...

Rafael Cantón (Commentator)[f]

...ses, University of Miami Miller School of Medicine, Miami, Florida, U... ...e, Miami, Florida, USA[b]; Department of Pharmacy, Jackson Memo... ...USA[d]; Department of Microbiology, University of Miami, Miami... ...vestigación Sanitaria (IRYCIS), Madrid, Spain[f]; Red Española...

COL + IMP
COL + MEM + TİG
COL + IMP + ERT
.....?

...case involving a multidrug-resistant organism. The... ...ct of mechanisms of resistance on clinical outcome. A...

**New antibiotic options are ur... ...needed for the treatment of carbapenem-resistant *Ente...* 64-year-old female with prolo... ...d hospitalization following an intestinal transplant who d... to a serine carbapenemase-pr...ucing pandrug-resistant isolate of *Klebsiella pneumoniae*. ... regimens, the patient was successfully treated.

FIG 1 Ceftazidime-avibactam (CAZ-AVI) and carbapenem disc diffusion susceptibility testing of the pandrug-resistant isolate of CRKP in a Mueller-Hinton agar. On the left side of the plate are the discs of ertapenem, meropenem, and imipenem (top to bottom) with no zones of inhibition. On the right side of the plate is the CAZ-AVI disc alone with a zone of 26 mm. In the center are three sets of discs of ertapenem, meropenem, and imipenem (top to bottom) alongside CAZ-AVI. Note that there is an enhancement in the zone of inhibition in each set of discs compared to that of CAZ-AVI alone, indicating a possible synergistic effect of these drug combinations.

CASE PRESENTATION

A 64-year-old female with a history of diabetes mellitus developed *Clostridium difficile* colitis with toxic megacolon requiring total

...mase [NDM], and Vero... ...mase [VIM]) and class I... ...emase genes were not detected. The isolate was resistant to

International Journal of Antimicrobial Agents 39 (2012) 86–89

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International Journal of Antimicrobial Agents

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

Short communication

In vitro activity of avibactam (NXL104) in combination with β-lactams against Gram-negative bacteria, including OXA-48 β-lactamase-producing *Klebsiella pneumoniae*☆

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[b] Department of Infectious Diseases and Clinical Microbiology, Gülhane Military Medical Academy, Haydarpaşa Training Hospital, Istanbul, Turkey

ARTICLE INFO

ABSTRACT

The objective of this study was to investigate the in vitro antibacterial activity of avibactam (formerly NXL104) in combination with imipenem, cefepime or ceftazidime against Gram-negative bacteria. The isolates included: *Pseudomonas aeruginosa* harbouring PER-1 β-lactamase ($n = 14$); *Acinetobacter baumannii* harbouring PER-1, OXA-51 and OXA-58 ($n = 20$); carbapenem-non-susceptible *Klebsiella pneumoniae* ($n = 25$) and *Escherichia coli* ($n = 1$) harbouring OXA-48; carbapenem-non-susceptible *E. coli* harbouring both IMP-1 metallo-β-lactamase and extended-spectrum β-lactamase; carbapenem-non-susceptible *Serratia marcescens* ($n = 1$); and carbapenem-susceptible *E. coli* and *K. pneumoniae* isolates ($n = 12$) with CTX-M-15 ESBL. Minimum inhibitory concentrations (MICs) of imipenem, cefepime and ceftazidime were determined in combination with 4 mg/L avibactam by the Clinical and Laboratory Standards Institute (CLSI) method on Mueller–Hinton agar. Imipenem/avibactam and ceftazidime/avibactam displayed limited potency against *A. baumannii* isolates, whereas cefepime/avibactam and ceftazidime/avibactam were active against *P. aeruginosa*. *Klebsiella pneumoniae* isolates with OXA-48 β-lactamase were resistant to imipenem [MIC for 90% of the organisms (MIC_{90}) ≥4 mg/L]. MIC_{90} values for the combination of avibactam 4 mg/L with imipenem, cefepime and ceftazidime were in the susceptible range for all strains ($MIC_{90} \leq 0.5$ mg/L). All *E. coli* and *K. pneumoniae* isolates with CTX-M-15 β-lactamase were inhibited at ≤1 mg/L for combinations with avibactam and 100% were susceptible by CLSI breakpoint criteria to imipenem, cefepime and ceftazidime. In conclusion, combinations of imipenem, cefepime and ceftazidime with avibactam may present a promising therapeutic strategy to treat infections due to *K. pneumoniae* with OXA-48 enzyme as well as *K. pneumoniae*

Avibactam (NXL-104)
Fosfomisin
ARCS-121
.....

SCIENTIFIC REPORTS

OPEN

Stepwise evolution of pandrug-resistance in *Klebsiella pneumoniae*

Hosam M. Zowawi[1,2,3,4,*], Brian M. Forde[2,5,*], Mubarak Alfaresi[6], Abdulqadir Alzarouni[7], Yasser Farahat[7], Teik-Min Chong[8], Wai-Fong Yin[8], Kok-Gan Chan[8], Jian Li[9], Mark A. Schembri[2,5], Scot[illegible]. Beatson[2,5] & David L. Paterson[1,2]

Received: 07 April 2015
Accepted: 01 September 2015
Published: 19 October 2015

OXA-181
Çoklu direnç mekanizmaları
Karbapenem ve kolistin
direnci..

Carb[illegible]teriaceae (CRE) pose an urgent risk to global human health. CRE [illegible]mmercially available antibiotics threaten to return us to the pre-[illegible]le Real Time (SMRT) sequencing we determined the complete [illegible]*bsiella pneumoniae* isolate, representing the first complete [illegible]to all commercially available antibiotics. The precise location [illegible]ments, including mobile elements carrying genes for the OXA-[illegible], were defined. Intriguingly, we identified three chromosomal copies of an [illegible]*tnp1-bla*$_{OXA-181}$ mobile element, one of which has disrupted the *mgrB* regulatory gene, accounting for resistance to colistin. Our findings provide the first description of pandrug-resistant CRE at the genomic level, and reveal the critical role of mobile resistance elements in accelerating the emergence of resistance to other last resort antibiotics.

JCM
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Expansion and Evolution of a Virulent, Extensively Drug-Resistant (Polymyxin B-Resistant), QnrS1-, CTX-M-2-, and KPC-2-Producing *Klebsiella pneumoniae* ST11 International High-Risk Clone

Leonardo Neves Andrade,[a] Lúcia Vitali,[b] Gilberto Gambero Gaspar,[b] Fernando Bellissimo-Rodrigues,[b] Roberto Martinez,[b] Ana Lú

Universi ibeirão Preto, Ribe Preto, São Pa a de Ribei

In this lutic nd char ne that was is atien rt and quino le or nd Feb- ruary he ge- netic e lal re- latedn phylog the *S1*-PF r 10 virule sts to analyz *pneu-* nd is- p 32, 32, er) as types.

These bacteria also harbored *ureA*, *fimH*, *uge*, *wabG*, a *mrkD*, code for virulence factors associated with binding, biofilm formation, and the ability to colonize and escape from phago sis. Our study describes the association of important coresistance and virulence factors in the *K. pneumoniae* ST11 internati al high-risk clone, which makes this pathogen successful at infections and points to the quick expansion and evolution of this m ltiresistant and virulent clone, leading to a pandrug-resistant phenotype and persistent bacteria in a Brazilian hospital.

Yüksek Virülans Özellik:
ÜreA
fimH
kfuBC
uge
wabG
magA
mrkD
allS
cf29a

DR
DR
mukovizkoz
lm kapasitesi
aktiviteden kaçış
tozdan korunma
tivitesini kırma
Hızl ç aktarımı

Yüksek Riskli Bakteri..
Tara, bul, ayır ve yok et..

