Nötropeni Ateş Tedavisinde Yenilikler-2016

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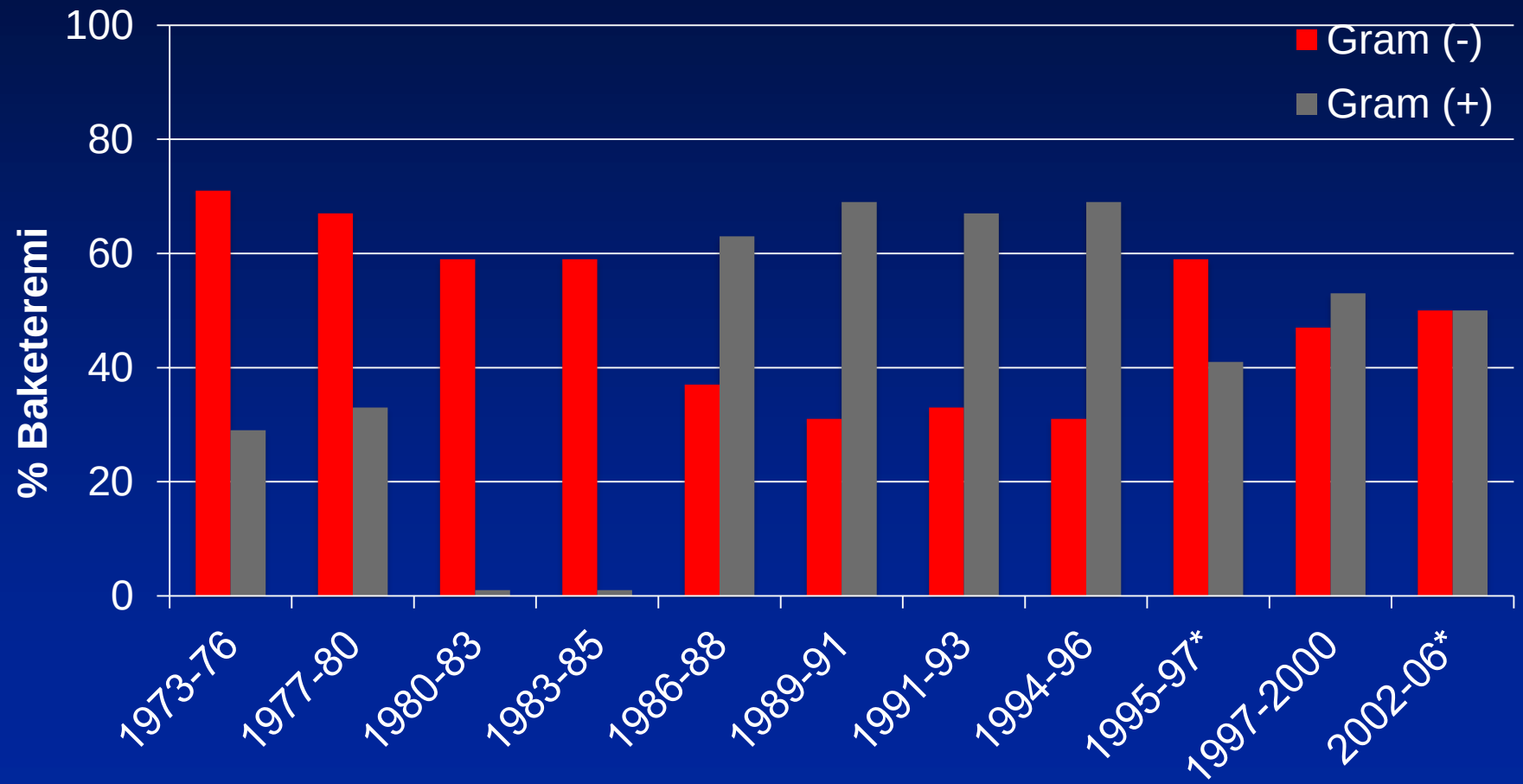
İnfeksiyon Hastalıkları
Ankara

EORTC-IATG Çalışmalarında Bakteremi Etkenleri



*** Düşük riskli hastalarla yapılan çalışmalar**

Adapted from Viscoli C. Eur J Cancer 2002;38(suppl 4):S82

Introduction to ECIL

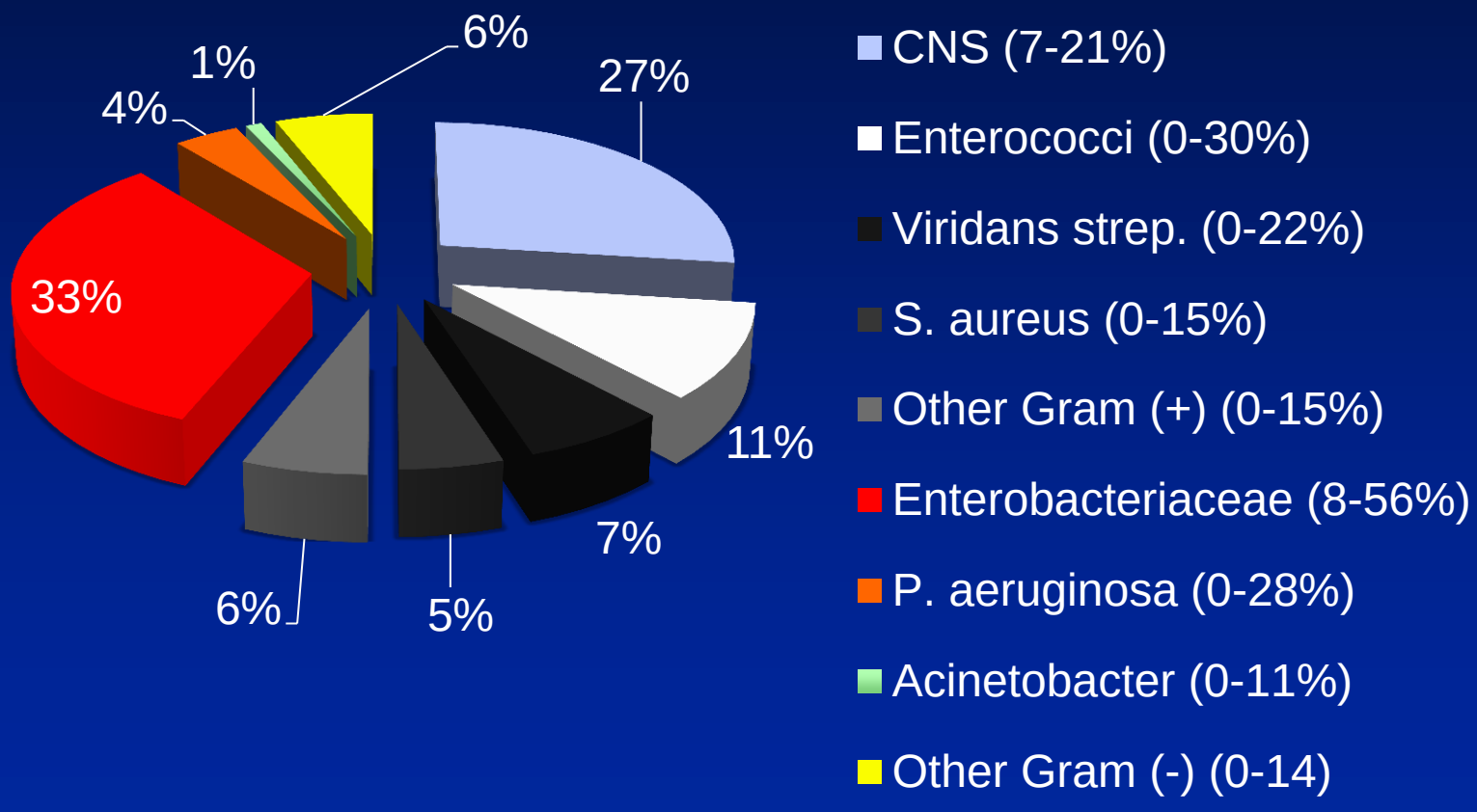
from ECIL1 to ECIL 4

Güncel Bakteremi Epidemiyolojisi

- Avrupa ve İsrail'den 34 merkez
- Median gözlem süresi, 4 yıl (1-13 yıl)
- 21 erişkin, 6 pediatrik, 7 karma merkez
- Gram (+) *vs* (-), %56 *vs* %44
- Gram (-) direnç oranları güney/doğu Avrupa'da belirgin daha yüksek

