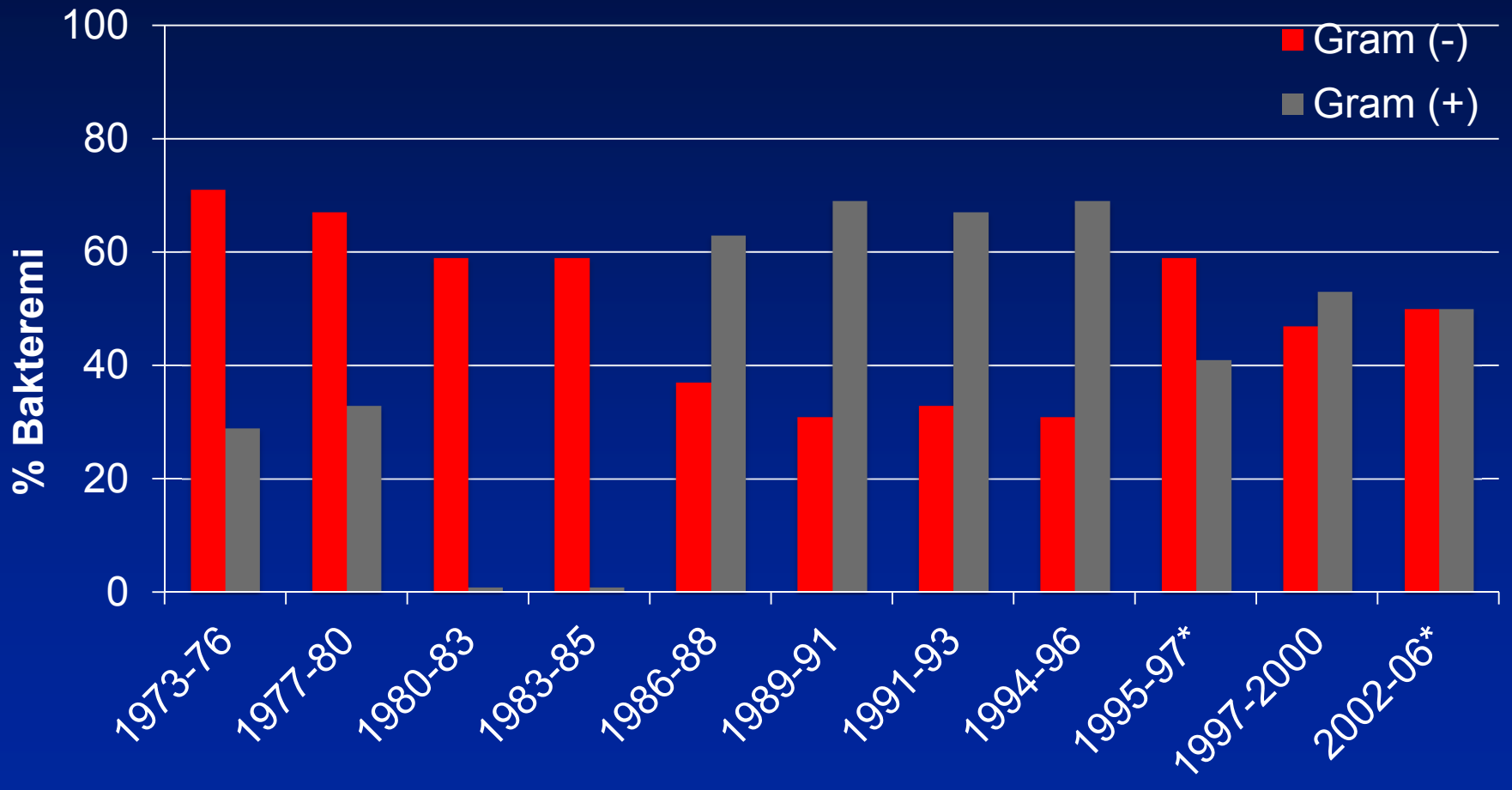
# Bakteriyel İnfeksiyonlar ve Tedavi Kılavuzları


## Dr. Murat Akova

**Hacettepe Üniversitesi Tıp Fakültesi**
**İç Hastalıkları Anabilim Dalı**
**İnfeksiyon Hastalıkları Ünitesi**
**Ankara**