International Journal of Antimicrobial Agents 47 (2016) 1–3

Contents lists available at ScienceDirect

International Journal of Antimicrobial Agents

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

Hot Topic

Emergence of colistin-resistant bacteria in humans without colistin usage: a new worry and cause for vigilance

ARTICLE INFO

Keywords:
Enterobacteriaceae
Cationic antimicrobial peptides
Veterinary

ABSTRACT

Colistin is currently regarded as one of the 'last-resort' antibiotics used for the treatment of critical infections caused by multidrug-resistant Gram-negative pathogens. There have been numerous reports of the emergence of colistin resistance in patients, most of whom had previously received colistin therapy or with acquisition via nosocomial transmission. However, there are also ample reports of colistin resistance in humans who have not received the drug previously or without nosocomial transmission. We have also observed a similar occurrence in our study involving colistin resistance from several countries along with a similar phenomenon being reported by researchers. The observation of colistin resistance in humans without prior colistin exposure is of particularly great clinical importance and concern because of the current importance of colistin in clinical medicine. Colistin use and colistin-resistant bacteria in animals have been recently reported, suggesting that animals could also be a source of transmission of colistin-resistant bacteria to humans. This is a real worry and calls for clinicians to be aware and vigilant of this phenomenon and of the possibility of independent resistance to colistin in some patients.

NATIONAL SUMMARY DATA

Estimated minimum number of illnesses and deaths caused by antibiotic resistance*:

At least **2,049,442** illnesses,

23,000 deaths

**bacteria and fungus included in this report*

+

Estimated minimum number of illnesses and death due to *Clostridium difficile* (*C. difficile*), a unique bacterial infection that, although not significantly resistant to the drugs used to treat it, is directly related to antibiotic use and resistance:

At least **250,000** illnesses,

14,000 deaths

WHERE DO INFECTIONS HAPPEN?

Antibiotic-resistant infections can happen anywhere. Data show that most happen in the general community; however, most deaths related to antibiotic resistance happen in healthcare settings, such as hospitals and nursing homes.

U.S. Department of Health and Human Services
Centers for Disease Control and Prevention

CS239559

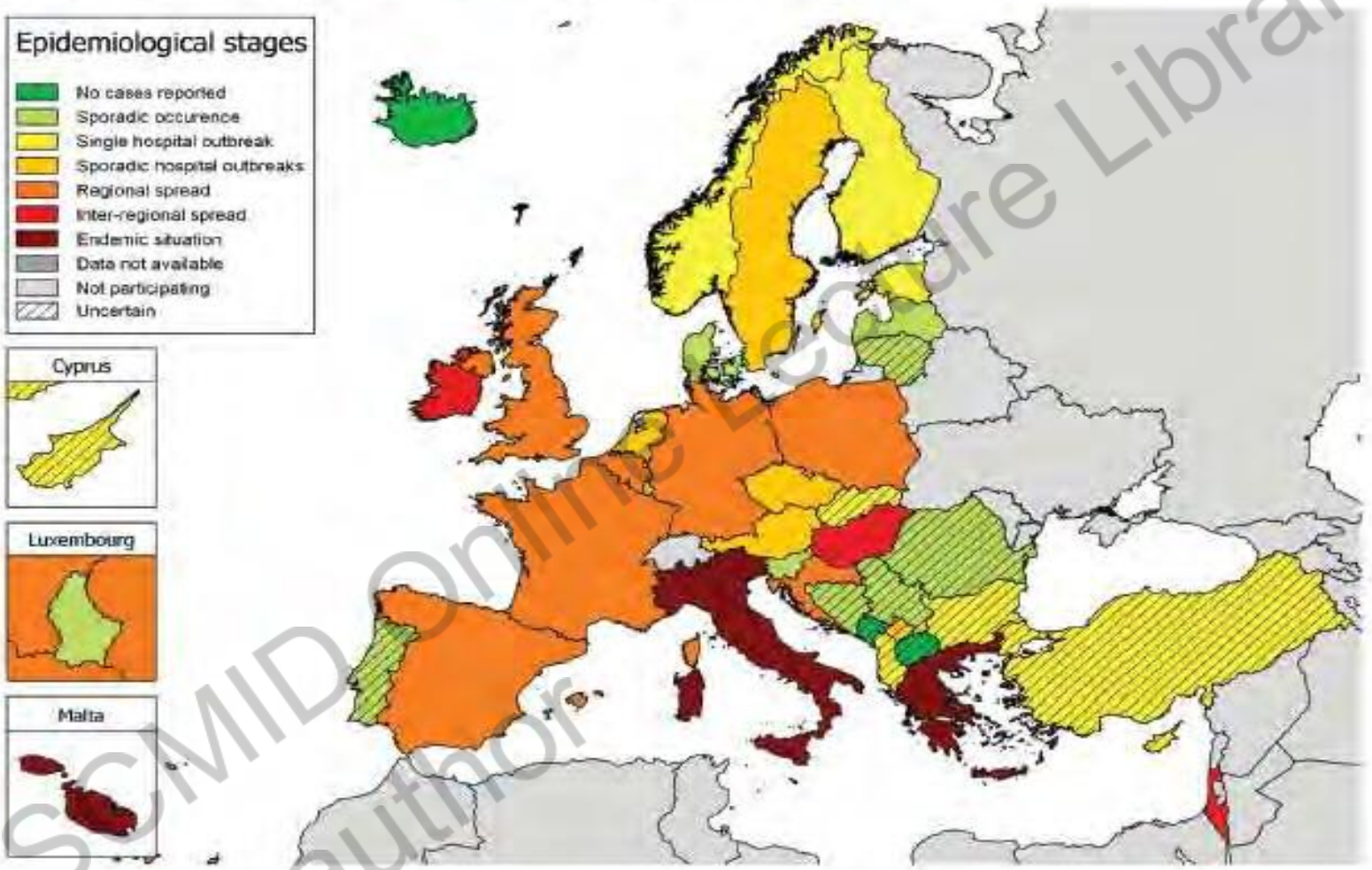
Antibiyotik Direncinin Önlenmesinde CDC'nin Dört Temel Yaklaşımı

- Dirençli Bakterinin İzlenmesi
- Yeni Antibiyotiklerin Geliştirilmesi ve Yeni Tanı Yöntemleri
- İnfeksiyonun ve Direnç Yayılımının Önlenmesi
- Antbiyiyoik Yönetimi

MDR'li Olgu Saptandıktan Sonra Ne Yapılmalı?

- İnfeksiyon kaynağı ve olası bulaş yolunu belirle (IA)
- Temas zincirini belirle ve izle (IA)
  - Hastanede 2-3 günlük bir gecikme, bulaşın en az 8-10 olguya olduğunu düşündürmelidir.
  - KIT, YBU gibi kritik yerlerde aynı anda yüksek bulaş riski
  - Temas izlemi şüpheli olgu nereye yatarsa yatsın yapılmalı, ya da hastanın tekrar hastaneye kabul edilişi ile başlatılmalıdır.
- Temas söz konusu ise geniş çaplı izlem oluştur ve negatif olguları da tekrar incele (inkübasyon periyodu) (IB)

Avrupa'da KRE Dağılımı - 2013



Glasner, Eurosurveillance 2013

Journal of Hospital Infection 91 (2015) 338–345

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Journal of Hospital Infection

journal homepage: www.elsevierhealth.com/journals/jhin

Organization of infection control in European hospitals☆

S. Hansen [a,*], W. Zingg [b], R. Ahmad [c], Y. Kyratsis [d], M. Behnke [a], F. Schwab [a], D. Pittet [b], P. Gastmeier [a] on behalf of the PROHIBIT study group[†]