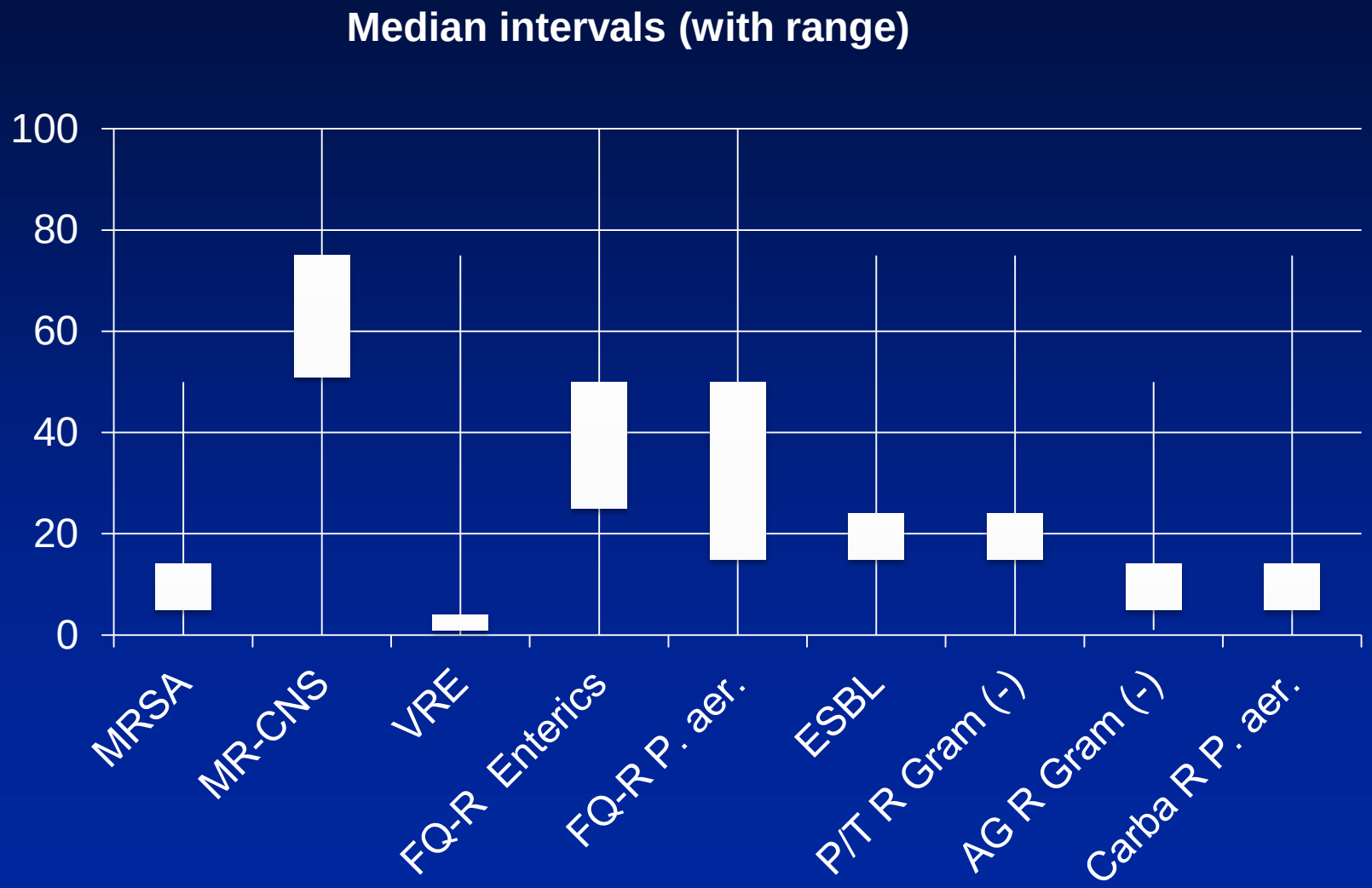
Mikulska M, et al. ECIL 4. J Infect 2014;68:321

Kanserli Hastalarda Bakteremi Nedenleri ECIL 4



Mikulska M, et al. ECIL 4. J Infect 2014;68:321

Direnç Oranları, ECIL 4



Mikulska M, et al. ECIL 4. J Infect 2014;68:321

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]

- **747 bakteremi**
  - **4 yıllık prospektif çalışma**
  - **372 (%49.7) Gram-negatif bakteri**
    - **51 (%13.7) MDR suşlar**
- **MDR-Gram negatifler 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 sık direnç mekanizması**
  - **ESBL yapımı (%45), *E. coli***
  - **AmpC hiperprodüksiyonu (%24)**

Kanserli Hastalarda MDR Bakteremi

Parametre	MDR (%)	Non-MDR (%)	p
Başlangıçta yetersiz ab tx	69	9	<.001
Uygun antibiyotik alımında gecikme	41	4	<.001
YBÜ yatışı	14	5	.023
Mekanik ventilasyon	14	3	.005
30 günlük mortalite	41	21	.003

Gudiol C, et al. J Antimicrob Chemother 2011;66:657

Nötropenik Hastalarda Bakteremi Etkenleri

	1991-1996	2006-2010	p
Bakteremi, n	272	283	
FQ profilaksisi	Var	Yok	
Gram (+) bakteremi	%64	%41	.001
Gram (-) bakteremi	%28	%49	.001
MDR Gram (-) bakteremi	%1	%6	.001
YBÜ yatışı	%3	%11	<.001
Mekanik ventilasyon	%2	%6	.018
48 saat, mortalite	%2	%5	.071
30 gün, mortalite	%19	%15	.25

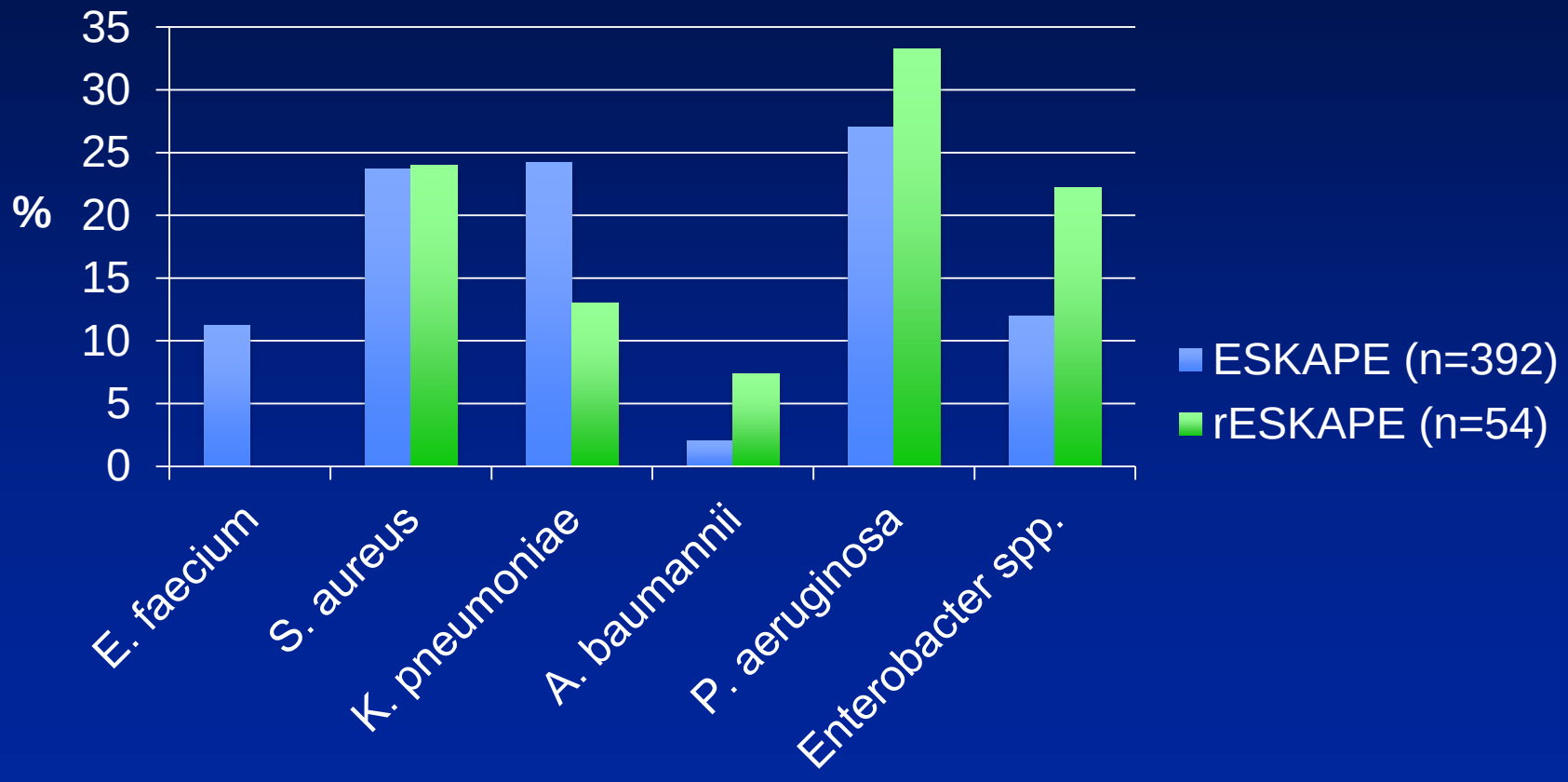
Gudiol C, et al. Clin Microbiol Infect 2013;19:474