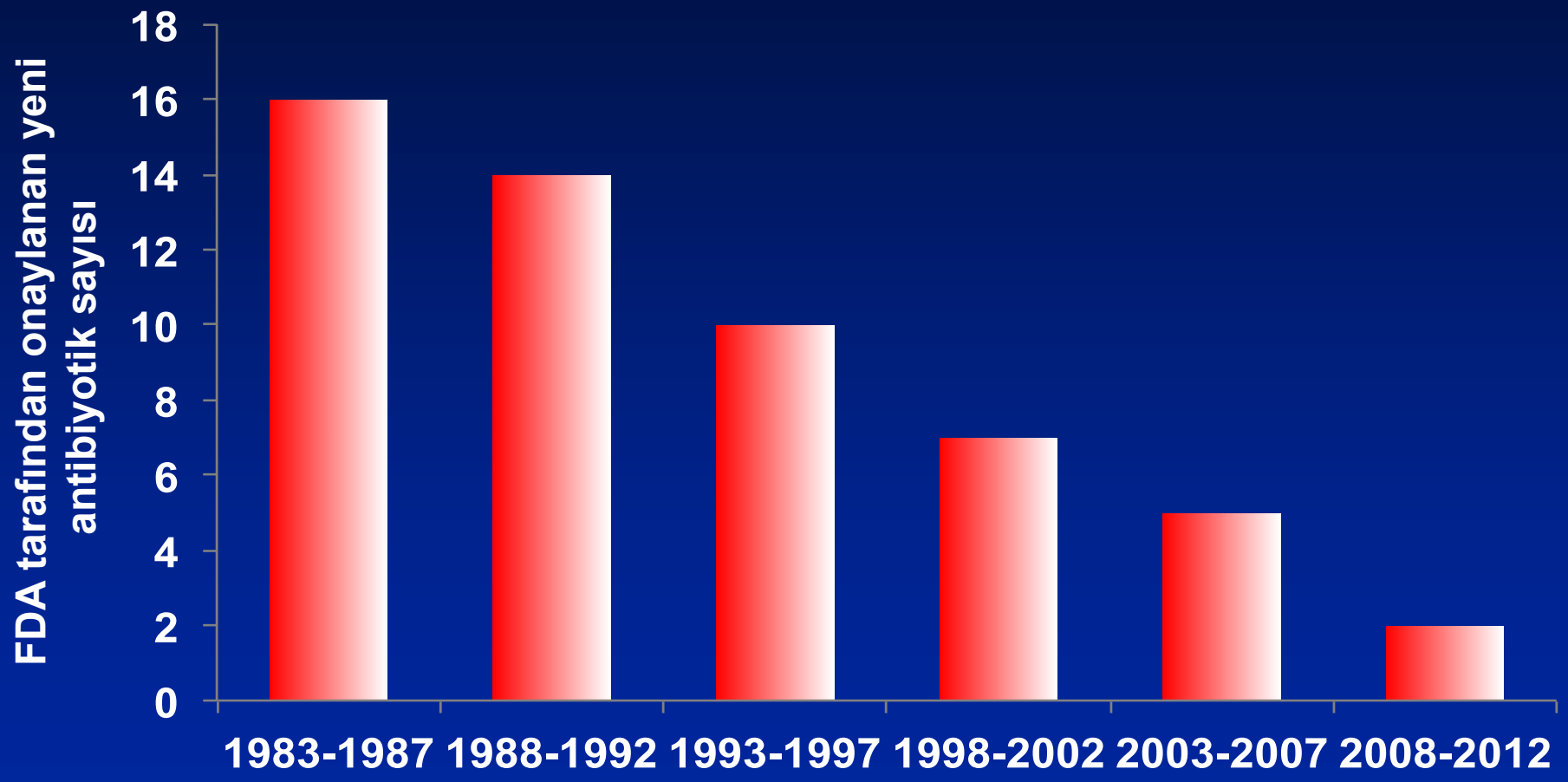

# EORTC-IATG Çalışmalarında Bakteremi Oranları




*** Düşük riskli nötropenik hastaların çoğunlukta olduğu çalışmalar**

**Adapted fromViscoli C. Eur J Cancer 2002;38(suppl 4):S82**

# Antibiyotiklerin Altın Çağı Bitti…




IDSA Public Policy. *Clin Infect Dis.* 2011;52(Suppl 5):S397

# ‘*Bad Bugs, No Drugs: No ESKAPE*’

- ***E**nterococcus faecium*, ***S**taphylococcus aureus*, ***K**lebsiella pneumoniae*, ***A**cinetobacter baumannii*, ***P**seudomonas aeruginosa*, ***E**nterobacter* spp
- Yeni antibiyotik gelişimi çok sınırlı
  - MRSA için önemli moleküller var
  - ESKAPE patojenleri için yeni molekül kısıtlı
  - MDR Gram (-) basiller (*A. baumannii* ve *P. aeruginosa*) için yeni ajan yok
  - Geliştirilenlerin eskilere kıyasla etkinliği farklı değil

Rice LB. *J Infect Dis*. 2008;197:1079
Boucher HW, et al. *Clin Infect Dis*. 2009;48:1

*J Antimicrob Chemother* 2011; **66**: 657–663
doi:10.1093/jac/dkq494 Advance Access publication 29 December 2010

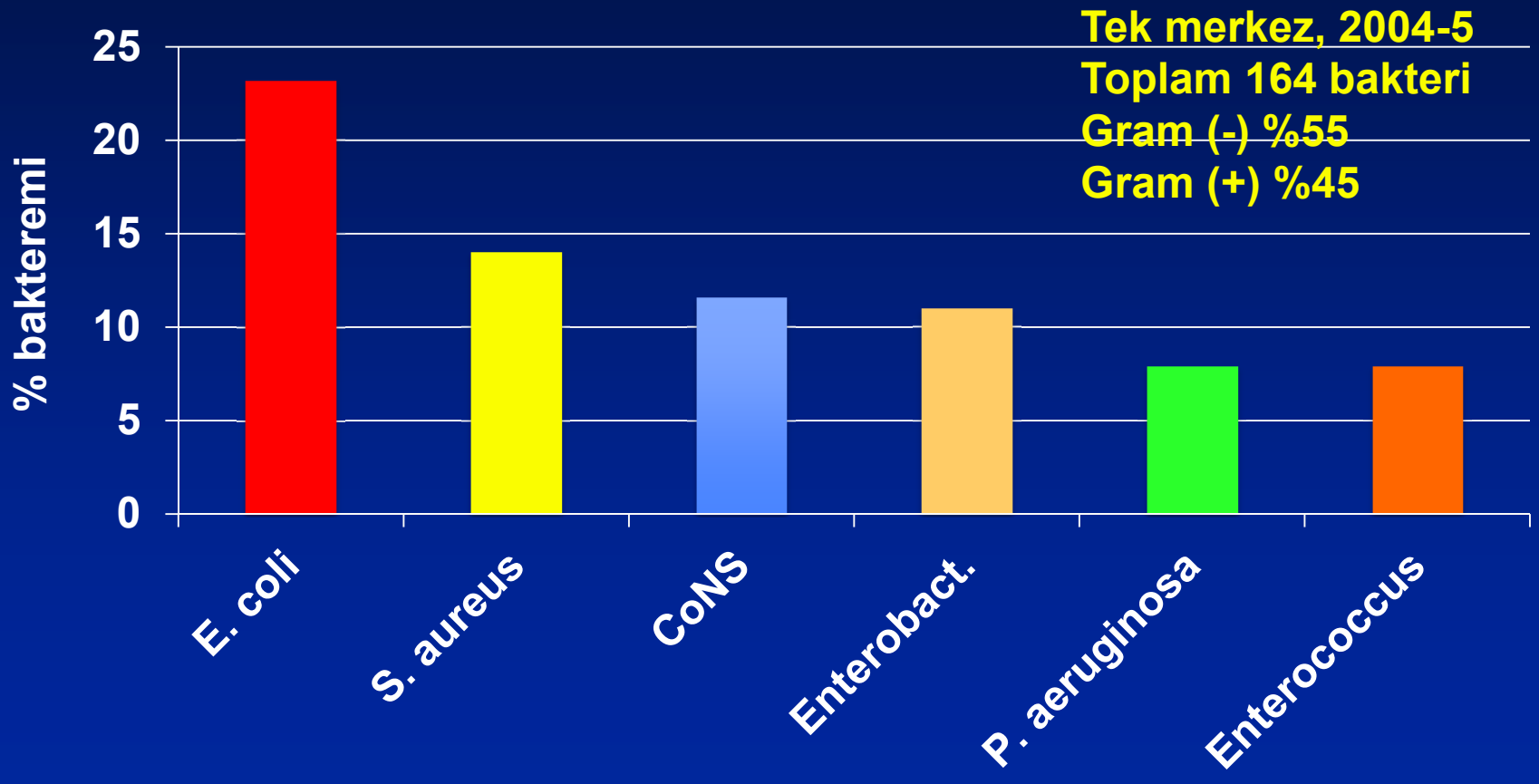
Journal of Antimicrobial Chemotherapy

# Bacteraemia due to multidrug-resistant Gram-negative bacilli in cancer patients: risk factors, antibiotic therapy and outcomes

C. Gudiol[1,2*], F. Tubau[3,4], L. Calatayud[3,4], C. Garcia-Vidal[1,2], M. Cisnal[3], I. Sánchez-Ortega[5], R. Duarte[5], M. Calvo[6] and J. Carratalà[1,2]

- **Kanserli hastalarda 747 bakteremi analiz**
  - **4-yıllık prospektif çalışma**
  - **372 (%49.7) Gram-negatif bakteriler tarafından**
    - **51 (%13.7) MDR suşlarla**
- **MDR suşlar için risk faktörleri**
  - **Önceden antibiyotik kullanımı (OR: 3.57, 95% CI: 1.63-7.80)**
  - **Üriner kateter (OR: 2.41, 95% CI: 1.01-5.74)**
- **En önemli direnç mekanizmaları**
  - ***E. coli*'de ESBL üretimi (%45)**
  - **AmpC aşırı üretimi (%24)**

# Hematolojik Kanserli Hastalarda Bakteriyel İnfeksiyonlar




Cattaneo C, et al. J Antimicrobial Agents 2008;61:721

# Hematolojik Kanserli Hastalarda Bakteriyel İnfeksiyonlar

- Kinolon direnci
  - Tüm izolatların %56'sı
  - *E. coli*'de %87
    - Tüm izolatların %20'si QR-*E. coli*
  - Kinolon profilaksisi ve >7 gün süren nötropeni ile ilişkili
- Metisilin direnci
  - Tüm stafilokokların %67'si
  - Kinolon profilaksisi ve santral venöz kateter kullanımı ile ilişkili

