Empirical Treatment Strategies of the Immunocompromised Host in the Era of MDR Organisms

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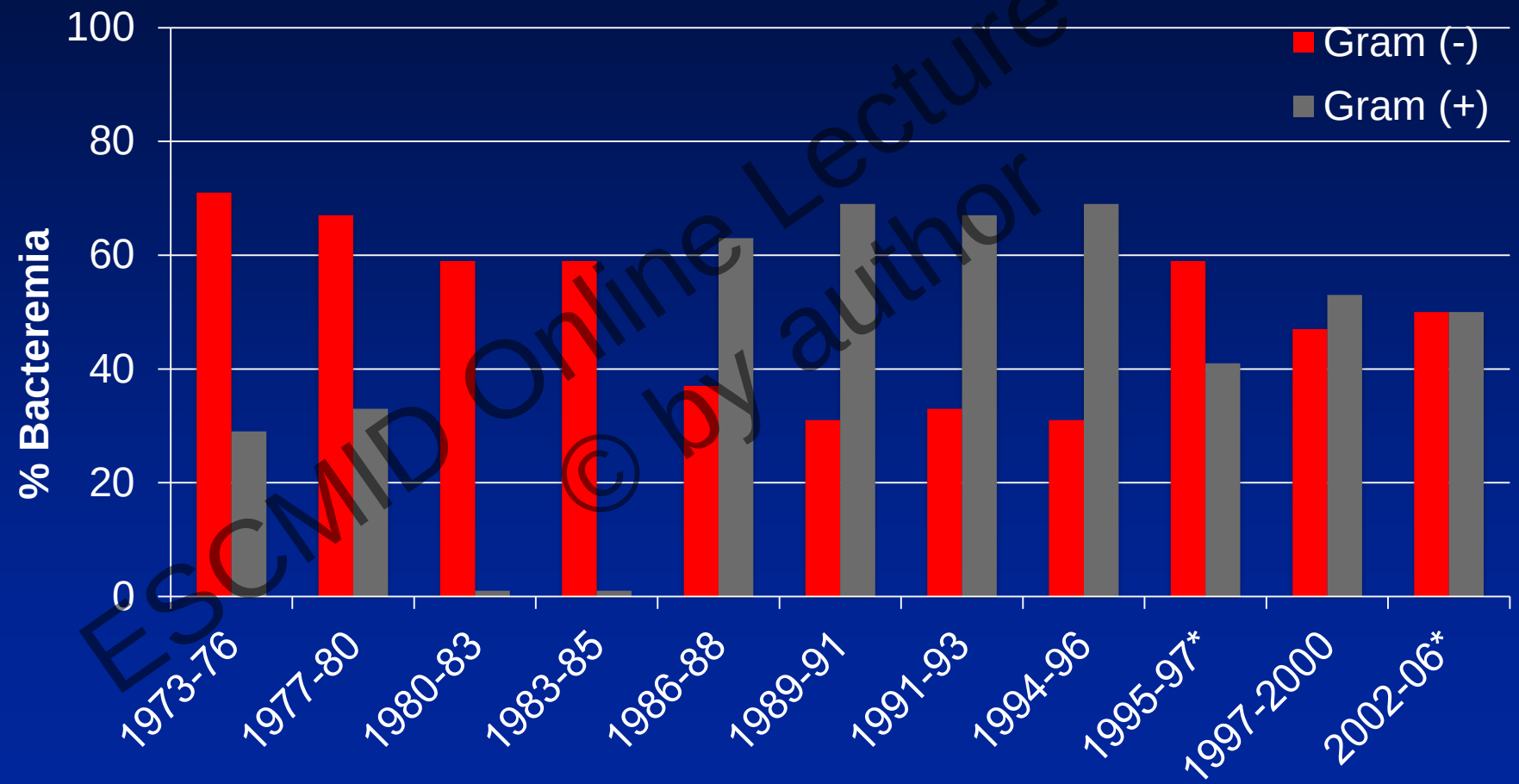
Single Agent Bacteremia in EORTC-IATG Trials



*** These studies predominantly included patients with low-risk neutropenia**

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

ESKAPE Pathogens

E	*Enterococcus faecium*
S	*Staphylococcus aureus*
K	*Klebsiella pneumoniae*
A	*Acinetobacter baumannii*
P	*Pseudomonas aeruginosa*
E	*Enterobacter* spp.