Kanserli Hastalarda ESKAPE Patojenleri

- **Erişkin kanserli hastalarda bakteremi, 2006-2011**
  - **1148 bakteremi atağı**
    - **392 (%34) ESKAPE patojenleri**
      - **54 (%4.7) rESKAPE**
        - **VRE**
        - **MRSA**
        - **ESBL (+) *K. pneumonia***
        - **Carba-R *A. baumannii***
        - **Carba- and Q-R *P. aeruginosa***
        - **Dereprese ve ESBL (+) *Enterobacter spp.***

Bodro M, et al. Support Care Cancer 2014;22:603-10

Kanserli Hastalarda ESKAPE Patojenleri



Bodro M, et al. Support Care Cancer 2014;22:603-10

rESKAPE Bakteremisi (n=54) Risk Faktörleri

Risk faktörleri *vs* ESKAPE	P
Komorbidite varlığı	.02
Önceden antibiyotik kullanımı (1 ay)	.001
Üriner kateter	.02
Üriner kökenli bakteremi	.04
***vs* bakteremisi olmayan kontrol grubu (n=54)**	
Önceden antibiyotik kullanımı (1 ay)	<.001
Üriner kateter	.05

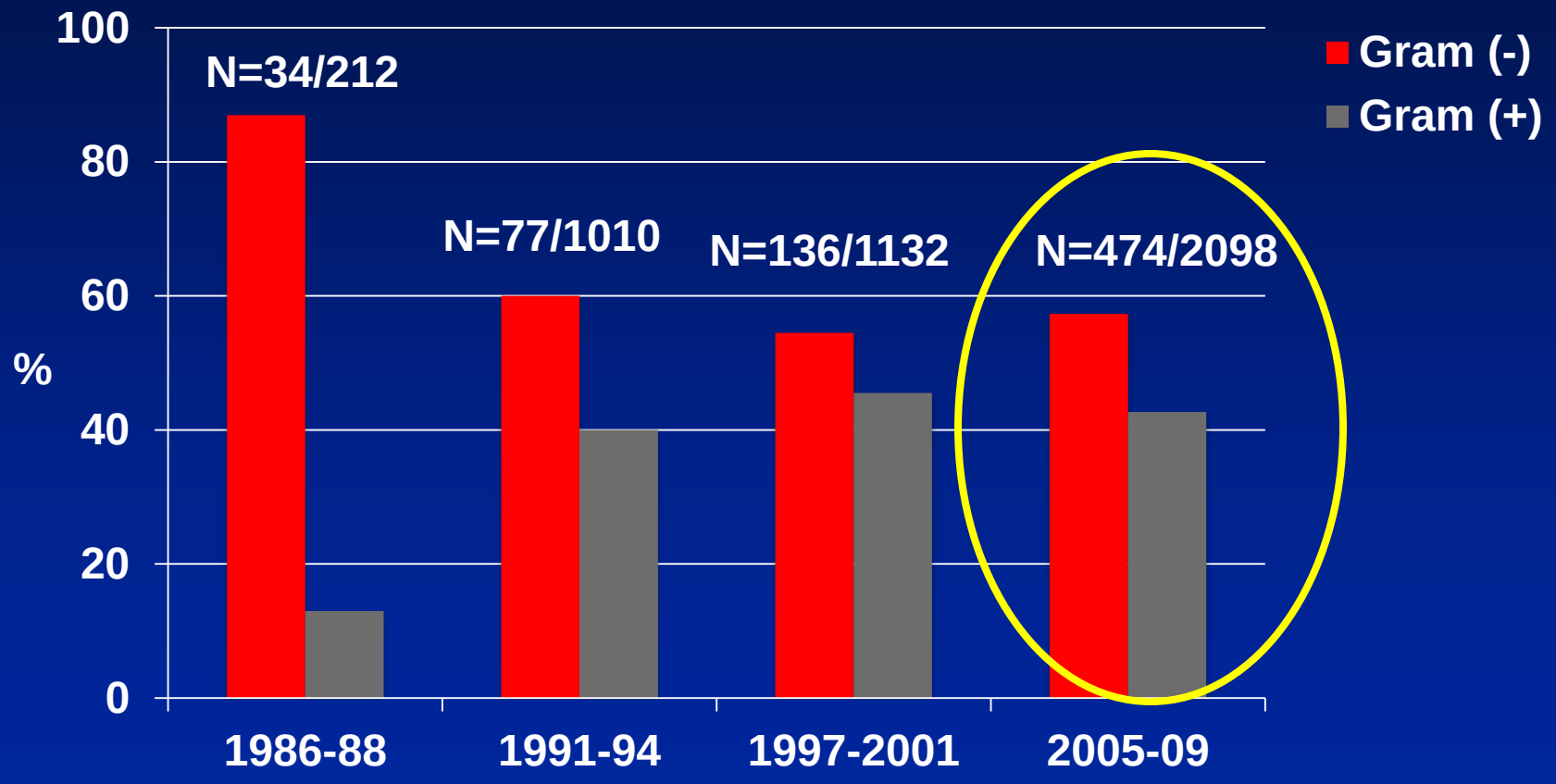
Bodro M, et al. Support Care Cancer 2014;22:603-10

rESKAPE Bakteremi (n=54)
30 Günlük Mortalite İçin Risk Faktörleri

Risk faktörleri	P
YBÜ yatışı	<.001
Perzistan sepsis	<.001
Steroid tedavisi	.007
Empirik, beta-laktam monoterapisi	.001
Koruyucu faktörler	
Başarılı infeksiyon tedavisi	<.001
Empirik, beta-laktam + aminoglikozid tedavisi	.03

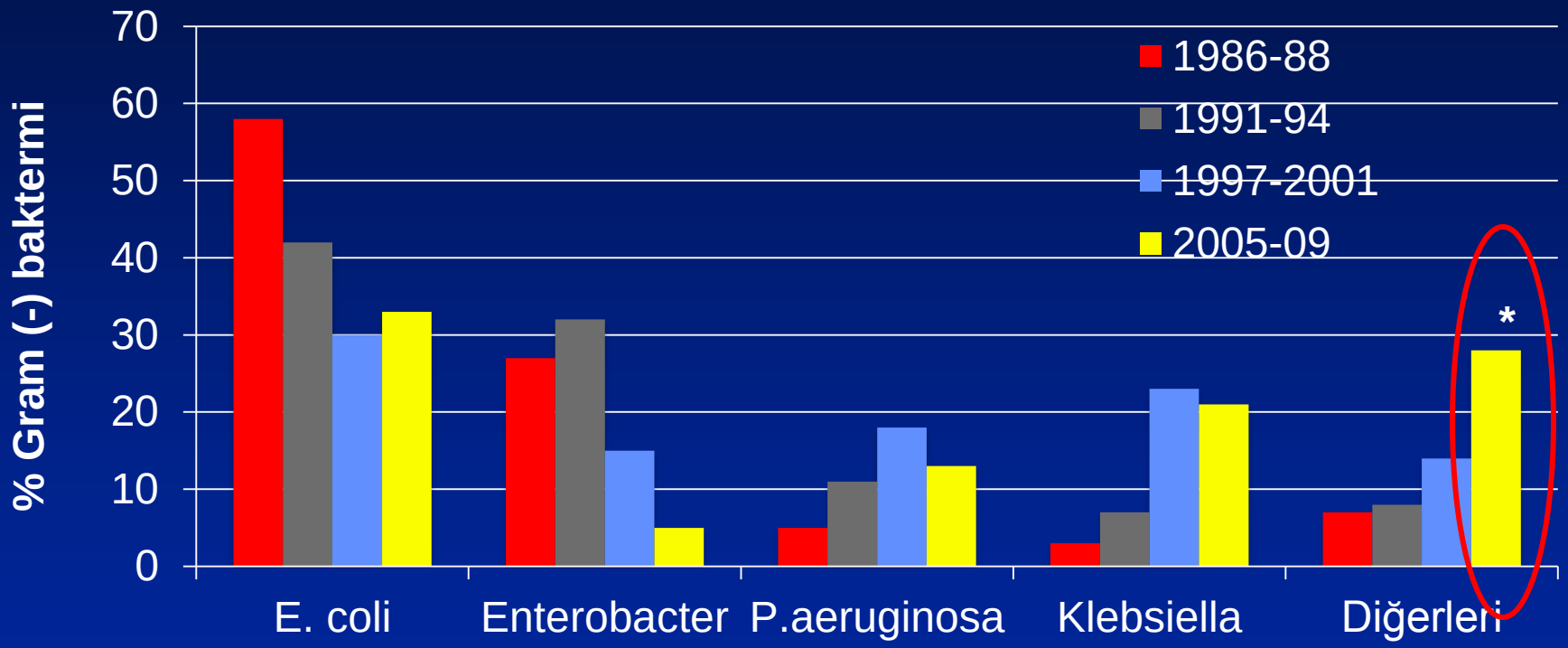
Bodro M, et al. Support Care Cancer 2014;22:603-10