[a] *Charité – University Medicine Berlin, Institute for Hygiene, Germany*
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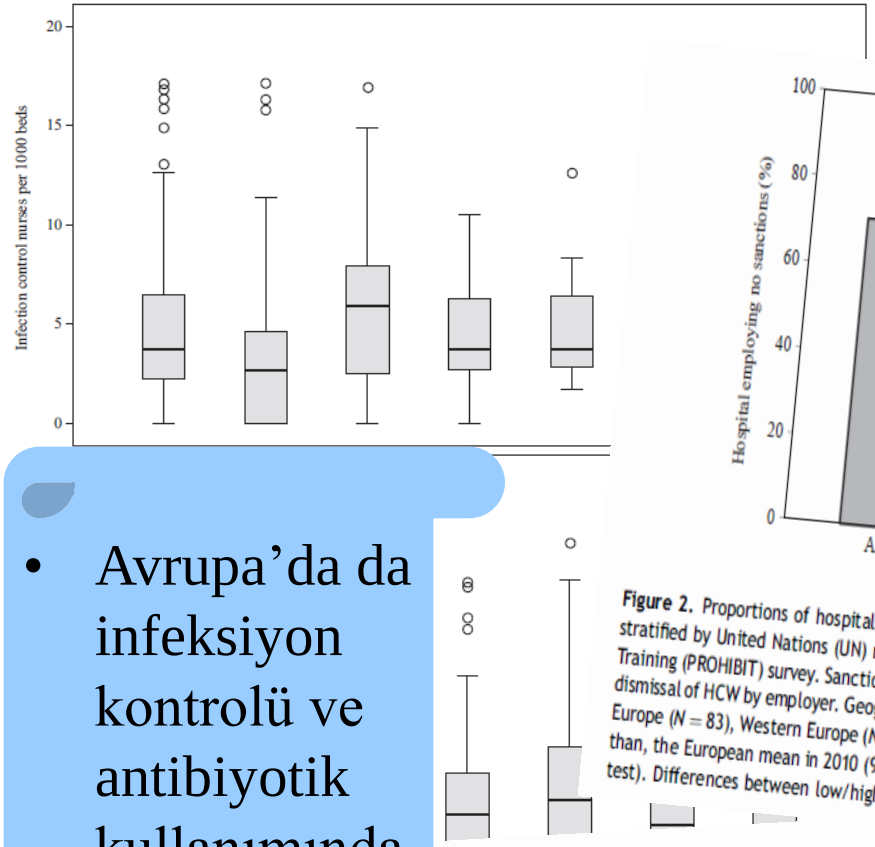
SUMMARY

Background: The Prevention of Hospital Infections by Intervention and Training (PROHIBIT) survey was initiated to investigate the status of healthcare-associated infection (HCAI) prevention across Europe.

Aim: This paper presents the methodology of the quantitative PROHIBIT survey and outlines the findings on infection control (IC) structure and organization including management's support at the hospital level.

Methods: Hospitals in 34 countries were invited to participate between September 2011 and March 2012. Respondents included IC personnel and hospital management.

Findings: Data from 309 hospitals in 24 countries were analysed. Hospitals had a median (interquartile range) of four IC nurses (2–6) and one IC doctor (0–2) per 1000 beds. Almost all hospitals (96%) had defined IC objectives, which mainly addressed hand hygiene (87%), healthcare-associated infection reduction (84%), and antibiotic stewardship (66%). Senior



- Avrupa'da da infeksiyon kontrolü ve antibiyotik kullanımında sorun vardı..

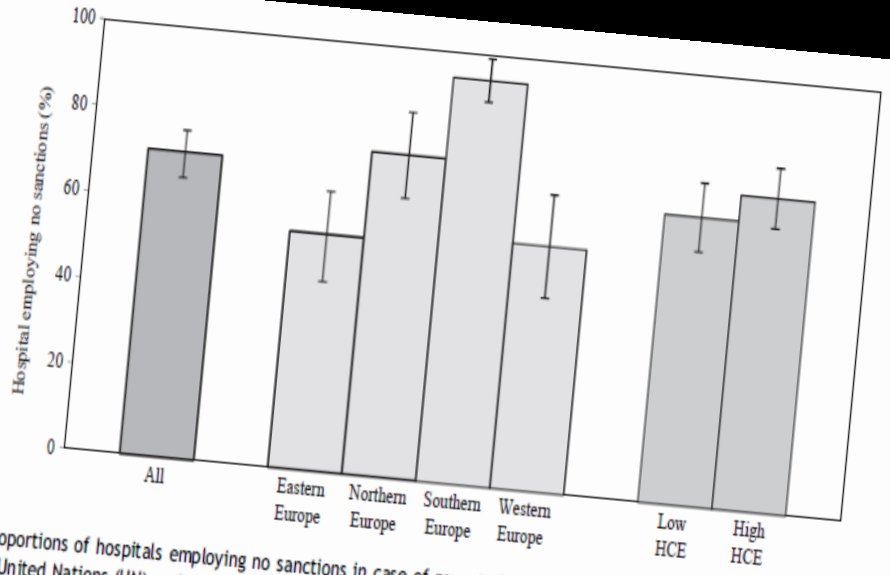


Figure 2. Proportions of hospitals employing no sanctions in case of repeated violation of infection prevention and control practices stratified by United Nations (UN) regions and healthcare expenditure (HCE) – The Prevention of Hospital Infection by Intervention and Training (PROHIBIT) survey. Sanctions were defined as: (i) review of healthcare worker (HCW) by supervisor; (ii) relocation of HCW; or (iii) dismissal of HCW by employer. Geographic regions according to UN grouping; Eastern Europe ($N = 88$), Northern Europe ($N = 73$), Southern Europe ($N = 83$), Western Europe ($N = 65$).[13] Low/high HCE defined as the share of the gross domestic product less or equal to, or greater than, the European mean in 2010 (9%); low HCE ($N = 135$), high HCE ($N = 174$).[14] Differences between UN regions, $P < 0.001$ (chi-square test). Differences between low/high HCE, $P = 0.286$ (chi-square test).

Figure 1. I
Th
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Nor

	All hospitals	Region[a]				Low HCE	High HCE
		Eastern Europe	Northern Europe	Southern Europe	Western Europe		
stablished (%)	66	65	70	59	72	64	68
Direct access to microbiology data[c,d] (%)	61	45	67	61	72	50	69

HCE, healthcare expenditure; IQR, interquartile range; IC, infection control; CEO, chief executive officer; ICN, infection control nurse; ICD, infection control doctor.

[a] Geographic regions according to United Nations (UN) grouping; Eastern Europe ($N = 88$), Northern Europe ($N = 73$), Southern Europe ($N = 83$), Western Europe ($N = 65$).[14]

[b] Low/high HCE defined as the share of the gross domestic product less or equal to, or greater than, the European mean in 2010 (9%); low HCE ($N = 135$), high HCE ($N = 174$).[15]

[c] Differences between UN regions: $P < 0.05$ (chi-square test).

[d] Differences between low/high HCE: $P < 0.05$ (chi-square test).

New Horizons for Pediatric Antibiotic Stewardship

Jennifer L. Goldman, MD, MS[a,b,*], Jason G. Newland, MD, MEd[c]

KEYWORDS

• Pediatrics • Antimicrobial stewardship • Antimicrobial resistance

KEY POINTS

- Inappropriate antimicrobial prescribing in pediatrics is common and the number of pediatric antimicrobial stewardship programs (ASPs) continues to grow.
- Many targets for pediatric ASP interventions differ compared with targets for adults due to differences in common diseases and prescribed antibiotics unique to children.
- Combating antimicrobial resistance is gaining recognition by government and policy makers, which reinforces the importance of stewardship.
- Collaborative efforts among ASPs nationally will continue to strengthen the approach to pediatric stewardship initiatives.