Rice LB. *J Infect Dis.* 2008;197:1079

Rice LB. *Infect Control Hosp Epidemiol.* 2010;31(Suppl 1):S7

Introduction to ECIL

from ECIL1 to ECIL 4

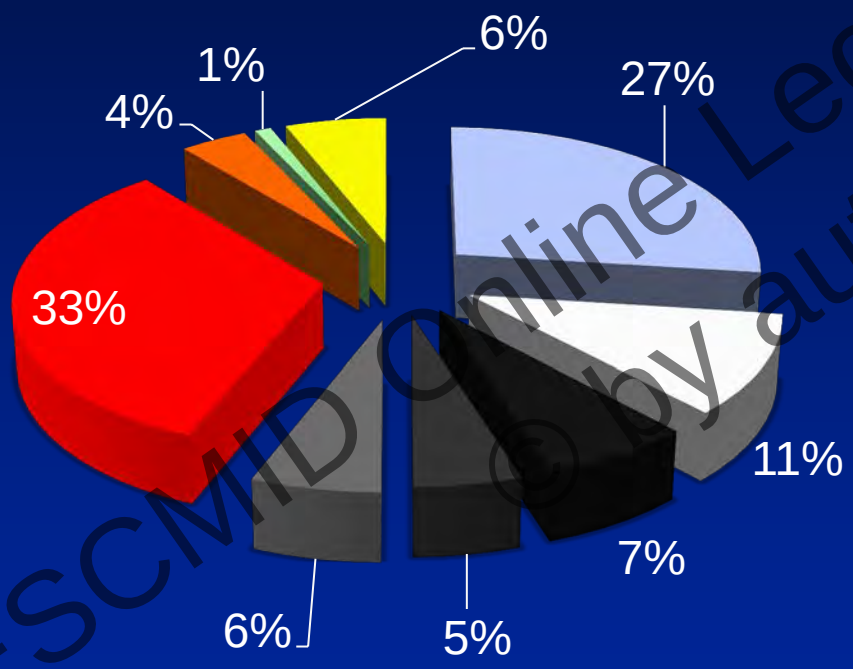
4th European Conference on Infections in Leukemia

Current Epidemiology of Bacteremia in Cancer Patients

- 34 centers from Europe and Israel
- Median observation period, 4 years (range 1-13)
- 21 adult-only, 6 children-only centers
- Gram (+) vs (-) pathogens, 56% vs 44%
- Resistance rates for Gram (-)s higher in south/east vs north/west countries