Kanserli Hastalarda Bakteremi



Kara O, et al. Infect Dis (Lond) 2015;47:686

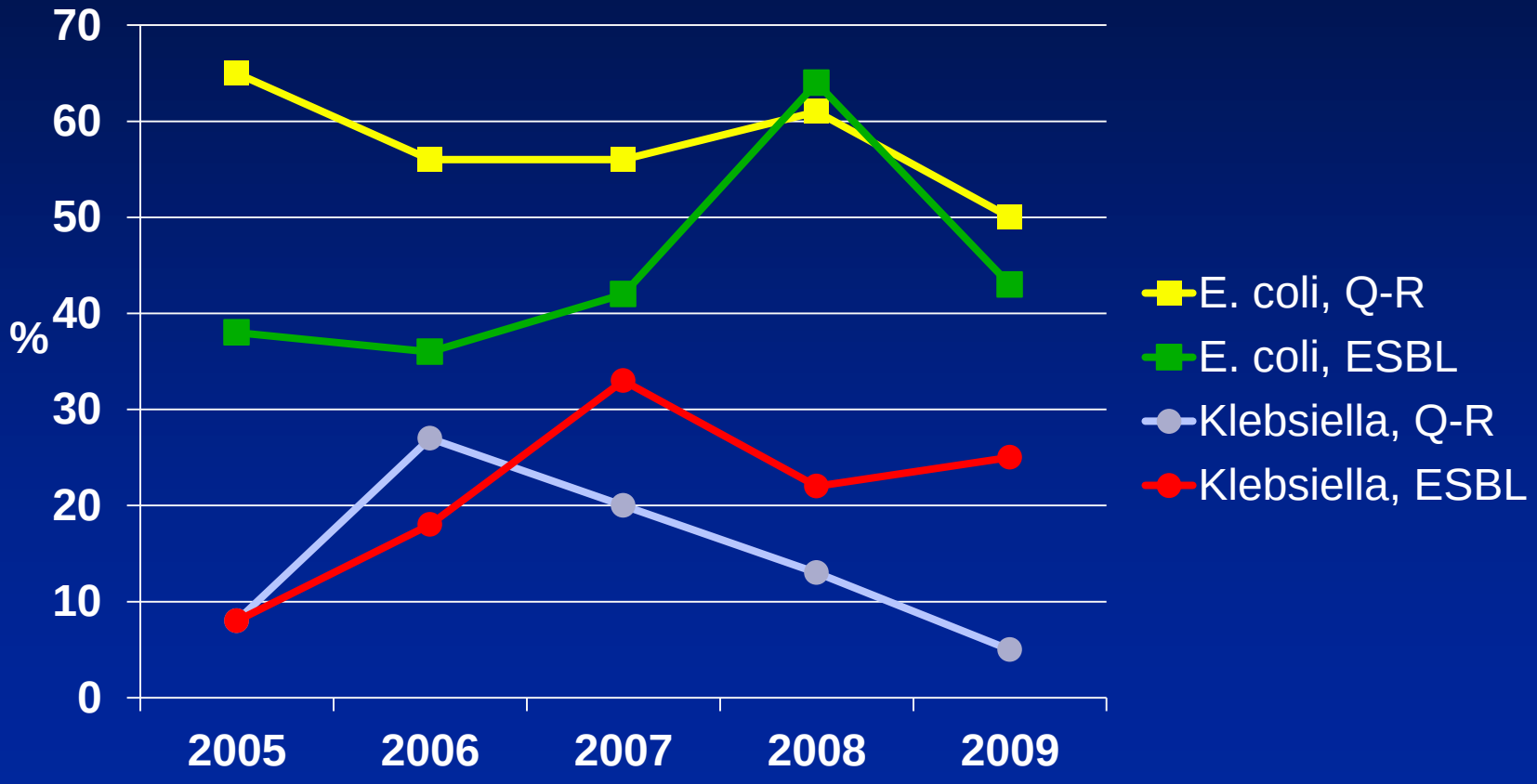
Gram (-) Bakteremi Etkenlerinin Dağılımı



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

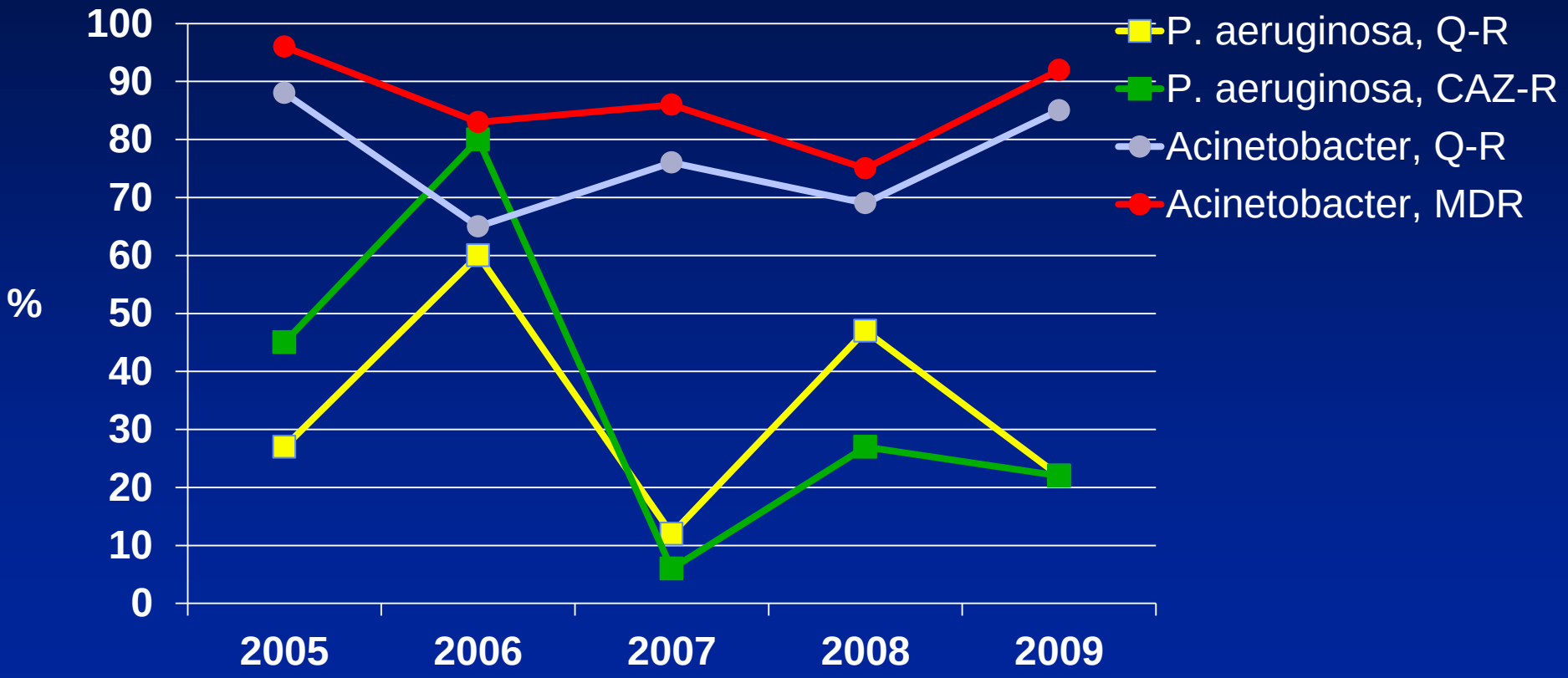
Kara O, et al. Infect Dis (Lond) 2015;47:686