Infect Dis Clin N Am 29 (2015) 503–511

INTRODUCTION

Antimicrobial resistance is a major health threat resulting in at least 2 million illnesses and 23,000 deaths in the United States annually. The cause of antimicrobial resistance is multifactorial with the overuse and inappropriate use of antimicrobials contributing to the development of resistance. Unfortunately, the threat of bacterial resistance is

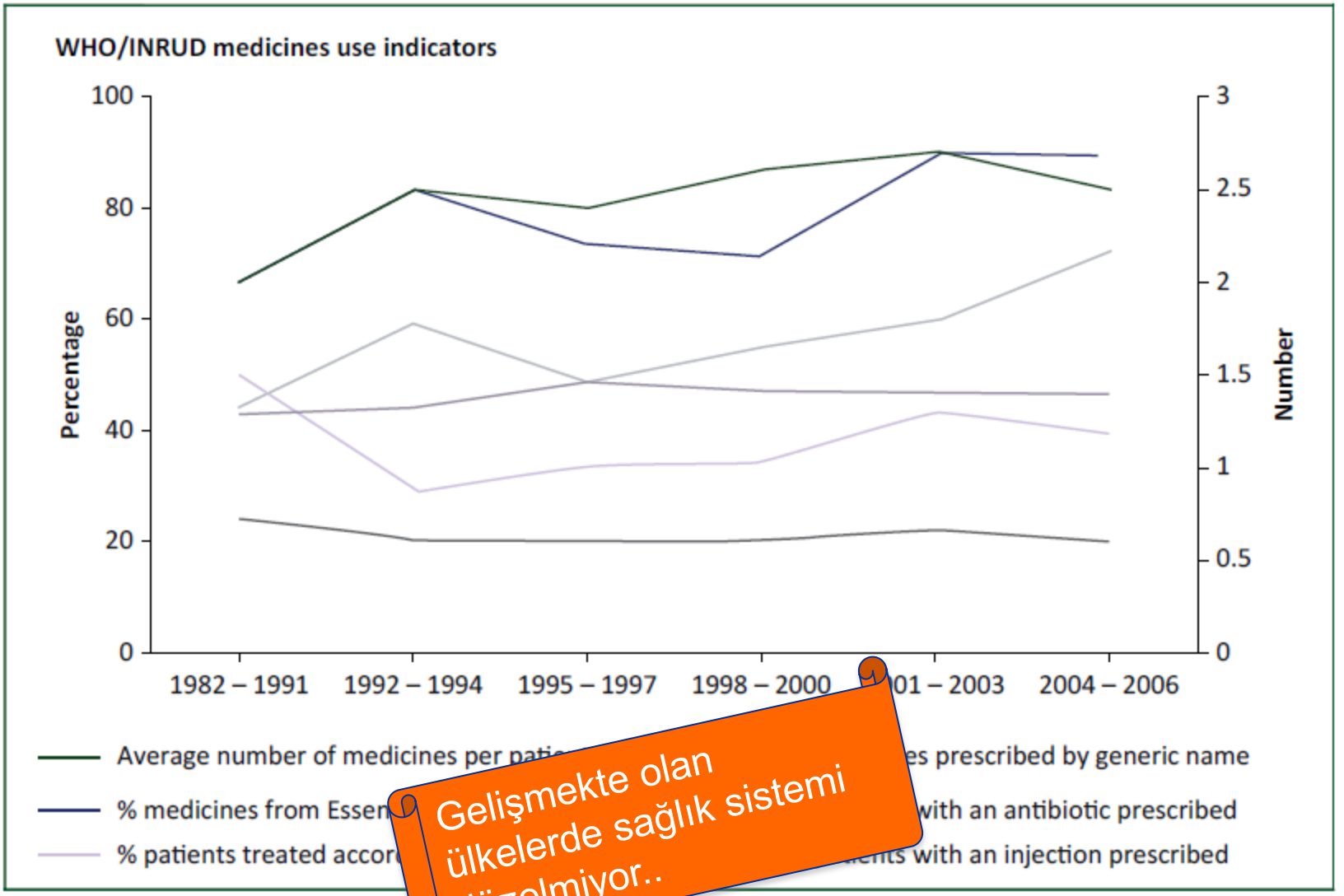


FIGURE 2. World Health ization (WHO) report on medicines use in primary care in developing and transitional countries over time, as reported in the *World Medicines Situation 2011* [48]. INRUD, International Network for the Rational Use of Drugs.

Ve bugün..

- Çoklu Antibiyotik Direncine sahip gram negatif
- Karbapeneme dirençli Enterik bakteriler
- Karbapeneme dirençli Pseuodomonaslar
- Karbapeneme dirençli Acinetobacter suşları
- Panrezistan gram negatifler..

- Çoklu Antibiyotik Direncine sahip gram negatif bakteriler giderek artıyor..

Antibiotic Use and Emerging Resistance

How Can Resource-Limited Countries Turn the Tide?