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

Current Epidemiology of Bacteremia in Cancer Patients, ECIL 4

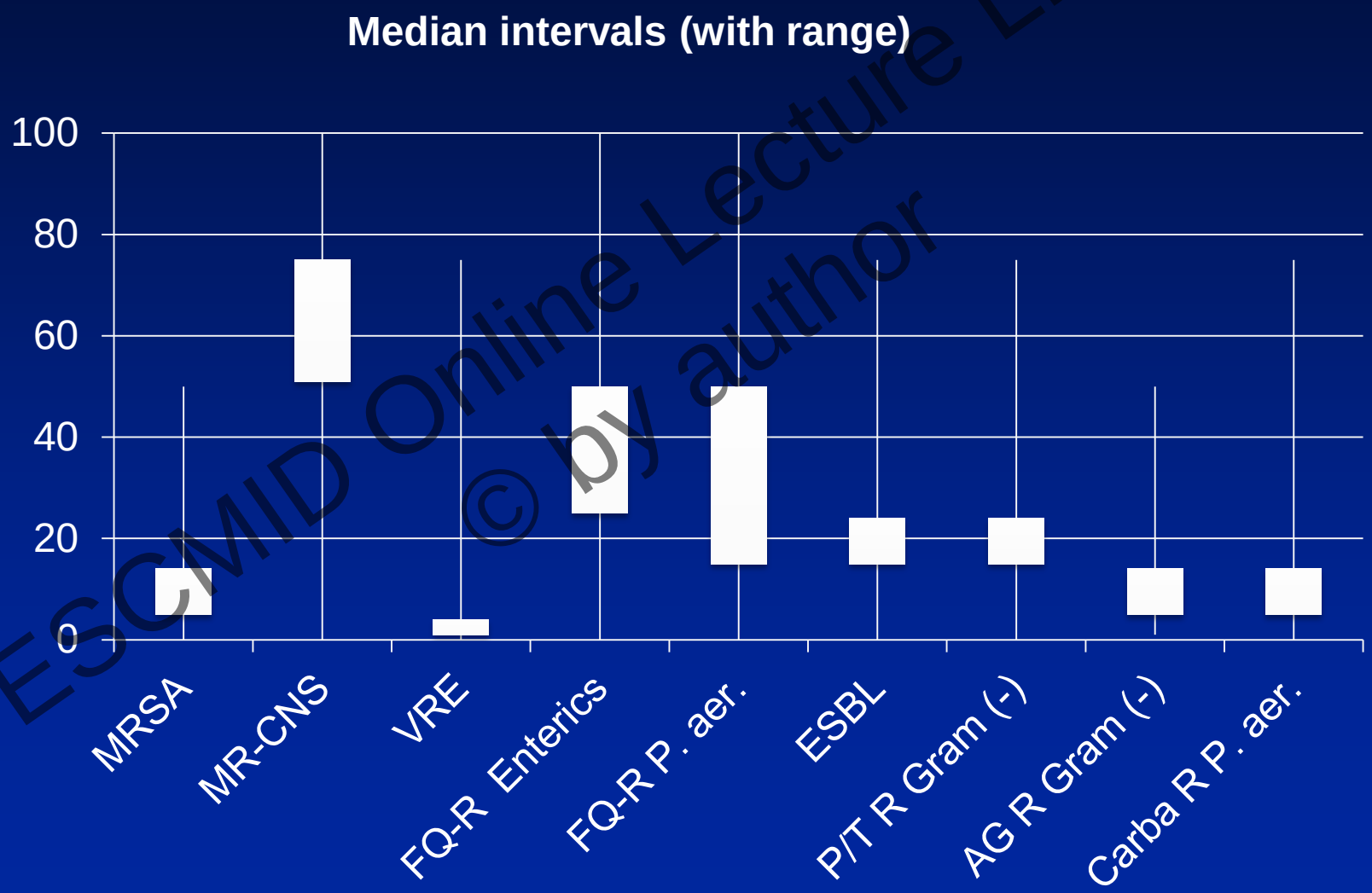


Median ratios

- CNS (7-21%)
- Enterococci (0-30%)
- Viridans strep. (0-22%)
- S. aureus (0-15%)
- Other Gram (+) (0-15%)
- Enterobacteriaceae (8-56%)
- P. aeruginosa (0-28%)
- Acinetobacter (0-11%)
- Other Gram (-) (0-14)

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

Current Resistance Rates, ECIL 4



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

ESKAPE Pathogens in Cancer Patients

- **Bacteremia in adult cancer patients, 2006-2011**
  - **1148 bacteremia episodes**
    - **392 (34%) ESKAPE pathogens**
      - **54 (4.7%) rESKAPE**
        - **VRE**
        - **MRSA**
        - **ESBL (+) *K. pneumonia***
        - **Carba-R *A. baumannii***
        - **Carba- and Q-R *P. aeruginosa***
        - **Derepressed and ESBL (+) *Enterobacter spp.***

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

rESKAPE Bacteremia (n=54)
Risk Factors

Risk factors *vs* ESKAPE	P value
Comorbidities	.02
Prior antibiotics (1 mo)	.001
Urinary catheter	.02
Urinary tract source	.04
***vs* matched controls *w/o* bacteremia (n=54)**	
Prior antibiotics (1 mo)	<.001
Urinary catheter	.05

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

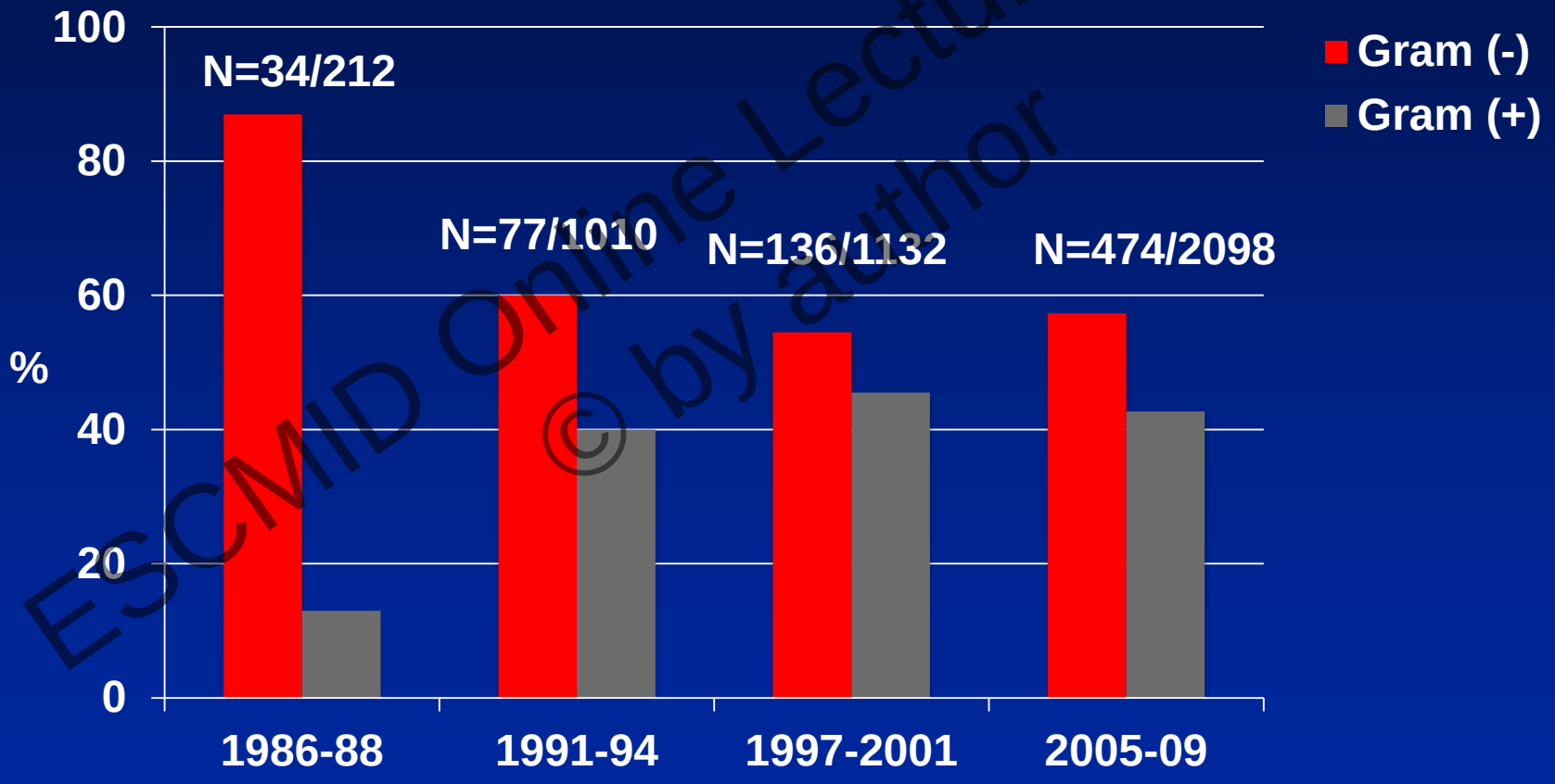
rESKAPE Bacteremia (n=54)