E. coli ve *Klebsiella* Suşlarında Direnç



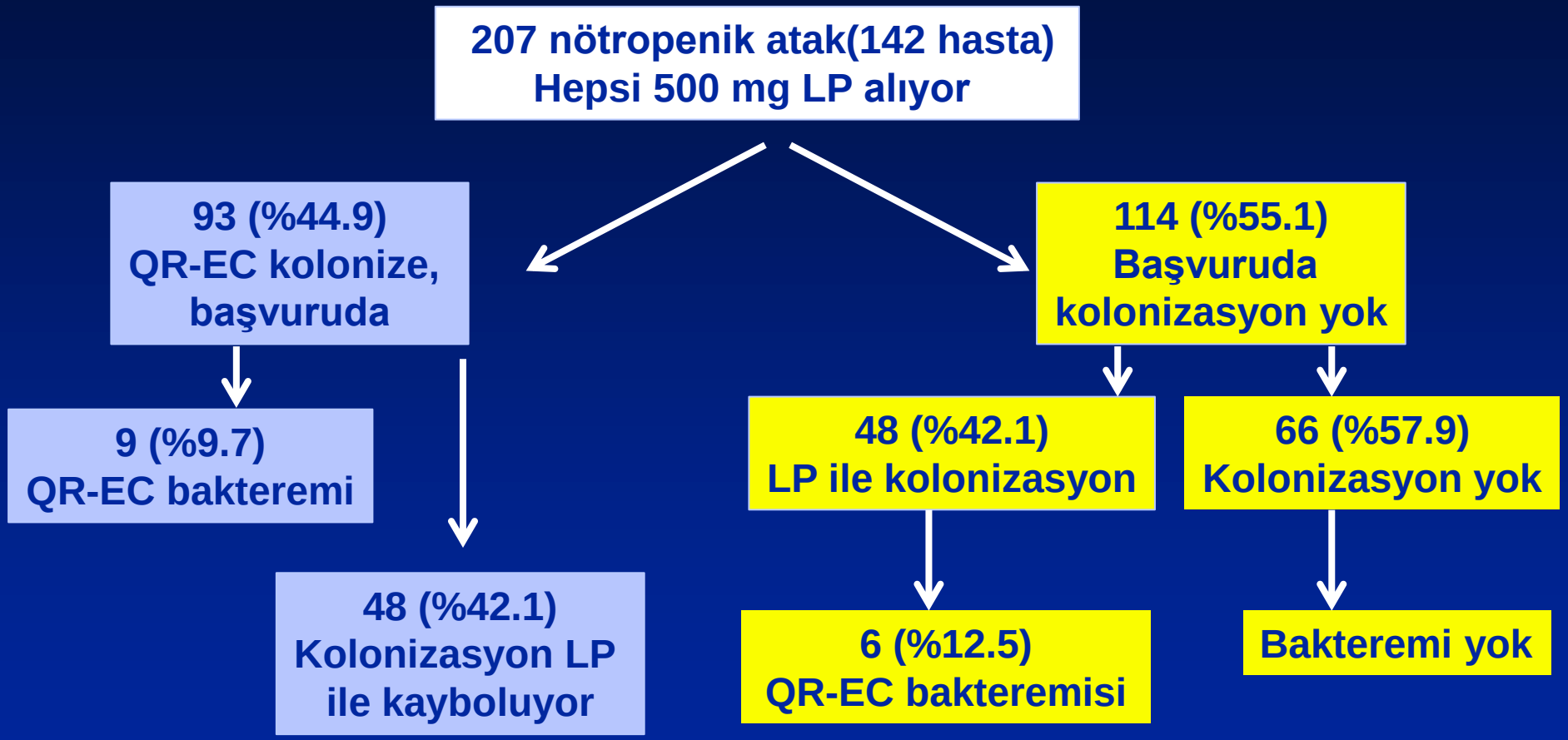
Kara O, et al. Infect Dis (Lond) 2015;47:686

P. aeruginosa ve Acinetobacter Suşlarında Direnç



Kara O, et al. Infect Dis (Lond) 2015;47:686

Nötropenik Hastalarda Quinolone-R *E. coli* (QR-EC) ve Levofloksasin Profilaksisi (LP)



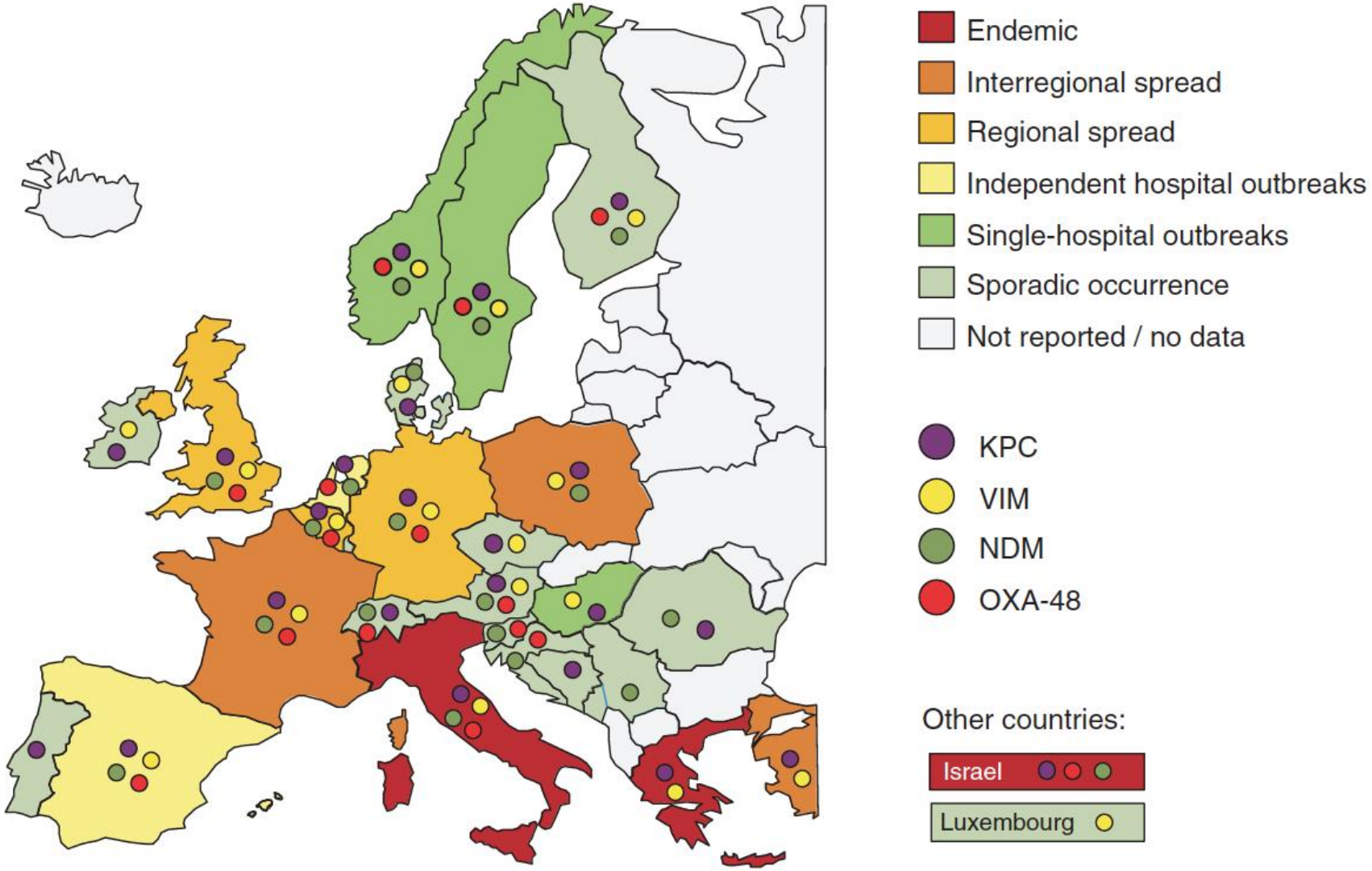
Etgül S, et al. ICAAC 2014 Abst no. C-1433

Diğer Veriler ve Yorum

- ESBL (+) olanların %40'ı ESBL (+)
  - Sadece karbapenem ve amikasin duyarlı
- Kolonizasyon ve bakteremi yapan suşların PFGE paternleri aynı
- Karbapenemler LP altında ateş gelişen hastalarda empirik tedavi için tercih edilmeli