Cattaneo C, et al. J Antimicrobial Agents 2008;61:721

# Kanserli Hastalarda ESBL (+) *E. coli* Bakteremisi

- İspanya'da tek merkez, 2006-2008
- 531 bakteremi atağı
  - 135 *E. coli* bakteremisi
  - 17 (%12.6) ESBL (+) suşlarla
    - %59 CTX-M tipinde
- Etkileyen faktörler
  - Kadın cinsiyet
  - Kinolon profilaksisi
- Mortalite sadece nötropeniklerde yüksek

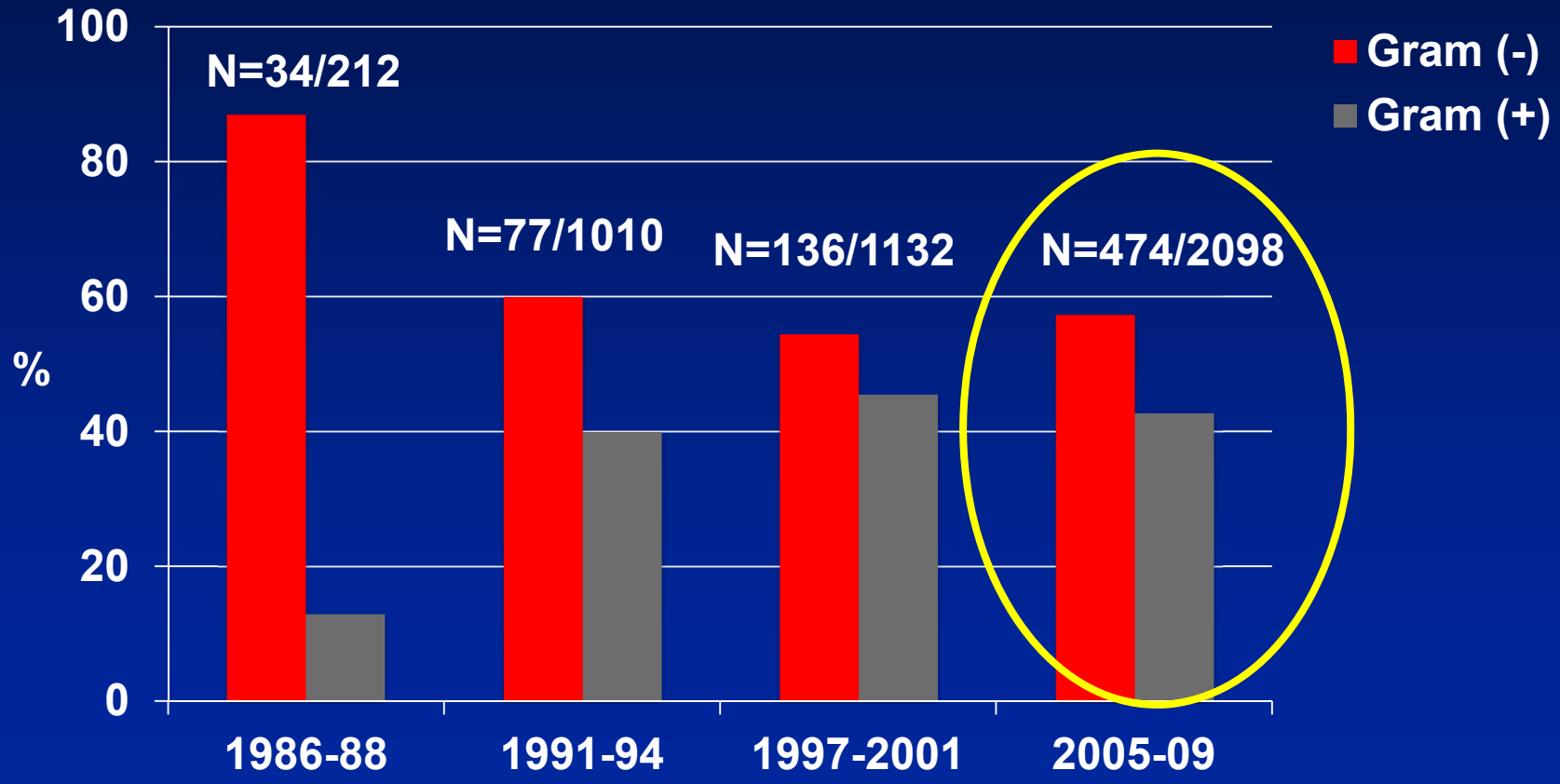
Gudiol C, et al. J Antimicrob Chemother 2010;65:333

# Erişkin Hematolojik Kanserli Hastalarda MDR *P. aeruginosa*

- 9 İtalyan merkezinde süregelen çalışma
- 39 *P. aeruginosa* bakteremisi
  - 27 MDR suş (%71)
- 30 günlük mortalite %32
  - %40 MDR *vs* %9 non-MDR (p=.06)
- Mortalite için en önemli faktör uygunsuz tedavi