Lisa M. Bebell*,†, Anthony N. Muiru‡

Boston, MA, USA

GLOBAL HEART, VOL. 9, NO. 3, 2014
September 2014: 347-358

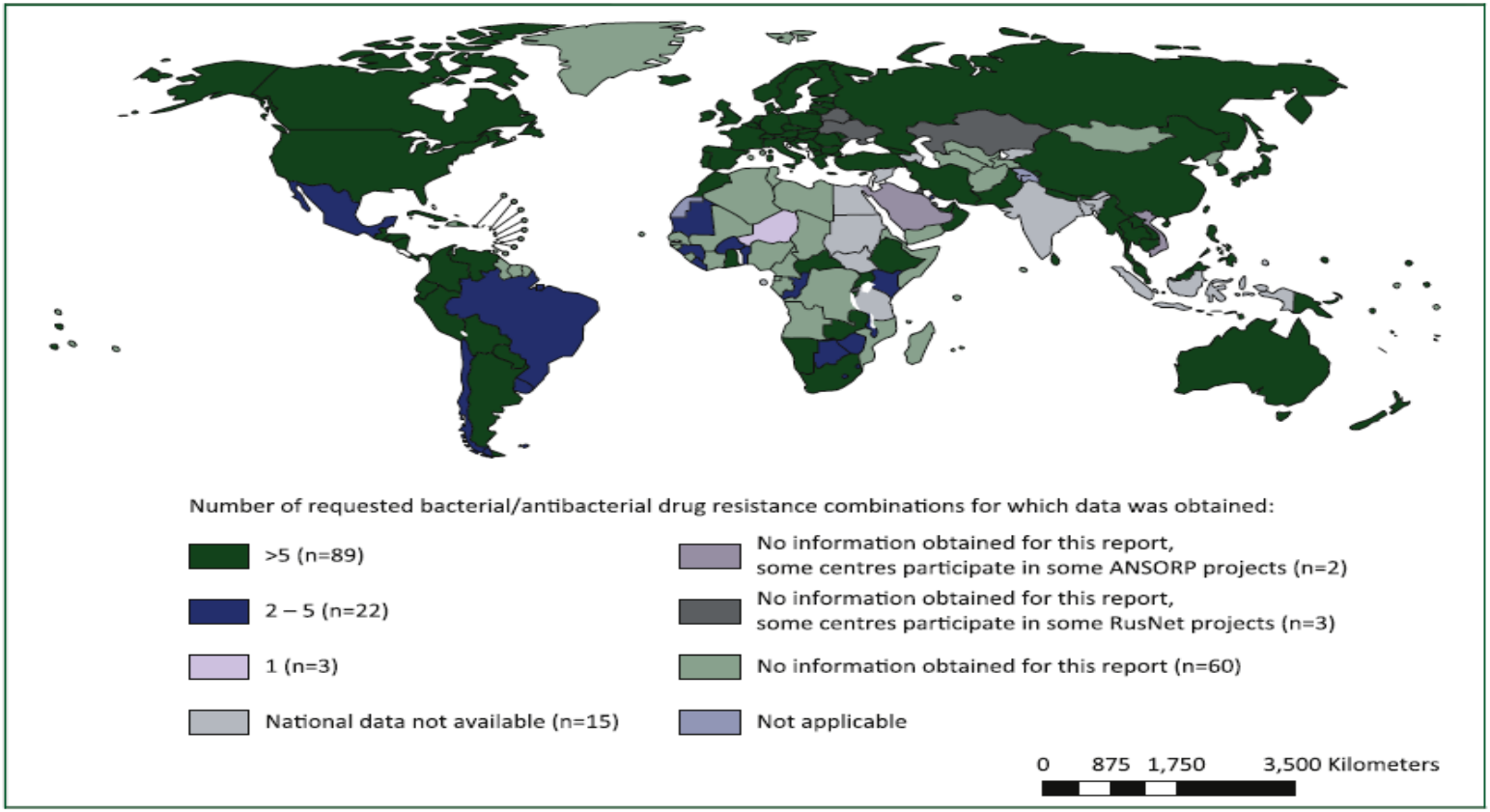
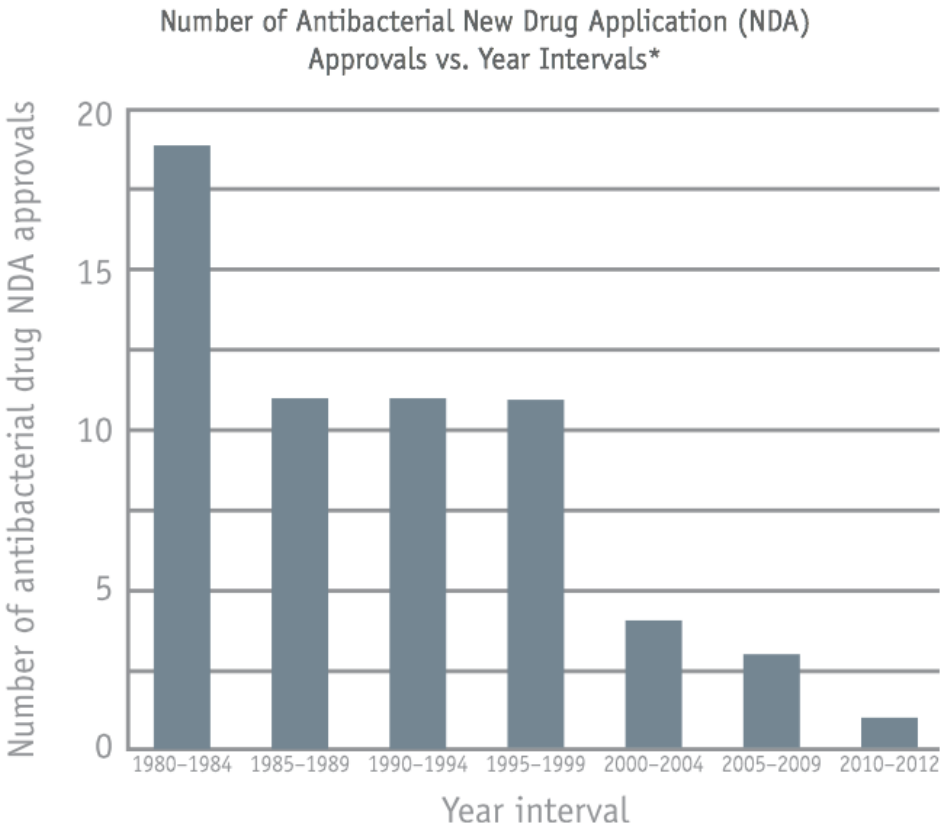


FIGURE 1. World Health Organization report on availability of data on resistance for selected bacteria-antibacterial drug combinations, 2013 [29]. Number of reported bacteria is based on the information obtained on the basis of request to national official sources on antibacterial susceptibility testing of ≥1 of the requested combinations, regardless of denominator data. Data from United Arab Emirates originate from Abu Dhabi only. ANSORP, Asian Network for Surveillance of Resistant Pathogens.

Tomorrow's Antibiotics: The Drug Pipeline

The number of new antibiotics developed and approved has steadily decreased in the past three decades, leaving fewer options to treat resistant bacteria.



*Intervals from 1980–2009 are 5-year intervals; 2010–2012 is a 3-year interval. Drugs are limited to systemic agents.
Data courtesy of FDA' s Center for Drug Evaluation and Research (CDER).

Mark Koba | @MarkKobaCNBC

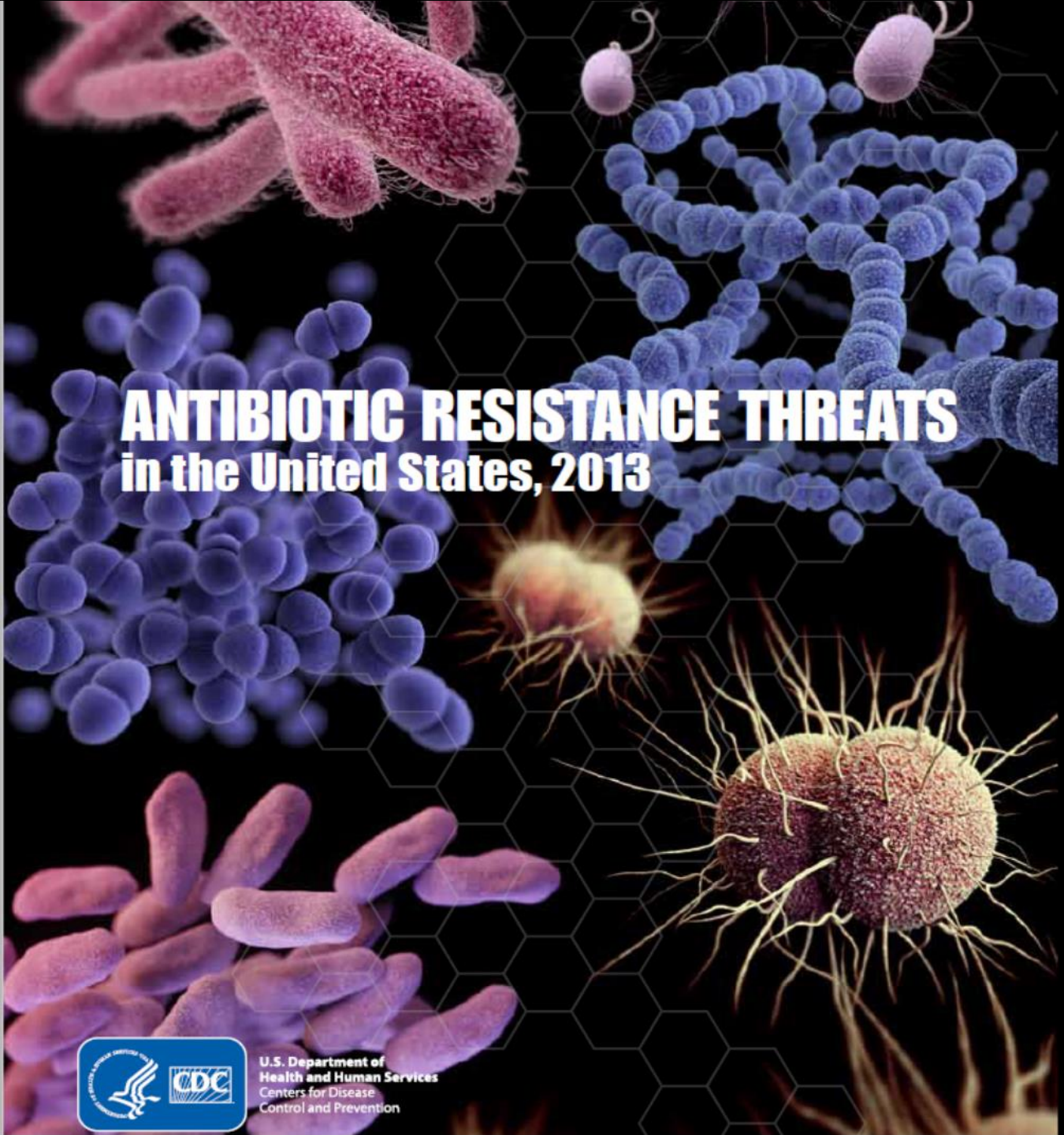
Tuesday, 23 Apr 2013 | 7:33 AM ET

CNBC

Olena Timashova | E+ | Getty Images

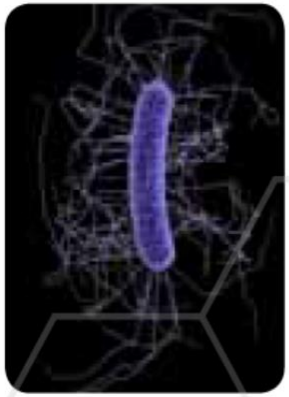
A looming shortage of antibiotic drugs threatens to derail efforts to fight the so called superbugs, according to a new report.