Risk Factors for Case Fatality Rate (30 days)

Risk factors	P value
ICU admission	<.001
Persistent sepsis	<.001
Steroid therapy	.007
Empirical, beta-lactam monotherapy	.001
Protective factors	
Infection recovery	<.001
Empirical, beta-lactam + aminoglycoside therapy	.03

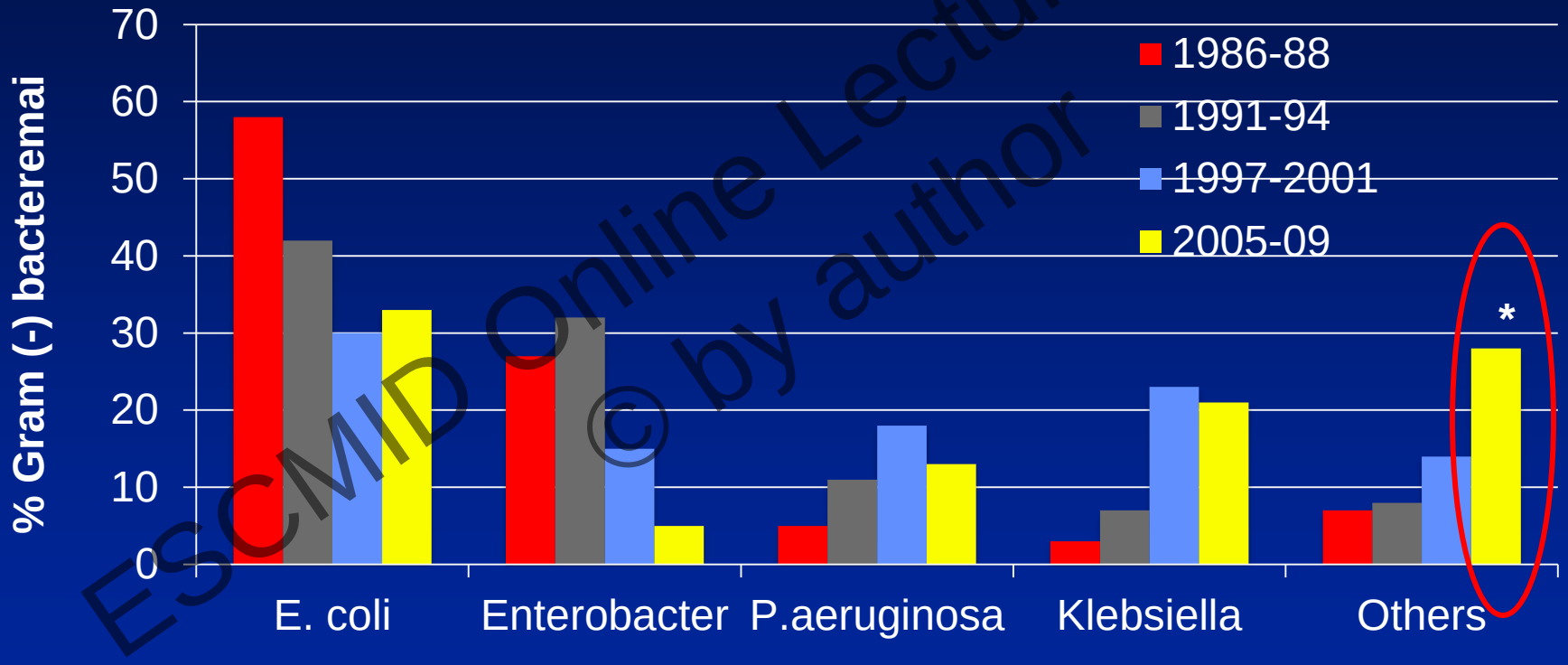
Bodro M, et al. Support Care Cancer 2014;22:603-10

Agents of Bacteremia in Cancer Patients



Guven GS, et al. Support Care Cancer 2006;14:52
Kara O, et al. Infect Dis 2015;29:1