Trecarichi EM, et al. Haematologica 2011;96:e1

# Kanserli Hastalarda Bakteremi Hacettepe Verileri



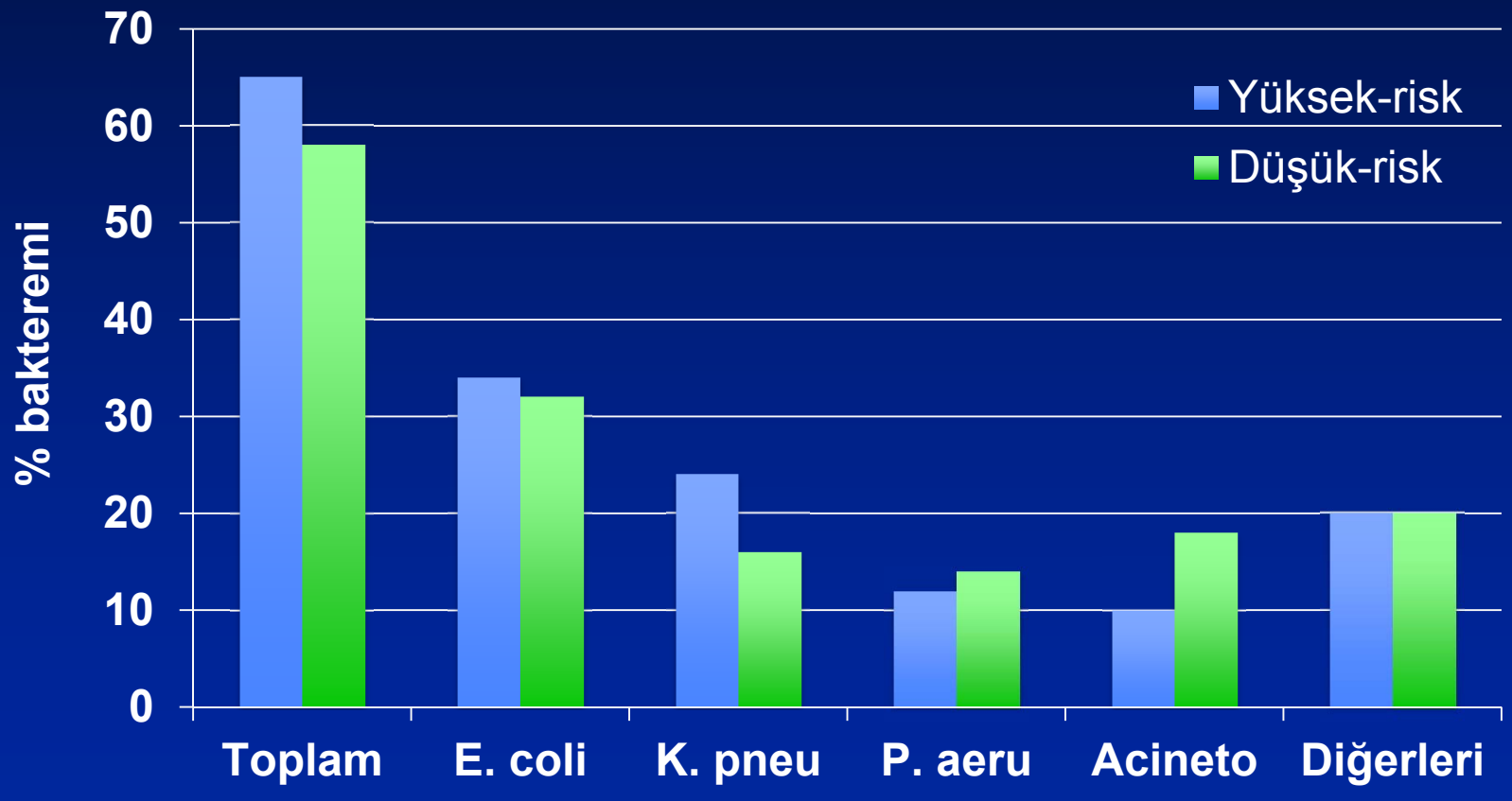

Modified from Guven GS, et al. Support Care Cancer 2006;14:52

# Kanserli Hastalarda Bakteremi
## *Hacettepe Verileri*

- Ocak 2005-Ekim 2009
- 2098 nötropenik hastada, 3703 ateşli atak
  - 239 yüksek riskli hastada 272 bakteremi
    - AML, ALL, MDS, KHT alıcısı
  - 189 düşük riskli hastada 202 bakteremi
    - Aplastik anemi, lenfoma, KML, KLL, MM