The Infectious Diseases Society of America, (IDSA) released a study last week stating that with just four of the big pharma firms researching



ANTIBIOTIC RESISTANCE THREATS
in the United States, 2013

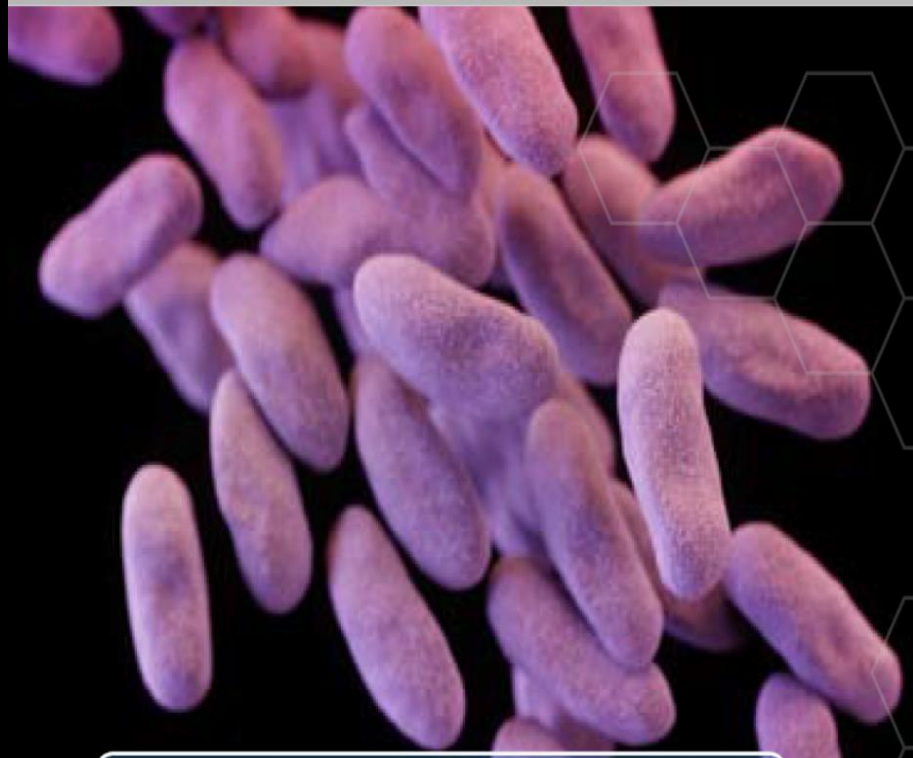
U.S. Department of Health and Human Services
Centers for Disease Control and Prevention



THREAT LEVEL
URGENT

These bacteria are immediate public health threats that require urgent and aggressive action.

MICROORGANISMS WITH A THREAT LEVEL OF URGENT



CARBAPENEM-RESISTANT ENTEROBACTERIACEAE

9,000 DRUG-RESISTANT INFECTIONS PER YEAR

600 DEATHS

CARBAPENEM-RESISTANT *KLEBSIELLA* SPP. **7,900**

1,400 CARBAPENEM-RESISTANT *E. COLI*

CRE HAVE BECOME RESISTANT TO ALL OR NEARLY ALL AVAILABLE ANTIBIOTICS

THREAT LEVEL **URGENT**

This bacteria is an immediate public health threat that requires urgent and aggressive action.

CARBAPENEM-RESISTANT ENTEROBACTERIACEAE

U.S. Department of Health and Human Services
Centers for Disease Control and Prevention

- Her yıl yaklaşık 140.000 SHİE *Enterobacteriaceae* infeksiyonu
- Bunların 9300/yıl CRE infeksiyonu
- CRE kaynaklı Kan Dolaşım Sistemi infeksiyonlarında %50 mortalite
- Olguların %18'i uzun süreli bakım merkezlerinde kalanlar

	Percentage of Enterobacteriaceae healthcare-associated infections resistant to carbapenems	Estimated number of infections	Estimated number of deaths attributed
Carbapenem-Resistant *Klebsiella* spp.	11%	7,900	520
Carbapenem-resistant *E. coli*	2%	1,400	90

- AB Direnci nedeniyle ..
- 20 milyar USD direkt
- 35 milyar USD dolaylı..
- GlaxoSmithKline, Pfizer, Astra Zenaca, Merck

Superbugs are a 'Costly War We Can't Win'

- 190 milyon doz AB / gün
- 133 milyon reçete
- Yaklaşık %50'si gereksiz..


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TABLE 1: National Targets to Combat Antibiotic-Resistant Bacteria
By 2020, the United States will:
For CDC Recognized Urgent Threats:
Reduce by 50% the incidence of overall *Clostridium difficile* infection compared to estimates from 2011.
Reduce by 60% carbapenem-resistant Enterobacteriaceae infections acquired during hospitalization compared to estimates.
Maintain the prevalence of ceftriaxone-resistant *Neisseria gonorrhoeae* below 2% compared to estimates from 2013.
For CDC Recognized Serious Threats:
Reduce by 35% multidrug-resistant *Pseudomonas spp.* infections acquired during hospitalization compared to estimates from 2011.
Reduce by at least 50% overall methicillin-resistant *Staphylococcus aureus* (MRSA) bloodstream infections by 2020 as compared to 2011.*
Reduce by 25% multidrug-resistant non-typhoidal *Salmonella* infections compared to estimates from 2010-2012.
Reduce by 15% the number of multidrug-resistant TB infections.[1]
Reduce by at least 25% the rate of antibiotic-resistant invasive pneumococcal disease among <5 year-olds compared to estimates from 2008.
Reduce by at least 25%the rate of antibiotic-resistant invasive pneumococcal disease among >65 year-olds compared to estimates from 2008.

* This target is consistent with the reduction goal for MRSA bloodstream infections (BSI) in the *National Action Plan to Prevent Healthcare-Associated Infections (HAI): Road Map to Elimination,* which calls for a 75% decline in MRSA BSI from the 2007-2008 baseline by 2020. Additional information is available at http://www.health.gov/hai/prevent_hai.asp#hai_plan.

[1] The TB activities identified in the NAP are included as they represent critical near-term public health activities that will support progress to reduce the burden of drug-resistant TB in the U.S. Additional domestic and global activities to address drug-resistant TB will be provided in a companion action plan specific to TB and will be submitted to the President no later than September, 2015. The companion action plan will build on recommendations of the Federal TB Task Force (http://www.cdc.gov/mmwr/pdf/rr/rr5803.pdf) as well the work of the interagency USG TB working group.