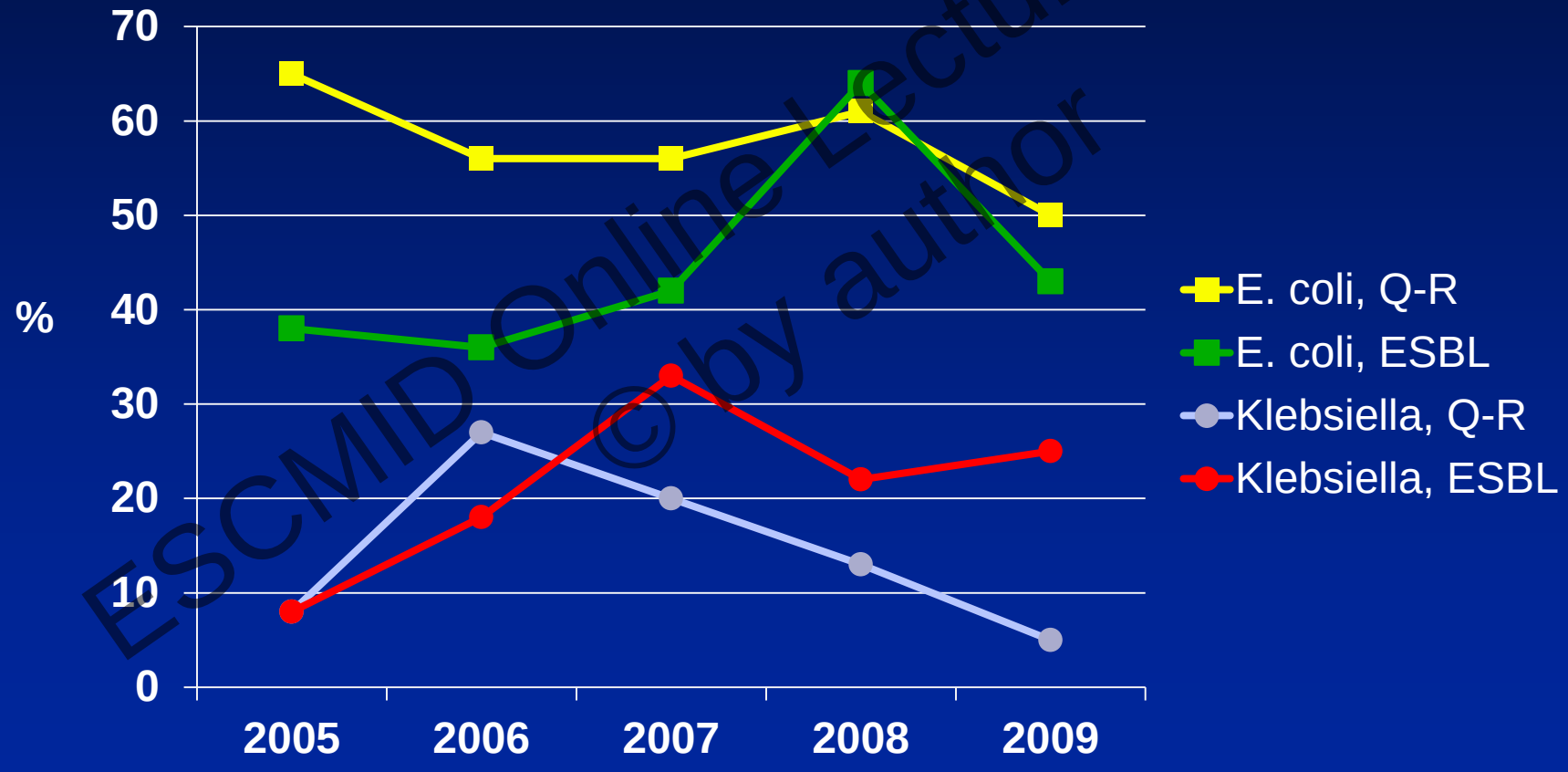
Distribution of Agents of Gram (-) Bacteremia