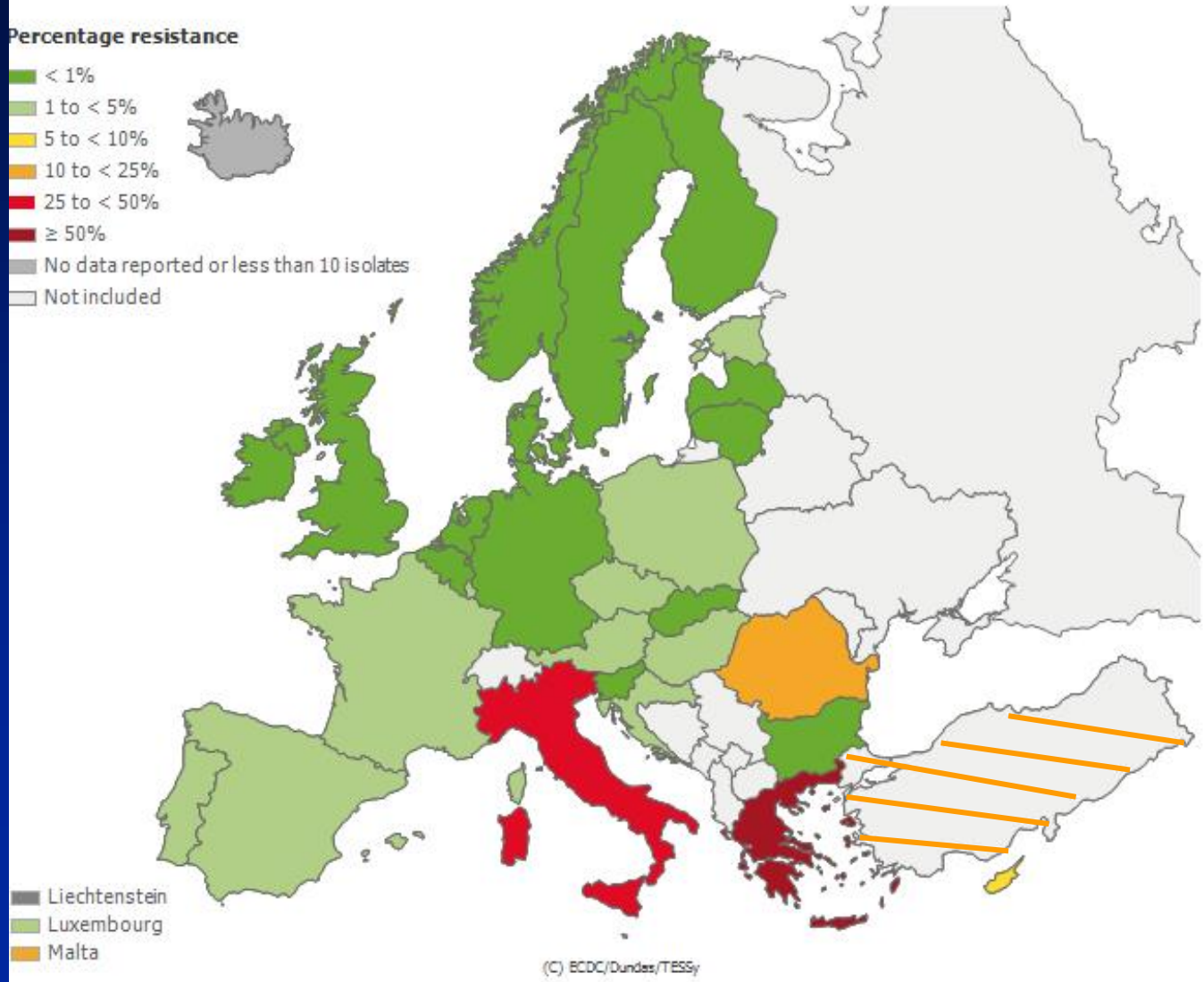
Etgül S, et al. ICAAC 2014 Abst no. C-1433

Avrupa'da Karbapenemaz (+) Enterobacteriaceae Dağılımı

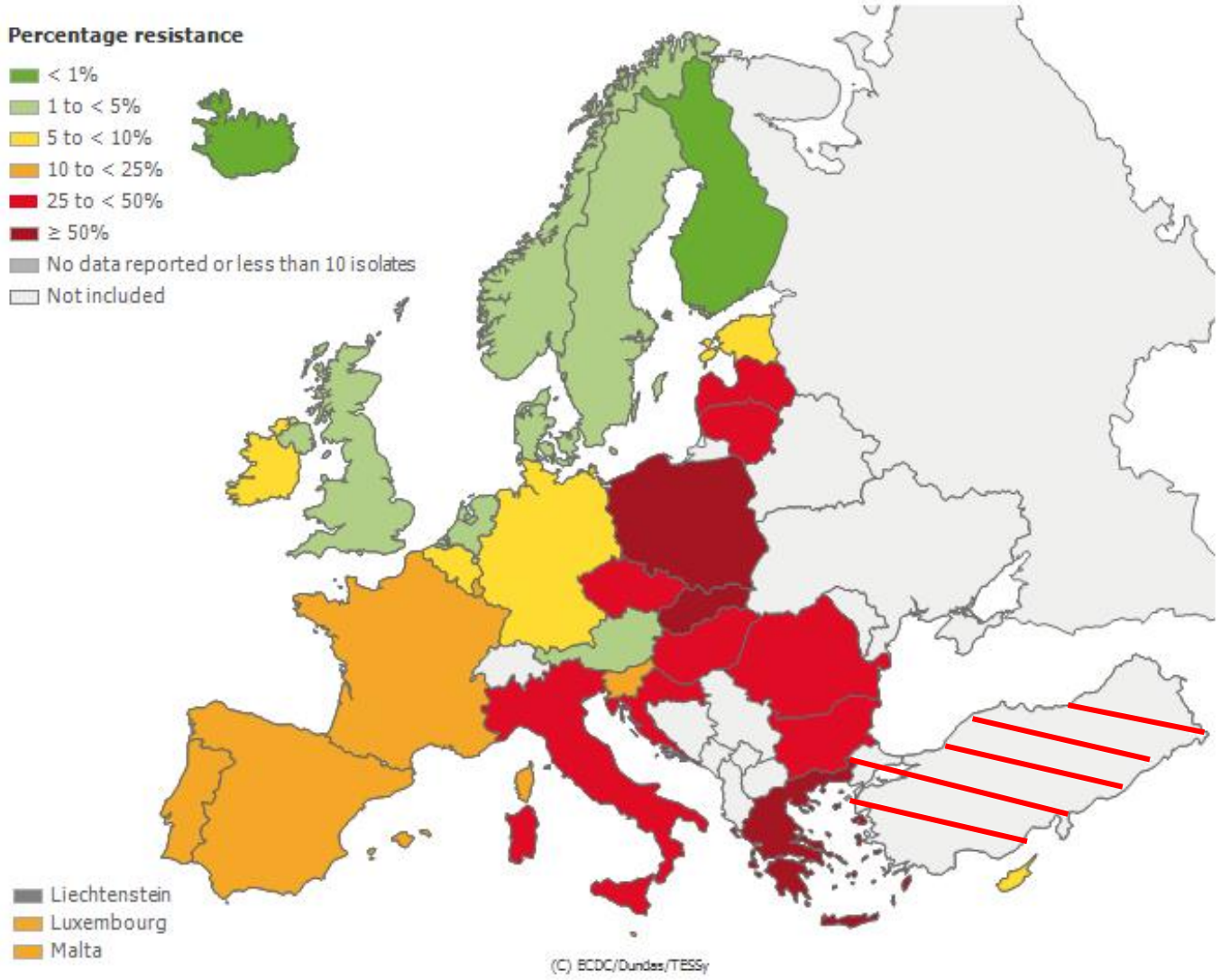


Canton R, Akova M, et al. Clin Microbiol Infect 2012;18:413

Proportion of Carbapenems Resistant (R+I) *Klebsiella pneumoniae* Isolates in Participating Countries in 2013



Multidrug-resistant Klebsiella pneumoniae Isolates in Participating Countries in 2013 (Resistant to Third-generation Cephalosporins, Fluoroquinolones and Aminoglycosides)



Eurosurveillance

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Eurosurveillance, Volume 19, Issue 42, 23 October 2014

Rapid communications

COLISTIN RESISTANCE SUPERIMPOSED TO ENDEMIC CARBAPENEM-RESISTANT KLEBSIELLA PNEUMONIAE: A RAPIDLY EVOLVING PROBLEM IN ITALY, NOVEMBER 2013 TO APRIL 2014

M. Monaco[1,2], T Giani[2,3], M Raffone[1,4], F Arena[3], A Garcia-Fernandez[1], S Pollini[3], Network EuSCAPE-Italy[5], H Grundmann[6], A Pantosti (annalisa.pantosti@iss.it)[1], G M Rossolini[3,7,8]

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2. MM and TG have equally contributed to this work
3. Department of Medical Biotechnologies, University of Siena, Siena, Italy
4. Federico II University Hospital, Neaples, Italy
5. The network EuSCAPE-Italy participants are listed at the end of this article
6. Department of Medical Microbiology, University of Groningen, University Medical Center Groningen, the Netherlands
7. Department of Experimental and Clinical Medicine, University of Florence, Florence, Italy
8. Clinical Microbiology and Virology Unit, Florence Careggi University Hospital, Florence, Italy

Citation style for this article: Monaco M, Giani T, Raffone M, Arena F, Garcia-Fernandez A, Pollini S, Network EuSCAPE-Italy, Grundmann H, Pantosti A, Rossolini GM. Colistin resistance superimposed to endemic carbapenem-resistant Klebsiella pneumoniae: a rapidly evolving problem in Italy, November 2013 to April 2014. Euro Surveill. 2014;19(42):pii=20939. Available online: http://www.eurosurveillance.org/ViewArticle.aspx?ArticleId=20939

Date of submission: 08 October 2014

Consecutive non-replicate clinical isolates (n=191) of carbapenem non-susceptible Enterobacteriaceae were collected from 21 hospital laboratories across Italy from November 2013 to April 2014 as part of the European Survey on Carbapenemase-producing Enterobacteriaceae (EuSCAPE) project. *Klebsiella pneumoniae* carbapenemase-producing *K. pneumoniae* (KPC-KP) represented 178 (93%) isolates with 76 (43%) respectively resistant to colistin, a key drug for treating carbapenamase-producing Enterobacteriaceae. KPC-KP colistin-resistant isolates were detected in all participating laboratories. This underscores a concerning evolution of colistin resistance in a setting of high KPC-KP endemicity.