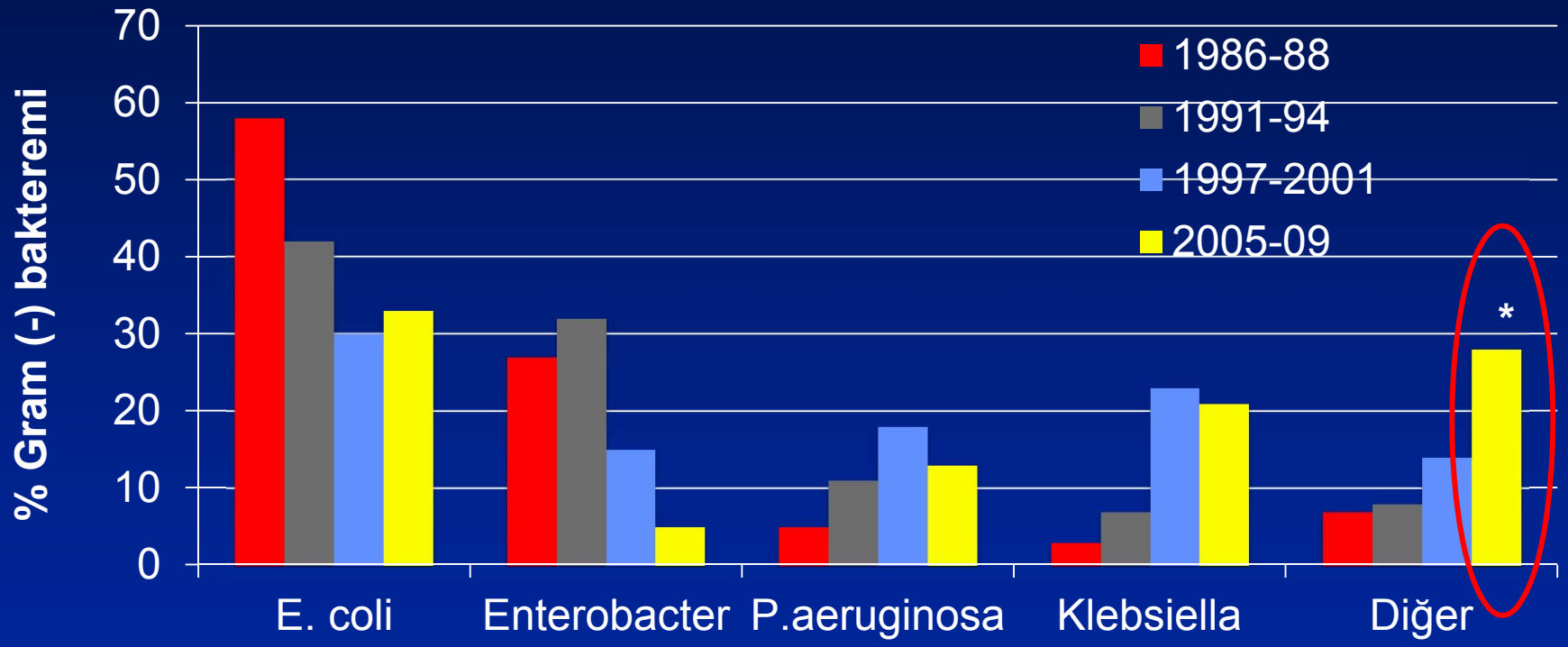
Kara, Ö, et al. ICAAC 2010, Boston, USA

# Gram-negatif Bakteremilerin Dağılımı




Kara, Ö, et al. ICAAC 2010, Boston, USA

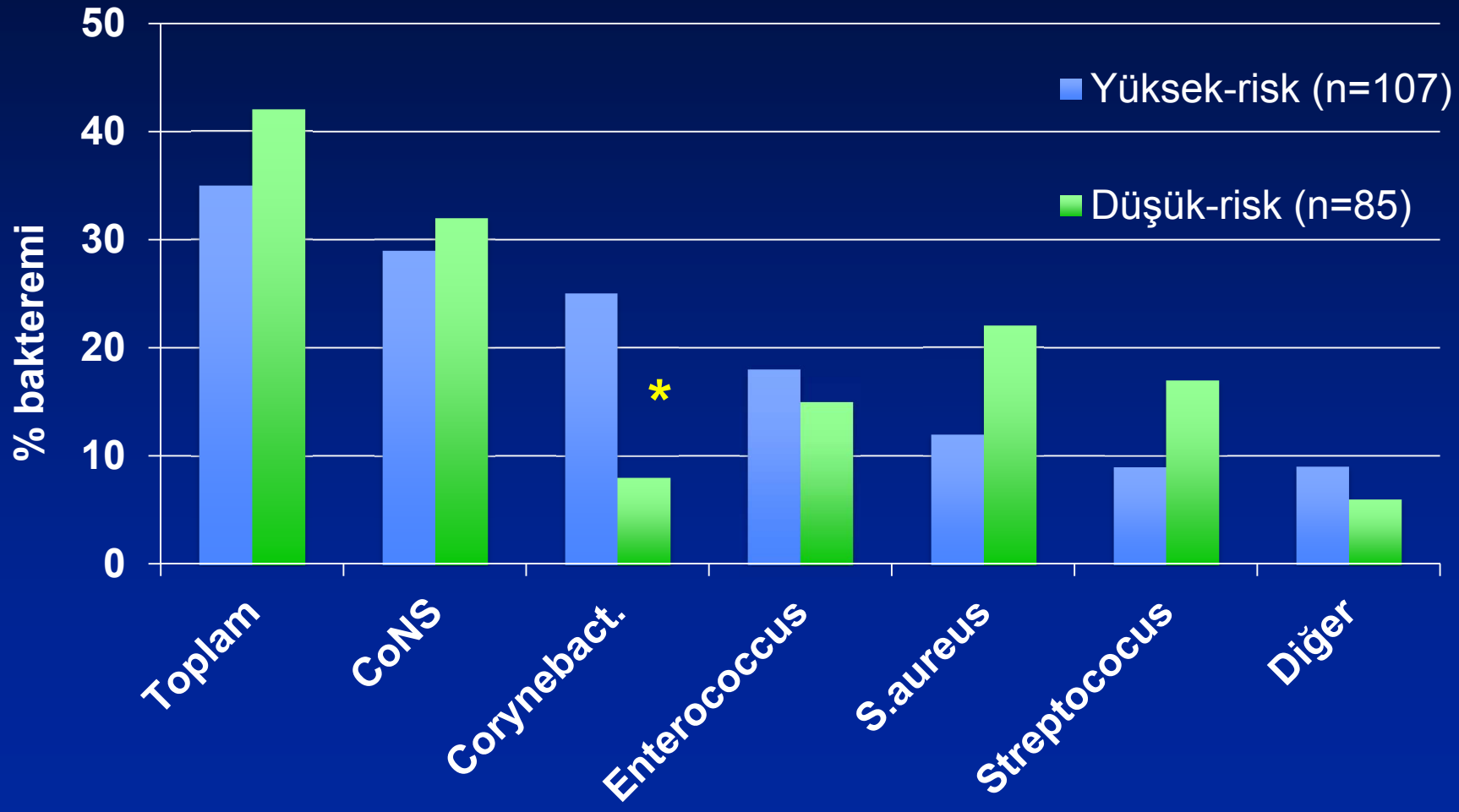
# Gram-negatif Bakteremilerin Dağılımı




*** %47,5 Acinetobacter spp.**

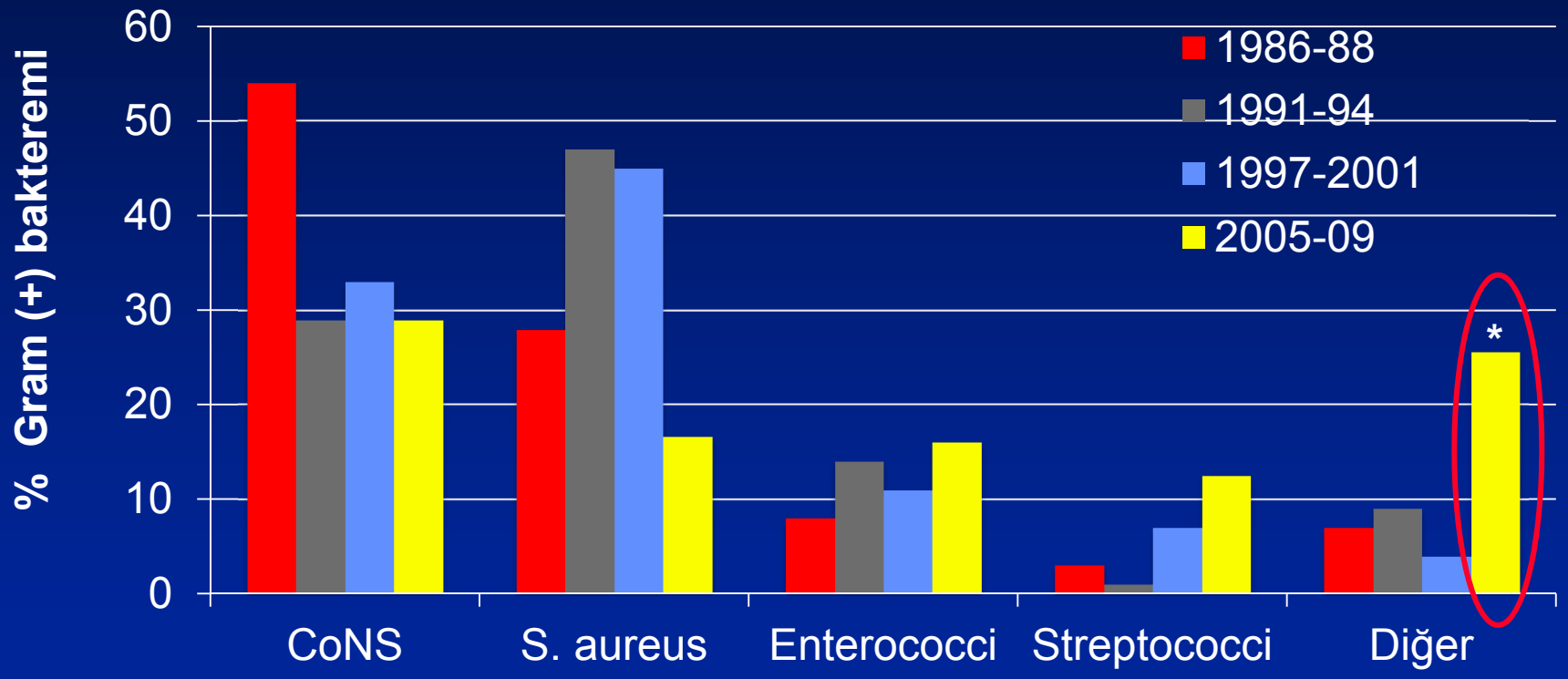
**Modified from Guven GS, et al. Support Care Cancer 2006;14:52**