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

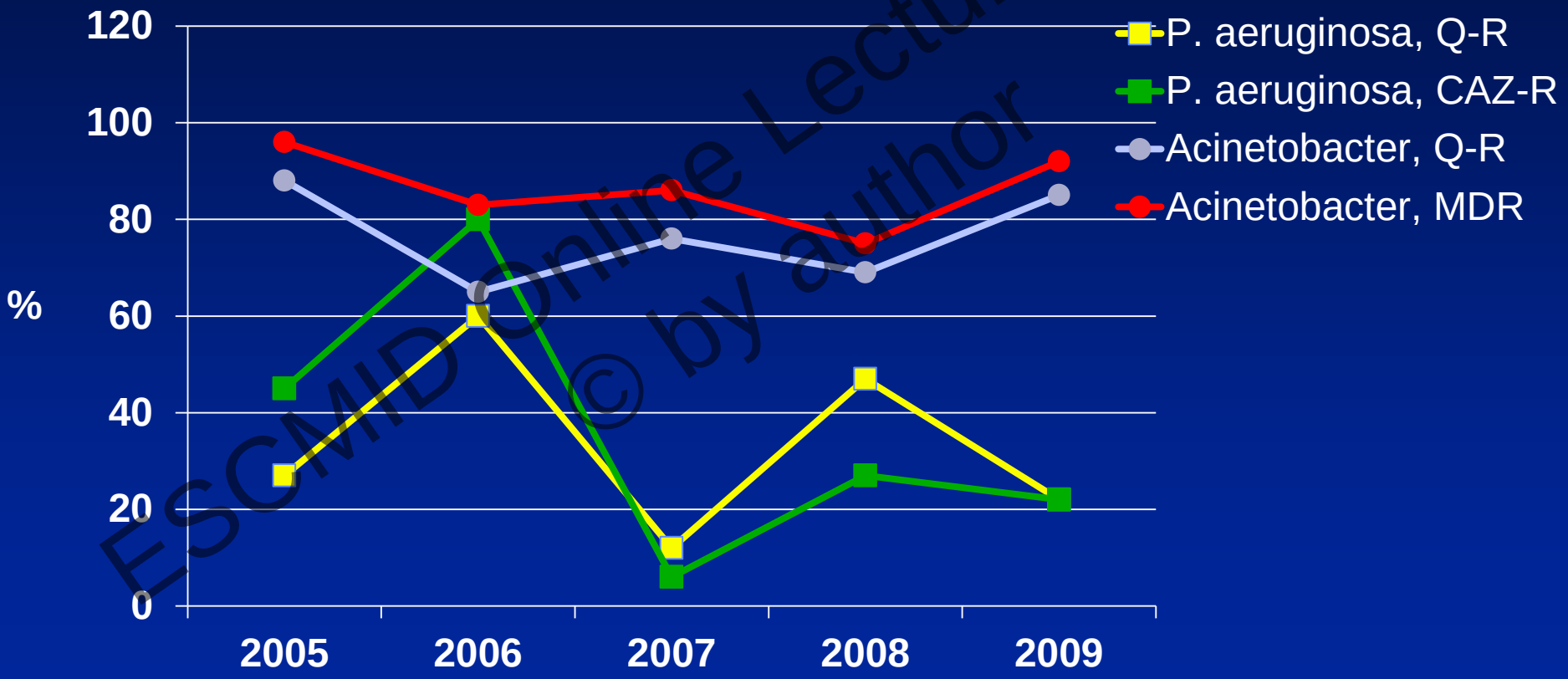
Guven GS, et al. Support Care Cancer 2006;14:52
Kara O, et al. Infect Dis 2015;29:1