We report the widespread and rapid dissemination of resistance against colistin, a key drug for treatment of carbapenamase-producing Enterobacteriaceae, among *Klebsiella pneumoniae* carbapenemase (KPC)-producing *K. pneumoniae* (KPC-KP) in Italy. As part of the European Survey on Carbapenemase-producing Enterobacteriaceae (EuSCAPE) project, consecutive non-replicate clinical isolates of carbapenem non-susceptible (resistant or intermediate) Enterobacteriaceae (n=191) were collected from 21 Italian hospital laboratories between November 2013 and April 2014. Most isolates 178 (93%) were KPC-KP, with 76 (43%) respectively resistant to colistin. This report details the findings and discusses potential implications for infection control.

KPC (+) *K. pneumoniae* ile Bakteremi

- Retrospektif, 1:2 eşlendirilmiş vaka kontrol çalışması
  - İtalya'da 5 merkez
- 657 hastadan KPC-Kp (+) klinik örnek
  - 426 hastada KPC-Kp infeksiyonları

Tumbarello M, et al. Antimicrob Agents Chemother 2014;58:3514

Bağımsız Faktörler

KPC-Kp İzolasyonu

- YBÜ yatış
- İdrar sondası
- Santral venöz kateter
- ≥2 hastaneye yatış
- Hematolojik kanser
- Kısa süre önce karbapenem veya kinolon tedavisi

KPC-Kp İnfeksiyonu

- Charlson indeks ≥3
- Santral venöz kateter
- Yakın zamanda cerrahi
- Nötropeni
- ≥2 hastaneye yatış
- Kısa süre önce karbapenem veya kinolon tedavisi

Tumbarello M, et al. Antimicrob Agents Chemother 2014;58:3514

Hematolojik Kanserli Hastalarda KPC-Kp Bakteremisi

	Herhangi bir Gram (-)		Non-KPC-Kp		KPC-Kp	
Yıl	Bakteremi, n	Ölüm, n (%)	Bakteremi, n	Ölüm, n (%)	Bakteremi, n	Ölüm, n (%)
2009	30	5 (16.6)	1	0	0	0
2010	39	7 (17.9)	2	0	1	1 (100)
2011	41	9 (24.3)	5	1 (20)	13	7 (53.8)
2012	37	11 (29.7)	4	1 (25)	12	7 (58.3)
Total	147	32 (21.7)	12	2 (16.6)	26	15 (57.6)

Pagano L, et al. Emerging Infect Dis 2014;20:1235

KİT Alıcılarında CR-Kp İnfeksiyonlar
İtalya 2010-2013

- 52 merkezde retrospektif sorgulama
  - %53.4 merkez CR-Kp infeksiyonu bildirmiş
    - 25 oto-KİT (%0.4) (2010'da %0.1, 2013'te %0.7)
    - 87 allo-KİT (%2%) (2010'da %0.4, 2013'de %2.9)
- Kolonizasyonu takiben infeksiyon
  - %25.8, oto-KİT
  - %39.2, allo-KİT

Girmenia C, et al. Bone Marrow Transplant 2015;50:282

KİT Alıcılarında CR-Kp İnfeksiyonlar
İtalya 2010-2013

- İnfeksiyonla ilişkili mortalite
  - %16%, oto-KİT
  - %64.4, allo-KİT
- Mortalite için risk faktörleri
  - Tx öncesi CR-Kp infeksiyonu
  - Birincil tedavide CR-KP'nin kapsanmaması

Girmenia C, et al. Bone Marrow Transplant 2015;50:282

Karbapenem R-*E. coli* ve *K. pneumoniae* Hacettepe Universitesi, 2009-13

Yıl	Taranan hasta sayısı	Kolonize hasta sayısı (%)	İnfekte hasta sayısı (%)
2009 (2. yarıyıl)	484	73 (15)	6 (1.2)
2010	837	62 (7.4)	4 (0.5)
2011	984	42 (4.3)	9 (1)
2012	1120	172 (15.4)	17 (1.5)
2013	754	112 (14,9)	53 (7.0)
Toplam	**3979**	**461 (11.6)**	**89 (2.4)**

Akova M, Yayınlanmamış veri

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

European guidelines for empirical antibacterial therapy for febrile neutropenic patients in the era of growing resistance: summary of the 2011 4th European Conference on Infections in Leukemia

Diana Averbuch,[1] Christina Orasch,[2] Catherine Cordonnier,[3] David M. Livermore,[4] Małgorzata Mikulska,[5] Claudio Viscoli,[5] Inge C. Gyssens,[6,7,8] Winfried V. Kern,[9] Galina Klyasova,[10] Oscar Marchetti,[2] Dan Engelhard,[1] and Murat Akova;[11] on behalf of ECIL4, a joint venture of EBMT, EORTC, ICHS, ESGICH/ESCMID and ELN

[1]Pediatric Infectious Diseases Unit, Hadassah-Hebrew University Medical Center, Jerusalem, Israel; [2]Infectious Diseases Service, Department of Medicine, Lausanne University Hospital, Switzerland; [3]APHP-Henri Mondor Hospital, Hematology Department and Université Paris Est -Créteil, France; [4]Norwich Medical School, University of East Anglia, Norwich, UK; [5]Division of Infectious Diseases, University of Genova, IRCCS San Martino-IST, Genoa, Italy; [6]Department of Medicine and Nijmegen Institute for Infection, Inflammation and Immunity (N4i), Radboud University Nijmegen Medical Centre, Nijmegen, The Netherlands; [7]Department of Medical Microbiology and Infectious Diseases, Canisius Wilhelmina Hospital, Nijmegen, The Netherlands; [8]Hasselt University, Diepenbeek, Belgium; [9]Center for Infectious Diseases and Travel Medicine, Department of Medicine, University Hospital, Albert-Ludwigs University, Freiburg, Germany; [10]National Research Center for Hematology, Moscow, Russia; and [11]Department of Medicine, Section of Infectious Diseases, Hacettepe University School of Medicine, Ankara, Turkey

ABSTRACT

Owing to increasing resistance and the limited arsenal of new antibiotics, especially against Gram-negative pathogens, carefully designed antibiotic regimens are obligatory for febrile neutropenic patients, along with effective infection control. The Expert Group of the 4th European Conference on Infections in Leukemia has developed guidelines for initial empirical therapy in febrile neutropenic patients, based on: i) the local resistance epidemiology; and ii) the patient's risk factors for resistant bacteria and for a complicated clinical course. An 'escalation' approach, avoiding empirical carbapenems and combinations, should be employed in patients without particular risk factors. A 'de-escalation' approach, with initial broad-spectrum antibiotics or combinations, should be used only in those patients with: i) known prior colonization or infection with resistant pathogens; or ii) complicated presentation; or iii) in centers where resistant pathogens are prevalent at the onset of febrile neutropenia. In the latter case, infection control and antibiotic stewardship also need urgent review. Modification of the initial regimen at 72-96 h should be based on the patient's clinical course and the microbiological results. Discontinuation of antibiotics after 72 h or later should be considered in neutropenic patients with fever of unknown origin who are hemodynamically stable since presentation and afebrile for at least 48 h, irrespective of neutrophil count and expected duration of neutropenia. This strategy aims to minimize the collateral damage associated with antibiotic overuse, and the further selection of resistance.