# Gram-pozitif Bakteremilerin Dağılımı




Kara, Ö, et al. ICAAC 2010, Boston, USA

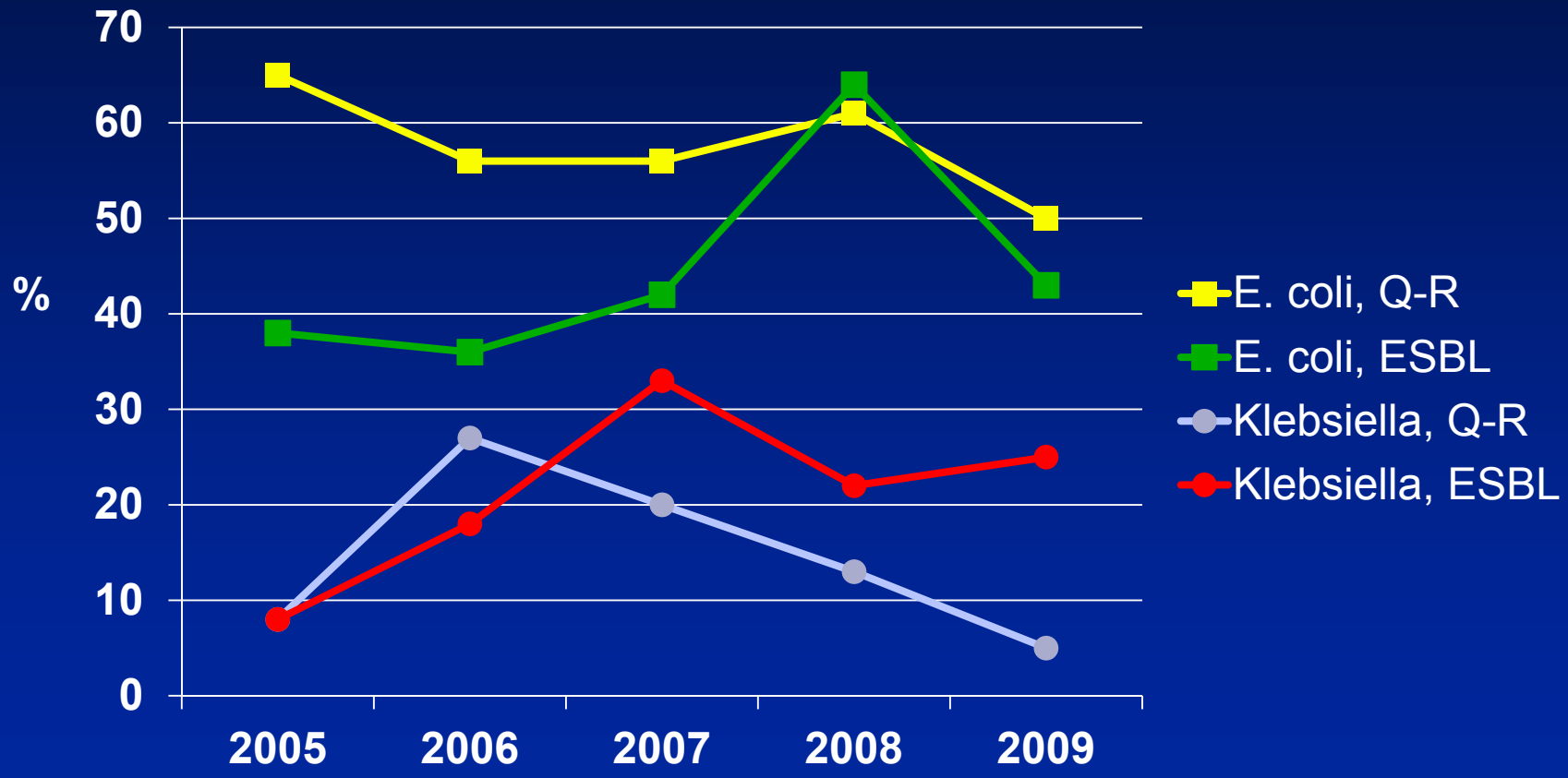
# Gram-pozitif Bakteremilerin Dağılımı




** %69 Corynebacterium spp.*

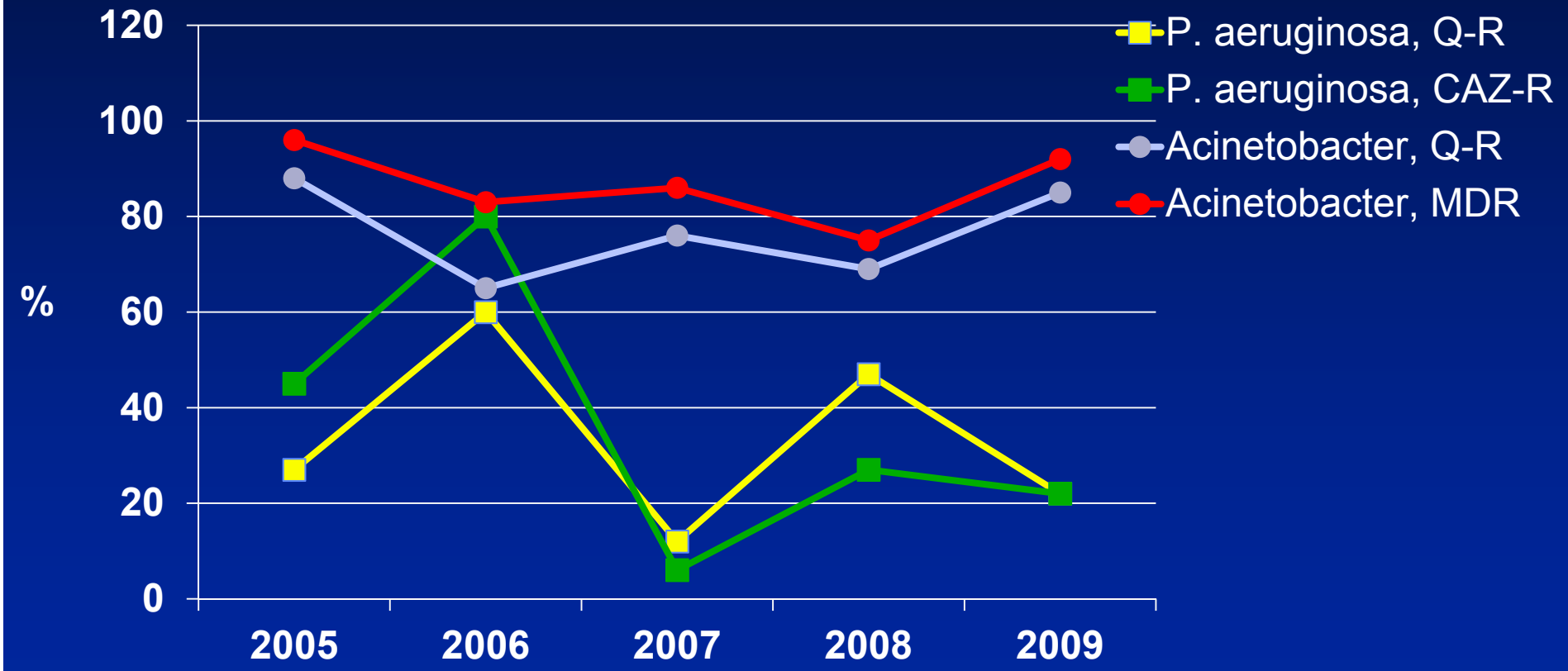
**Modified from Guven GS, et al. Support Care Cancer 2006;14:52**

# Kanserli Hastalarda
# *E. coli* ve *Klebsiella spp.* Direnci




Kara, Ö, et al. ICAAC 2010, Boston, USA

# Kanserli Hastalarda
# *P. aeruginosa and Acinetobacter spp.*
# Direnci




Kara, Ö, et al. ICAAC 2010, Boston, USA

IDSA GUIDELINES

# Clinical Practice Guideline for the Use of Antimicrobial Agents in Neutropenic Patients with Cancer: 2010 Update by the Infectious Diseases Society of America

**Alison G. Freifeld,[1] Eric J. Bow,[9] Kent A. Sepkowitz,[2] Michael J. Boeckh,[4] James I. Ito,[5] Craig A. Mullen,[3] Issam I. Raad,[6] Kenneth V. Rolston,[6] Jo-Anne H. Young,[7] and John R. Wingard[8]**