Resistance Patterns in *E. coli* and *Klebsiella spp.* in Cancer Patients



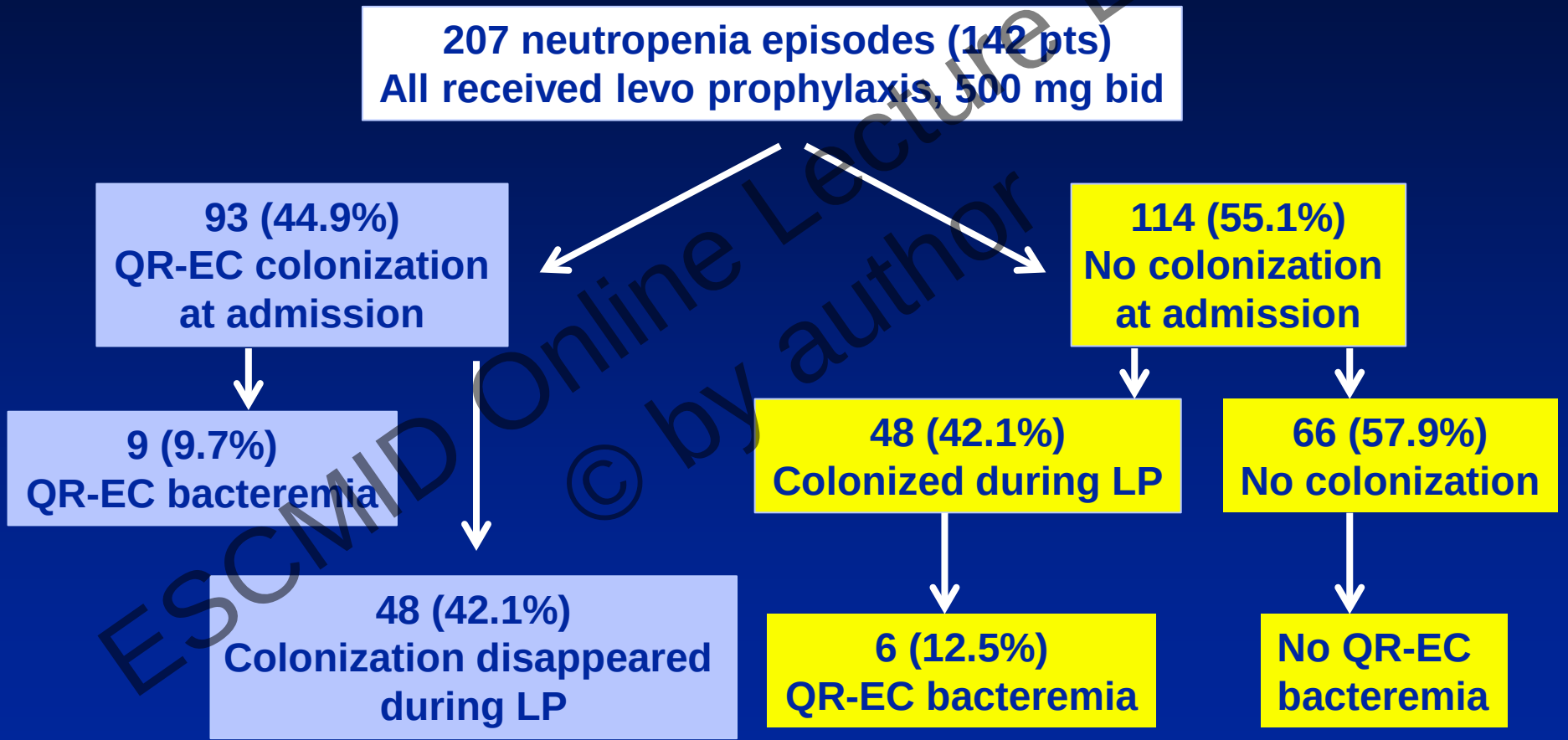
Kara, Ö, et al. Infect Dis 2015, 29:1

Resistance Patterns in *P. aeruginosa and Acinetobacter spp.* in Cancer Patients



Kara, Ö, et al. Infect Dis 2015:29:1

Quinolone-R *E. coli* in Neutropenic Cancer Patients with Levofloxacin Prophylaxis



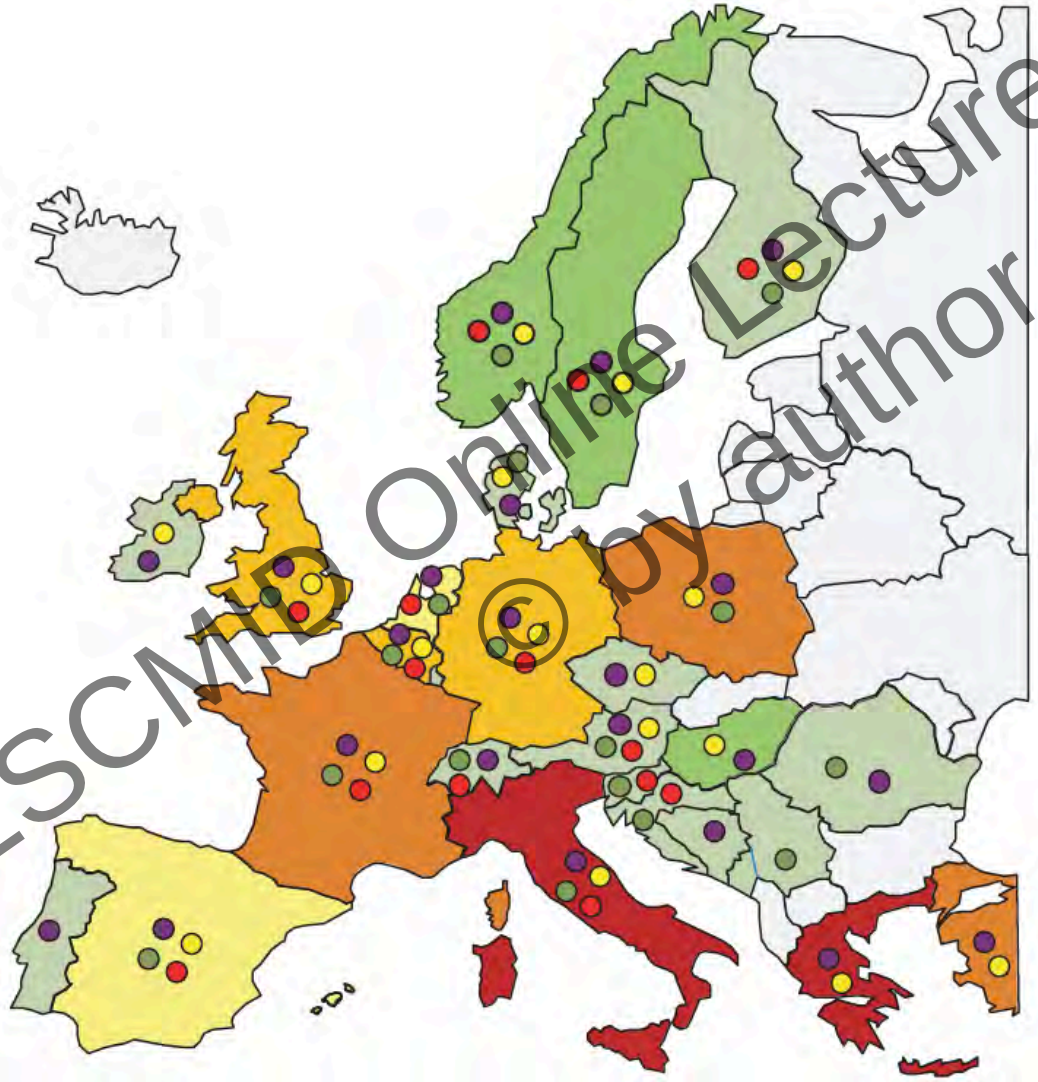
Etgül S, et al. ICAAC 2014 Abst no. C-1433