TABLE 2: GOALS AND OBJECTIVES: Combating Antibiotic-Resistant Bacteria	
GOAL 1: Slow the Emergence of Resistant Bacteria and Prevent the Spread of Resistant Infections	
Objectives	
1.1	Implement public health programs and reporting policies that advance antibiotic-resistance prevention and foster antibiotic stewardship in healthcare settings and the community.
1.2	Eliminate the use of medically-important antibiotics for growth promotion in food- producing animals and bring other agricultural uses of antibiotics, for treatment, control, and prevention of disease, under veterinary oversight.
1.3	Identify and implement measures to foster stewardship of antibiotics in animals.
GOAL 2 : Strengthen National One-Health Surveillance Efforts to Combat Resistance Objectives	
2.1	Create a regional public health laboratory network to strengthen national capacity to detect resistant bacterial strains and a specimen repository to facilitate development and evaluation of diagnostic tests and treatments.
2.2	Expand and strengthen the national infrastructure for public health surveillance and data reporting, and wprovide incentives for timely reporting of antibiotic-resistance and antibiotic use in all healthcare settings.
2.3	Develop, expand, and maintain capacity in State and Federal veterinary and food safety laboratories to conduct antibiotic susceptibility testing and characterize select zoonotic and animal pathogens.
2.4	Enhance monitoring of antibiotic-resistance patterns, as well as antibiotic sales, usage, and management practices, at multiple points in the production chain for food animals and retail meat.
GOAL 3: Advance Development and Use of Rapid and Innovative Diagnostic Tests for Identification and Characterization of Resistant Bacteria	
Objectives	
3.1	Develop and validate new diagnostics—including tests that rapidly distinguish between viral and bacterial pathogens and tests that detect antibiotic-resistance—that can be implemented easily in a wide range of settings.
3.2	Expand availability and use of diagnostics to improve treatment of antibiotic-resistant infections, enhance infection control, and facilitate outbreak detection and response in healthcare and community settings.
GOAL 4: Accelerate Research to Develop New Antibiotics, Other Therapeutics, Vaccines, and Diagnostics	
Objectives	
4.1	Conduct research to enhance understanding of environmental factors that facilitate the development of antibiotic-resistance and the spread of resistance genes that are common to animals and humans.
4.2	Increase research focused on understanding the nature of microbial communities, how antibiotics affect them, and how they can be harnessed to prevent disease.
4.3	Intensify research and development of new therapeutics and vaccines, first-in-class drugs, and new combination therapies for treatment of bacterial infections.
4.4	Develop non-traditional therapeutics and innovative strategies to minimize outbreaks caused by resistant bacteria in human and animal populations.
4.5	Expand ongoing efforts to provide key data and materials to support the development of promising antibacterial drug candidates.

İnfeksiyon Kontrol Yöntemleri Network Sistemi

FIGURE 1. Distribution of Society for Healthcare Epidemiology of America Research Network members responding to the survey.

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The Society for Healthcare Epidemiology of America

Five Things Providers and Patients Should Question

1 Don't continue antibiotics beyond 72 hours in hospitalized patients unless patient has clear evidence of infection.

Antibiotics are often started when a patient is possibly infected. After three days, laboratory and radiology information is available and antibiotics should either be deescalated to a narrow-spectrum antibiotic based on culture results or discontinued if evidence of infection is no longer present. Lessening antibiotic use decreases risk of infections with *Clostridium difficile (C. difficile)* or antibiotic-resistant bacteria.

2 Avoid invasive devices (including central venous catheters, endotracheal tubes and urinary catheters) and, if required, use no longer than necessary. They pose a major risk for infections.

Invasive devices are often necessary for patient support; however, they are a major risk for healthcare-associated infections (HAIs). We are learning they can often be avoided and, if used, can be quickly removed with the help of clinical reminders and protocols. They should never be used for convenience.

3 Don't perform urinalysis, urine culture, blood culture or *C. difficile* testing unless patients have signs or symptoms of infection. Tests can be falsely positive leading to overdiagnosis and overtreatment.

Although important for diagnosing disease when used in patients with appropriate signs or symptoms, these tests often are positive when an infection is not present. For example, in the absence of signs or symptoms, a positive blood culture may represent contamination, a positive urine culture could represent asymptomatic bacteriuria, and a positive test for *C. difficile* could reflect colonization. There are no perfect tests for these or most infections. If these tests are used in patients with low likelihood of infection, they will result in more false positive tests than true positive results, which will lead to treating patients without infection and exposing them to risks of antibiotics without benefits of treating an infection.

4 Don't use antibiotics in patients with recent *C. difficile* without convincing evidence of need. Antibiotics pose a high risk of *C. difficile* recurrence.

C. difficile can be a life threatening illness and is generally caused by antibiotics killing normal bacteria in the intestine. Patients recovering from *C. difficile* are three times as likely to have a recurrence if they receive an antibiotic in the following month. However, unnecessary antibiotics are often used in this population – primarily for misdiagnosed urinary tract infection or pneumonia.

5 Don't continue surgical prophylactic antibiotics after the patient has left the operating room.

Prophylactic antibiotics during surgery can significantly decrease the risk of surgical site infections; however, they only have benefit if used immediately around the time of surgery. When antibiotics are used for longer than necessary, they increase the risk of infection with antibiotic-resistant bacteria and *C. difficile*.

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Five Things Providers and Patients Should Question

1

Hastaların yatışından 72 saat sonra halen infeksiyon kanıtları yetersizse antibiyotikleri kes

- Hastaların ilk yatışında çoğu merkezlerde antibiyotikler infeksiyon şüphesiyle başlanır. 72 saat sonra kültür sonuçlarına göre de-eskalasyon uygulanır ya da infeksiyonları klinik, laboratuar ve radyolojik bulguların desteklemediği hastalarda antibiyotikler kesilir. Bu hem dirençli patojenleri hem de *Clostridium difficile* infeksiyonlarını önler.

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Five Things Providers and Patients Should Question

2

Santral ve üriner kateter ile endotrakeal tüp gibi invazif girişimlerden kaçın. Girişim yapılmış hastalarda en kısa sürede çıkarma çabası göster. İnvazif girişimlerin infeksiyon riskini artıran en önemli faktör olduğunu unutma..

- İnvazif girişimler hastaların tedavi desteğini sağlayan önemli unsurlardır. Gereksiz uygulamalar infeksiyon riskini artırmaktadır. Tedavi süresince hastalara önlem amacıyla invazif girişimler uygulanmamalı, gereksiz yere tutulmamalıdır.

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Five Things Providers and Patients Should Question

3

Gereksiz yere idrar analizi, idrar kültürü, kan kültürü ya da *C.difficile* toksini bakma. Yalancı pozitif sonuçlar hatalı infeksiyon tanısı ve antibiyotik tedavisine neden olabilir.

- Tanı testleri semptom ve bulguları olan hastalarda önemli işlev görmekle birlikte, bazen normal hastalarda da yalancı pozitif sonuçlar verebilir. Kan kültürü kontaminasyon nedeniyle, idrar kültürü asemptomatik bakteriüri nedeniyle, *C.difficile* toksin taşıyıcılık nedeniyle pozitiif sonuçlanabilir. Bunların dikkate alınması ile hatalı tanı ve tedavi yapılacağından gereksiz istemlerden kaçınılmalıdır.

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4

C.difficile için güçlü kanıtların olmadığı sürece antibiyotik kullanma. Gereksiz antibiyotik tedavisi *C. difficile* infeksiyonlarının artışına neden olabilir.

- *C.difficile* için klinik bulgular ve semptomlar olmadan elde edilen laboratuar sonuçlarını şüpheyle karşıla. Doğruluğundan şüphe duyduğun olgulara antibiyotik kullanma. Gereksiz antibiyotik kullanımı *C.difficile* kontrolü yerine artışına neden olabilir.