[1]Department of Medicine, University of Nebraska Medical Center, Omaha, Nebraska; [2]Department of Medicine, Memorial Sloan-Kettering Cancer Center, New York; [3]Department of Pediatrics, University of Rochester Medical Center, Rochester, New York; [4]Vaccine and Infectious Disease Division, Fred Hutchinson Cancer Research, Seattle, Washington; [5]Division of Infectious Diseases, City of Hope National Medical Center, Duarte, California; [6]Department of Infectious Diseases, Infection Control and Employee Health, The University of Texas M.D. Anderson Cancer Center, Houston, Texas; [7]Department of Medicine, University of Minnesota, Minneapolis, Minnesota; [8]Division of Hematology/Oncology, University of Florida, Gainesville, Florida; and [9]Departments of Medical Microbiology and Internal Medicine, the University of Manitoba, and Infection Control Services, Cancer Care Manitoba, Winnipeg, Manitoba, Canada

**Freifeld A, et al. Clin Infect Dis 2011;52:e56**

# Başlangıçta Empirik Tedavi IDSA-2010

- Yüksek riskli hastalarda, iv monoterapi
  - Sefepim, karbapenem, pip-tazo (A-I)
  - Aminoglikozidler ve kinolonlar **eklenebilir** (B-III)
    - Hipotansiyon, pnömoni
    - Antimikrobiyal direnç şüphesi

Freifeld A, et al. Clin Infect Dis 2011;52:e56

# Empirik Anti-Gram-Pozitif Kullanımı IDSA 2010

- Başlangıç tedavisinde önerilmez (A-I)
- Özel koşullar
  - Şüpheli kateterle-ilişkili infeksiyon
  - Cilt-yumuşak doku infeksiyonu
  - Pnömoni
  - Hemodinamik bozulma

Freifeld A, et al. Clin Infect Dis 2011;52:e56

# Başlangıç Tedavisinin Modifikasyonu IDSA 2010

- İnfeksiyon riski: eklenecek tedavi
  - MRSA: vankomisin, linezolid, daptomisin (B-III)
  - VRE: linezolid, daptomisin (B-III)
  - ESBL: karbapenem
  - KPC türü enzimler: kolistin, tigesiklin

Freifeld A, et al. Clin Infect Dis 2011;52:e56

# Diğer Empirik Tedavi Önerileri IDSA 2010

- İnfeksiyon bulgusu olan hastalar, ateşleri olmasa da tedavi edilmelidir (B-III)
- Düşük riskli hastalar hastanede oral veya iv tedavi almalı (A-I)
  - Tedavi altında erken taburcu edilebilirler

Freifeld A, et al. Clin Infect Dis 2011;52:e56

# Tedavi Sırasında Modifikasyon IDSA 2010

- Ateşi süren, genel durumu iyi olan hastalarda tedavi değişkliği gereksiz (A-I)
- Kültürler negatifse vankomisin tedavisi 2. günde kesilebilir
- Ateşli, genel durumu bozulan hastalarda tedavi spektrumu genişletilmeli
  - Gram (+), Gram (-), anaerob, antifungal (A-III)
- Ateşi düşen, düşük riskli hastalarda antibiyotik spektrumu daraltılabilir

Freifeld A, et al. Clin Infect Dis 2011;52:e56

# Empirik Tedavi Süresi
# IDSA 2010

- Nçtropeniden çıkıncaya kadar (>500/mm$^3$) (B-II)
  - İnfeksiyonun kanıtlandığı durumlarda, gerekirse daha uzun (B-III)
  - Kanıtlanmış bir infeksiyon yeterli süre tedavi edildiyse, hastaya kinolon profilaksisi verilerek tedavi kesilebilir

Freifeld A, et al. Clin Infect Dis 2011;52:e56

# Yanıt Bekleyen Sorular…

- Direnç ne düzeyde ise karbapenem monoterapisi verilebilir?
  - Önceden antibiyotik kullanımının rolü
- MDR-non-fermentatif basillere yönelik ne zaman tedavi verilmeli?
- PK/PD özellikleri
- Geniş spektrumlu tedavilerin '*yandaş*' etkileri

# Introduction to ECIL

## *from ECIL1 to ECIL 4*

4th European Conference on Infections in Leukemia

# Bacterial Resistance in Haematology-ECIL 4 Study Groups & Participants

- **Epidemiology & resistance**
  - M Mikulska*, M Akova, D Averbuch, G Klyasova, DM Livermore, C Orasch, M Tumbarello
- **Empirical & targeted antibacterial therapy**
  - D Averbuch*, C Cordonnier, WV Kern, C Viscoli
- **Duration of antibacterial therapy**
  - C Orasch*, G Klyasova, P Munoz
- **Antibiotic stewardship**
  - IC Gyssens*, WV Kern, DM Livermore

***Group leader: Murat AKOVA***

*Meeting: September 8-10th, 2011*

*Final version: Feb 14th, 2012*

* Presenting authors

# Questions to answer for febrile neutropenia

1. What are the key parameters in choosing empirical antibiotics in an era of increasing resistance?
2. Should we replace commonly used escalation therapy with de-escalation?
3. What should be done at 24-72h?
    *a) In escalation approach*
    *b) In de-escalation approach*
4. What are the best therapies for documented infections due to resistant bacteria?

# Q1: Factors in choosing a regimen

- Local bacterial epidemiology and resistance patterns
- Patient's prior colonization or infection by resistant pathogens, particularly:
  - *MRSA and MRSE, especially with vancomycin MICs ≥2 mg/L*
  - *Vancomycin-resistant enterococci*
  - *ESBL- or carbapenemase- producing Enterobacteriaceae*
  - *A. baumannii, Pseudomonas* spp. & *S. maltophilia*
- Other patient-related factors
  - *Other risk factors for infection due to resistant pathogens*
  - *Clinical presentation*

# ECIL Guidelines for Empirical Treatment of Febrile Neutropenia

## Escalation Strategy

**Escalation should be employed for patients with**

- *An uncomplicated presentation*
- *Without specific risk factors for resistant pathogens*
- *In centres were infections due to resistant pathogens are rarely seen at the onset of febrile neutropenia* ***BII***

# ECIL Guidelines for Empirical Treatment of Febrile Neutropenia

## De-escalation Strategy

**De-escalation should be applied for patients**

- *With complicated presentations*
- *With individual risk factors for resistant pathogens,*
- *In centres where resistant pathogens are regularly seen at the onset of febrile neutropenia* ***BII***

- Review of infection control is mandatory

# Q2: Is antibiotic de-escalation better than escalation in febrile neutropenia?

## *Defining commonly used 'escalation'*

- Initial empirical therapy covers typical Enterobacteriaceae and *P. aeruginosa*, but not ESBL or carbapenemase producers, nor multi-resistant non-fermenters
  - *(e.g. ceftazidime, cefepime or piperacillin-tazobactam)*
- If the patient deteriorates, or a resistant pathogen is isolated, therapy is 'escalated', e.g. to a carbapenem

# Q2: Is antibiotic de-escalation better than escalation in febrile neutropenia?

## *Defining de-escalation*

- Initial empirical regimen is very broad, with coverage of multi-resistant Gram +ve and –ve pathogens (e.g ESBL-producers)
  - *e.g. carbapenem + anti-MRSA agent*
- Therapy is de-escalated to a simpler or narrower spectrum ('targeted') therapy once the microbiology lab does not report resistant pathogens

# Suggested initial regimens in an escalation strategy

- **Use non-carbapenem β-lactam**
  - *No coverage vs. resistant Gram +ve bacteria such as MRSA & vancomycin-resistant enterococci*
  - *No combination with aminoglycoside / quinolone*