Averbuch D, et al. Haematologica 2013;98:1826-35

Yüksek Riskli Hastalarda Eskalasyon Tedavisi

- **İndikasyonlar (BII)**
  - Komplike olmayan klinik tablo
  - Dirençli bakteri kolonizasyonu veya önceden infeksiyon yok
  - Dirençli bakteri infeksiyonlarının görülmediği merkezler
- **Başlangıç tedavisi**
  - Anti-psödomonal sefalosporin (AI)
  - Piperasilin-tazobaktam (AI)
  - Tikarsilin-klavulanat, sulbaktam-sefoperazon, piperasilin + gentamisin

Averbuch D, et al. Haematologica 2013;98:1826-35

De-eskalasyon Tedavisi

- **İndikasyonlar (BII)**
  - Komplike klinik tablo
  - Dirençli bakteri ile kolonizasyon veya önceden infeksiyon
  - Dirençli bakteri infeksiyonlarının sık görüldüğü merkezler
- **Başlangıç tedavi seçenekleri**
  - Karbapenem monoterapisi (BII)
  - Kombinasyon tedavisi ve Gram (+) kapsama

Averbuch D, et al. Haematologica 2013;98:1826-35

Empirik Tedavi Süresi

- **Nötropeni düzelinceye kadar (>500/mm^3) (B-II)**
  - **Dökümante edilmiş infeksiyonlarda daha uzun olabilir (B-III)**
  - **Dökümante infeksiyon tedavisi sonrası hala nötropenik olanlarda kinolon profilaksisi**

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

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

Averbuch D, et al. Haematologica 2013;98:1826-35

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*

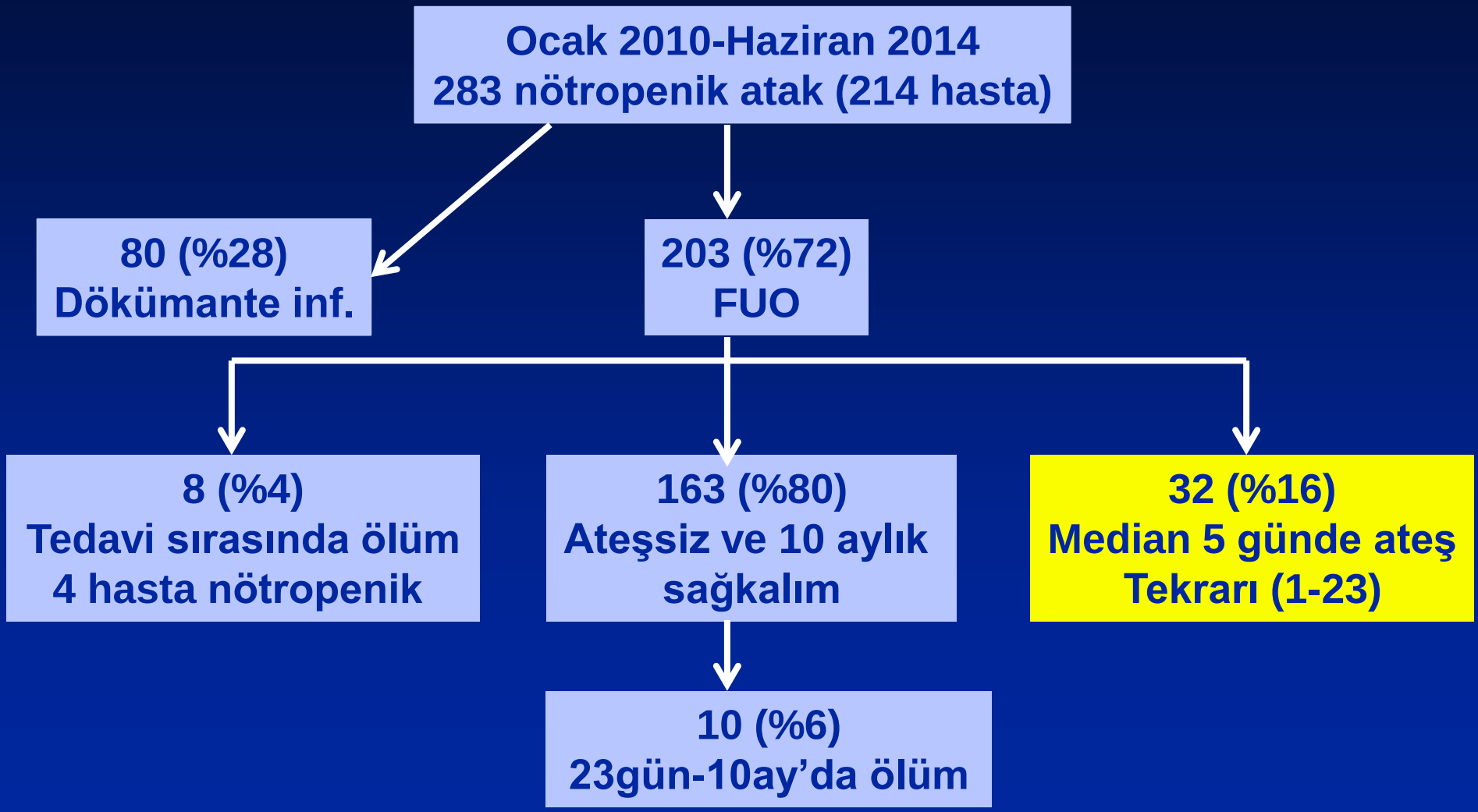
BIII

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

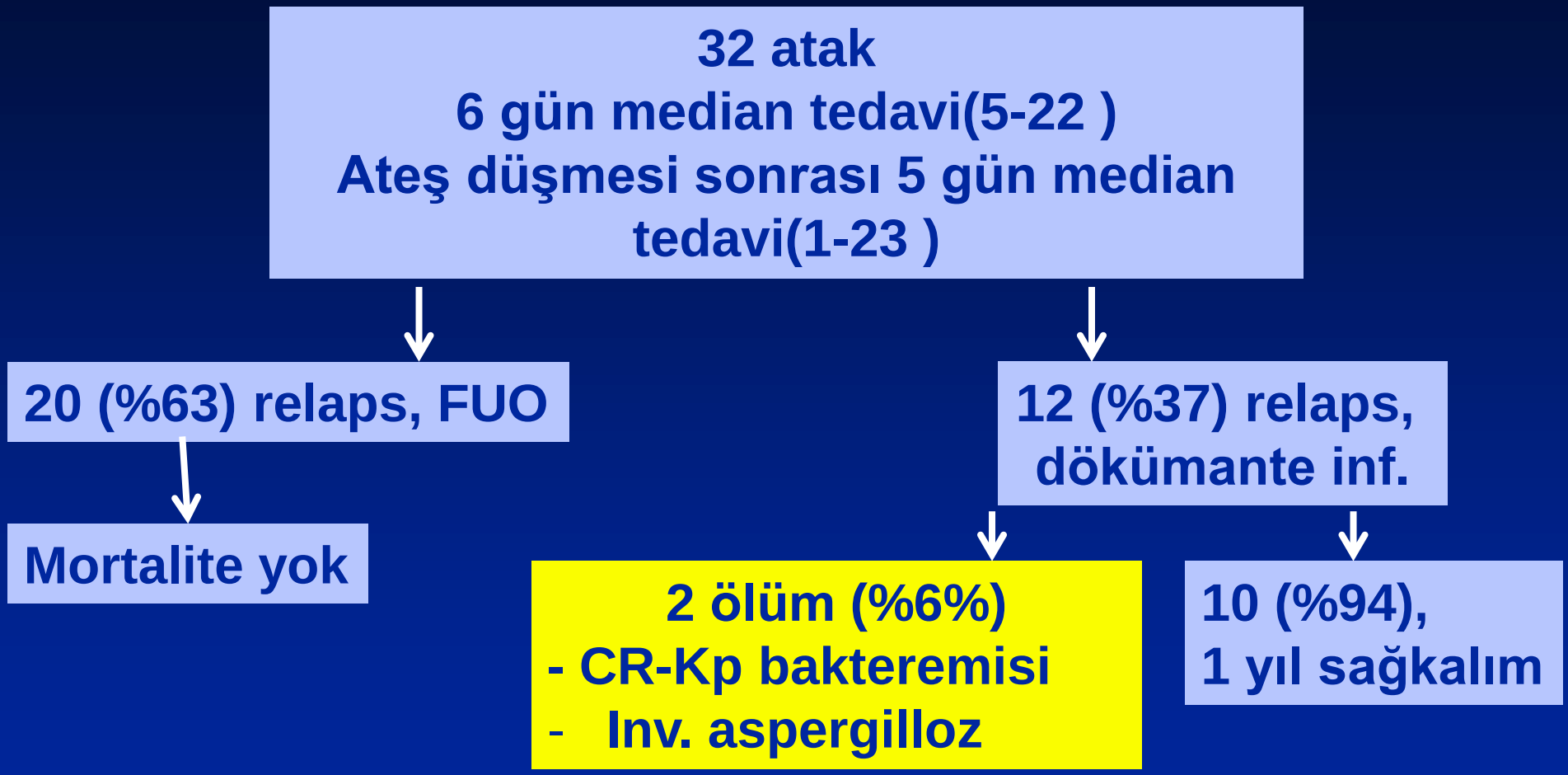
Averbuch D, et al. Haematologica 2013;98:1826-35

Erken Tedavi Sonlandırımı-Hacettepe Deneyimi



Korucu B & Akova M. ECCMID 2015'te sunuldu

Ateşin Tekrarladığı 32 Atak Analizi



Korucu B & Akova M. Accepted to be presented in ECCMID 2015

Yorum

- **Dirençli ESKAPE patojenleri febril nötropenide de önemli bir sorun**
- **Klasik empirik tedavi biçimleri bu grup hastada etkisiz kalabilir**
- **FUO ve febril nötropenisi olan hastalarda kısa süreli empirik tedavi başarılı**


İÇ HASTALIKLARI ANABİLİM DALI
İnfeksiyon Hastalıkları A.D.

Teşekkürler…