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Five Things Providers and Patients Should Question

5 Cerrahi proflaksi hasta ameliyathaneden çıkmadan önce sonlandırılmalıdır.

- Cerrahi proflaksi uygun zamanda ve uygun dozda yapıldığında infeksiyon kontrolü açısından yararlı bir uygulamadır. Ancak uzamış cerrahi proflaksi antibiyotik direnç gelişimine ve *C.difficile* infeksiyonlarına neden olmaktadır.

GUIDELINES
Pocketcard

IDSA

SHEA
The Society for Healthcare Epidemiology of America

Society of Infectious Diseases Pharmacists

Antimicrobial Stewardship

Strategies, Barriers, Solutions

Consultant:
Thomas M. Hooton, MD
Professor of Clinical Medicine
University of Miami Miller School of Medicine

GuidelineCentral.com®

Key Points

- Optimizing antimicrobial therapy minimizes antimicrobial resistance and adverse drug reactions.
- In one large cohort study of hospitalized patients, antimicrobials were the second most common cause of adverse events.
- In another study, antimicrobials were the class most frequently associated with prescribing errors.
- Many antimicrobials have been associated with superinfection due to *Clostridium difficile*, causing morbidity ranging from diarrhea to life threatening colitis.
- A properly framed discussion regarding implementation of a program must present usage and resistance data specific to the hospital, unit, and patient population in addition to the general issues of antimicrobial resistance.
- The main responsibility for an antimicrobial stewardship program rests on physicians and pharmacists.
- Antimicrobial stewardship must operate 24/7 to be effective.
- Educational activities are integral to successful antimicrobial stewardship – both its clinical and administrative aspects.
  - A public-access web site is an excellent way to accomplish this.
- Active auditing of prescribing practices is essential for determining the needs and targets of intervention.
- It is highly unlikely that any antimicrobial stewardship effort could be effective in the absence of information technology support.
- An adequate, institution-appropriate budget including personnel compensation is necessary for a successful program.
- Recent payment rules from the Centers for Medicare and Medicaid Services specify that hospitals will no longer be reimbursed for certain nosocomial infections that are perceived to be avoidable. Other third-party payers are likely to follow suit.
- Restriction of selected agents is often difficult to implement:
  - entirely unavailable (formulary-based restriction)
  - available for only certain indications (criteria-based restriction)
  - available only after approval by some authority (preauthorization-based restriction)

Strategy

General Management and Implementation Issues

Auditing and feedback

- Real-time auditing helps optimize therapy on an individual-patient basis.
- Constructive and patient-specific feedback from experts in antimicrobial therapy is essential.
- The optimal method of communicating the recommendation to the provider—that is, feedback—must be defined.
- Match the mode of communication to the level of acuity and complexity.

Prescriber education

- Passive education about appropriate antimicrobial use can include grand rounds, newsletters, and written guidelines.
- Passive education should be distinguished from active education that occurs in the context of auditing and feedback or preauthorization for specific patients.
- Education about the program itself should not be overlooked.
- A public, up-to-date Web site is an excellent way to inform providers about their institutional antimicrobial stewardship program and offers easy access to information about current strategies:

Informational Websites
www.nebraskamed.com/asp
www.hosp.uky.edu/pharmacy/AMT/default.html
www.ucsf.edu/idmp

Guideline implementation

- Guidelines must be regularly re-evaluated and, if necessary, revised to reflect recent developments reported in the scientific literature.

Application of information technology

- Applications on the Web or on personal digital assistants can greatly facilitate rapid updating and dissemination of information compared with paper-based sources.

- **Computerized physician order entry further expands the potential for intervening at the time of prescribing.**
  - *Examples of tools are stop-order reminders and/or flags, order sets containing prophylaxis and treatment recommendations, assistance with dosing, information about formulary availability, and approval criteria for restricted antibiotics.*
- **Many commercially available clinical decision support systems integrate electronic medical records and can facilitate both back-end and front-end approaches to providing real-time, patient-specific recommendations, although they cannot replace clinical judgment.**

Specific Antimicrobial Issues

Restriction and/or preauthorization

- **Formulary based restriction: Agents that are entirely unavailable**
- **Criteria-based restriction: Agents that are available for only certain indications**
- **Preauthorization-based restriction: Agents that are available only after approval by some authority**

Intravenous-to-oral switch

- **Antimicrobial intravenous-to-oral switch can achieve substantial economic benefits.**
- **Program staff should consider which drugs to target, criteria for switching, and how the switch is performed.**
- **Third-party payer criteria for inpatient status may not be affected by intravenous-to-oral switching.**

De-escalation or streamlining

- **De-escalation or streamlining is a subclass of auditing and feedback that focuses on changing from initial broad-spectrum (often combination) empiric therapy to a narrower-spectrum (often monotherapy) agent when culture identification and susceptibility results become available.**
- **Its role in limiting use of broad-spectrum antimicrobials can be fraught with complications.**
- **Successful strategies must offer clear, predefined criteria for narrowing or discontinuing antimicrobials, while allowing for clinical judgment.**

Table 1. Antimicrobial Stewardship Strategies with Associated Barriers and Solutions

Strategy	Barriers to Effective Implementation	Potential Solutions
Auditing and feedback	Problems in identifying patients who are receiving suboptimal therapy	Use rules-based computer systems that combine pharmacy and microbiologic data to flag patients of interest. Manually review antimicrobial order sheets. Review microbiologic data to identify targeted organisms.
	Difficulty communicating recommendations to providers	Approve policy delineating appropriate means of communicating recommendations.
	Lack of clarity in appropriate methods for providing feedback	Create nonpermanent forms for written communication in the medical record.
	Medicolegal concerns about providing feedback in the medical record	Time communication for greatest likelihood of impact (eg, before rounds). Hold intermittent, regularly scheduled antibiotic rounds between the stewardship team and staff from services that heavily use antimicrobials.
Restriction and/or preauthorization	Perceived challenge to physician autonomy	Have an approved policy by the medical executive committee. Grant time-restricted approvals (eg, for 24-72 hrs) to balance physicians' and stewardship concern. Regularly review the use of restricted agents to evaluate their continued restriction.
	Integration of restriction policies into workflow	Use computerized physician order-entry systems to give restriction notifications automatically. Use dedicated pagers for restricted agents to minimize delays in authorization. Establish clear procedures for authorization after hours.
Prescriber education	Lack of knowledge about the role of stewardship programs	Hold antimicrobial stewardship grand rounds to explain the program and provide hospital-specific data.
Guideline implementation	Poor knowledge of, and adherence to, guidelines for antimicrobial use	Disseminate information in printed handbooks, integrate it in order sets, and provide easy access on Internet or intranet. Involve opinion leaders from multiple specialties in developing guidelines.
Application of information technology	Considerable investment of financial and human resources	Emphasize its importance in patient safety and the potential to avoid substantial costs.
Intravenous-to-oral switch	Identification of eligible patients	On a daily basis, review patients receiving intravenous forms of highly bioavailable antimicrobials. Develop criteria to help clinicians determine candidacy for switch (eg, body temperature, white blood cell count).
De-escalation or streamlining	Unwillingness of providers to de-escalate or streamline	Refer to studies that demonstrated safety of de-escalation or streamlining when resistant organisms were not identified.
Dosage optimization	Nursing concerns regarding administration and drug incompatibility	Create protocols for administration and list compatible drugs. Consider extended infusion instead of continuous infusion.

Sonuçlar

AB tedavisinden daha önemlisi

Erken Dönemde Belirle

Kolonizasyon ve Yayılımı Önle

İzolasyon Uygula

Network sisteminin kurulması

İnfeksiyon Kontrol Önlemleri

KLİMİK

TÜRK KLİNİK MİKROBİYOLOJİ VE
İNFEKSİYON HASTALIKLARI DERNEĞİ

Bilimle Sağlıkla

30 .Yıl

Tesekkürler..