# Suggested initial regimens in a de-escalation strategy

- Carbapenem monotherapy
- Combination of anti-pseudomonal β-lactam + aminoglycoside or quinolone
  - *With carbapenem as the β-lactam in seriously ill-patients*
- Colistin + β-lactam or rifampicin *etc.*
- Early coverage of resistant-Gram +ves with a glycopeptide or newer agent
  - *If risk factors for Gram +ves present*

# Initial empirical therapy for febrile, high-risk patients with uncomplicated neutropenia

- Anti-pseudomonal ceph (cefepime*, ceftazidime*) **AI**
- Piperacillin-tazobactam **AI**
- Other possible options include:
  - Anti-pseudomonal carbapenem** **AI**
  - Ticarcillin-clavulanate, cefoperazone-sulbactam

* Avoid if ESBLs are prevalent

** AI for efficacy, but should be avoided in uncomplicated patients lacking risk factors for resistant bacteria, to preserve activity for seriously-ill patients

# First-line carbapenems should be reserved for situations where:

- Known colonization or previous infection with:
  - *ESBL-producing Enterobacteriaceae*
  - *Gram -ves resistant to narrower-spectrum β-lactams* **BII**
- Seriously-ill patients
  - *e.g. presentation with septic shock, pneumonia* **BII**
- Centres with a high prevalence of infections due to ESBL-producers at the onset of febrile neutropenia
  - *Should also prompt infection control review* **BIII**

# Is there a 'cut-off' prevalence of resistance to prompt changing initial empirical therapy?

- Lack of literature data precludes any recommendation
- Several ways to measure the burden of resistance
  - *% Resistance rate in ≥1 key species*
  - *Incidence of infections due to resistant bacteria*
  - *Attributable morbidity and mortality due to these infections*

***% resistance may be high, but incidence of infections low ….***

# Initial therapy in patients colonised or previously infected by resistant Enterobacteriaceae

| Resistance type | Treatment |
|---|---|
| ESBL | *Carbapenem** ***BII*** |
| Carbapenemase | *Colistin** ***CIII*** + β-Lactam<br>+/- <u>one</u> of :<br>*Tigecycline** ***CIII*** *or*<br>*Aminoglycoside* ***CIII*** *or Fosfomycin* ***CIII*** |

*Freifeld *et al. Clin Infect Dis* 2011

# Initial therapy in patients colonised or previously infected by resistant non-fermenters BIII

| Bacteria | Treatment |
|---|---|
| *β-lactam* resistant *P. aeruginosa* | Colistin + *β-lactam* +\- fosfomycin |
| *β-lactam* resistant *Acinetobacter* | Colistin + *β-lactam* +/- tigecycline |
| *S. maltophilia* | Co-trimoxazole + *β-lactam* (preferable ticarcillin-clavulanate) +\- moxifloxacin |

Hachem *et al. Antimicrob Agents Chemother* 2007
Falagas *et al. J Antimicrob Chemother* 2008
Peleg *et al. Clin Microbiol Rev* 2008

# When is combination with an aminoglycoside indicated? BIII

- In seriously-ill patients
  - *e.g. septic shock, pneumonia*
- If resistant non-fermenters likely, based upon
  - *Local epidemiology*
  - *Previous colonization or infection with these pathogens,*
  - *Previous use – during the last month – of carbapenems*
- If piperacillin or ticarcillin (without β-lactamase inhibitors) is used as initial empirical therapy

# Actions at 24-72 h in neutropenic patients in an escalation approach-III

**No bacteria isolated, patient deteriorating BII**

- Diagnostic work-up (e.g., repeat cultures, galactomannan, imaging); also consider fungi and other aetiologies
- Consider resistant Gram-ve bacteria &, if likely, switch to a carbapenem possibly +aminoglycoside, quinolone or colistin
- Consider resistant Gram +ve bacteria and, if likely, (e.g. if using a 3rd generation ceph) add appropriate agent
- **In all cases,** choices should reflect patient history, colonisation and other risk factors

# Duration of antibacterial treatment in FUO: Key points

- Relapse of fever and bacterial infection are independent of discontinuing antibiotic therapy during neutropenia or after its resolution
- With appropriate antibiotic therapy, FUO has low mortality, unless patient is in septic shock

# Duration of antibiotics in FUO: Evidence & Recommendations

- Discontinue **iv** empirical antibacterials after ≥ 72h

  - *If patient has been afebrile ≥ 48h and is **stable***
  - *Irrespective of neutrophil count or **expected** duration of neutropenia **BII***

Joshi *et al., Am J Med* 1984
Jones *et al., J Pediatr* 1994
Cornelissen *et al., Clin Infect Dis* 1995
Horowitz *et al., Leuk Lymphoma* 1996
Santoloya *et al., Clin Infect Dis* 1997
Lehrnbecher *et al., Infection* 2002
Cherif *et al., Scand J Infect Dis* 2004
Slobbe *et al., Eur J Cancer* 2009

# Duration of therapy in documented infections

## Continue targeted antibiotics for clinically- or microbiologically- documented infection

- *Until infection is microbiologically eradicated &*
- *Until all clinical signs of infection are resolved*
- *At least 7 days, of which at least 4 days afebrile*

**BIII**

Eggimann *et al., J Antimicrob Chemother* 1993
Cometta *et al., Antimicrob Agents Chemother* 1995
Cordonnier *et al., Clin Infect Dis* 1997
Biron *et al., J Antimicrob Chemother* 1998
Elting *et al., J Clin Oncol* 2000
Feld *et al., J Clin Oncol* 2000

Giamarellou *et al., Antimicrob Agents Chemother* 2000
Viscoli *et al., Clin Microbiol Infect.* 2002
Sanz *et al., J Antimicrob Chemother* 2002
Tamura *et al., Am J Hematol* 2002
Cometta *et al., Clin Infect Dis* 2003
Raad *et al., Cancer* 2003

# Individualising dosing regimens

- Haematology /critically-ill patients have large volumes of distribution/capillary leak syndrome
- Three patterns of activity among antibiotics
  - *Concentration-dependent killing: aminoglycosides, fluoroquinolones and daptomycin*
  - *Time-dependent killing; little persistent effect: β-lactams*
  - *Time-dependent killing; prolonged persistent effect: azithromycin, tetracyclines (inc tigecycline) & clindamycin*

Scaglione & Paraboni. *Expert Rev Anti Infect Ther* 2006
van Zanten *et al. J Crit Care* 2008
Roberts *et al. Br J Clin Pharmacol* 2011

# Individualising glycopeptide dosing

- Best correlate of efficacy … debated!
- $AUC_{0\text{-}24}$/MIC ratio >400 correlates with outcome, as do trough levels >15 mg/L
- Use loading dose (up to 35 mg/kg) then dose q12h or by continuous infusion
- Nephrotoxic if combined with other nephrotoxic drugs
- Monitoring: ensure optimal trough levels

Del Mar *et al. Intensive Care Med* 2007
Rybak *et al. Clin Infect Dis* 2009

# Summary of Recommendations for Haematological Centres

- Produce epidemiological data on blood isolates and colonization cultures (if prophylaxis is used) regularly
- Record infection-related outcome data (bacteraemia, candidaemias, attributable mortality)
- Discuss above data with ID / microbiologists / haematologists
- Develop multidisciplinary protocols and algorithms on diagnosis, treatment and prophylaxis for FUO
  - *Provide ID training for haematologists and*
  - *Clinical haematology training for ID / microbiologists*
  - *Try to understand each other!*

# Teşekkürler…