Other Results and Conclusions

- 40% QR-EC were ESBL producers
  - Only carbapenems and amikacin effective in vitro
- Colonizing and bacteremia strains shared the same PFGE patterns
- Carbapenems should be the empirical choice for patients under levo prophylaxis

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

Carbapenemase-producing Enterobacteriaceae in Europe



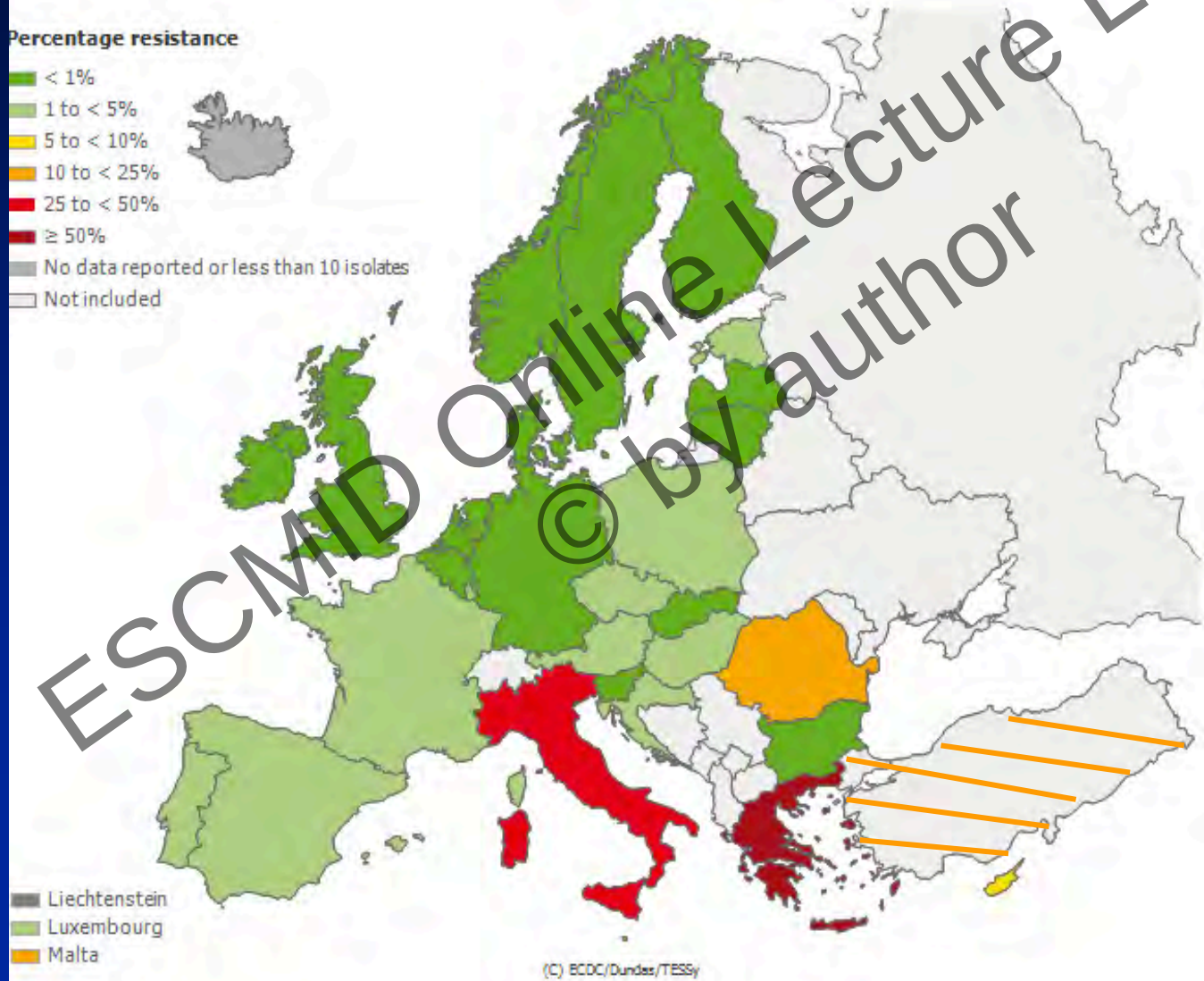
Endemic
Interregional spread
Regional spread
Independent hospital outbreaks
Single-hospital outbreaks
Sporadic occurrence
Not reported / no data

KPC
VIM
NDM
OXA-48

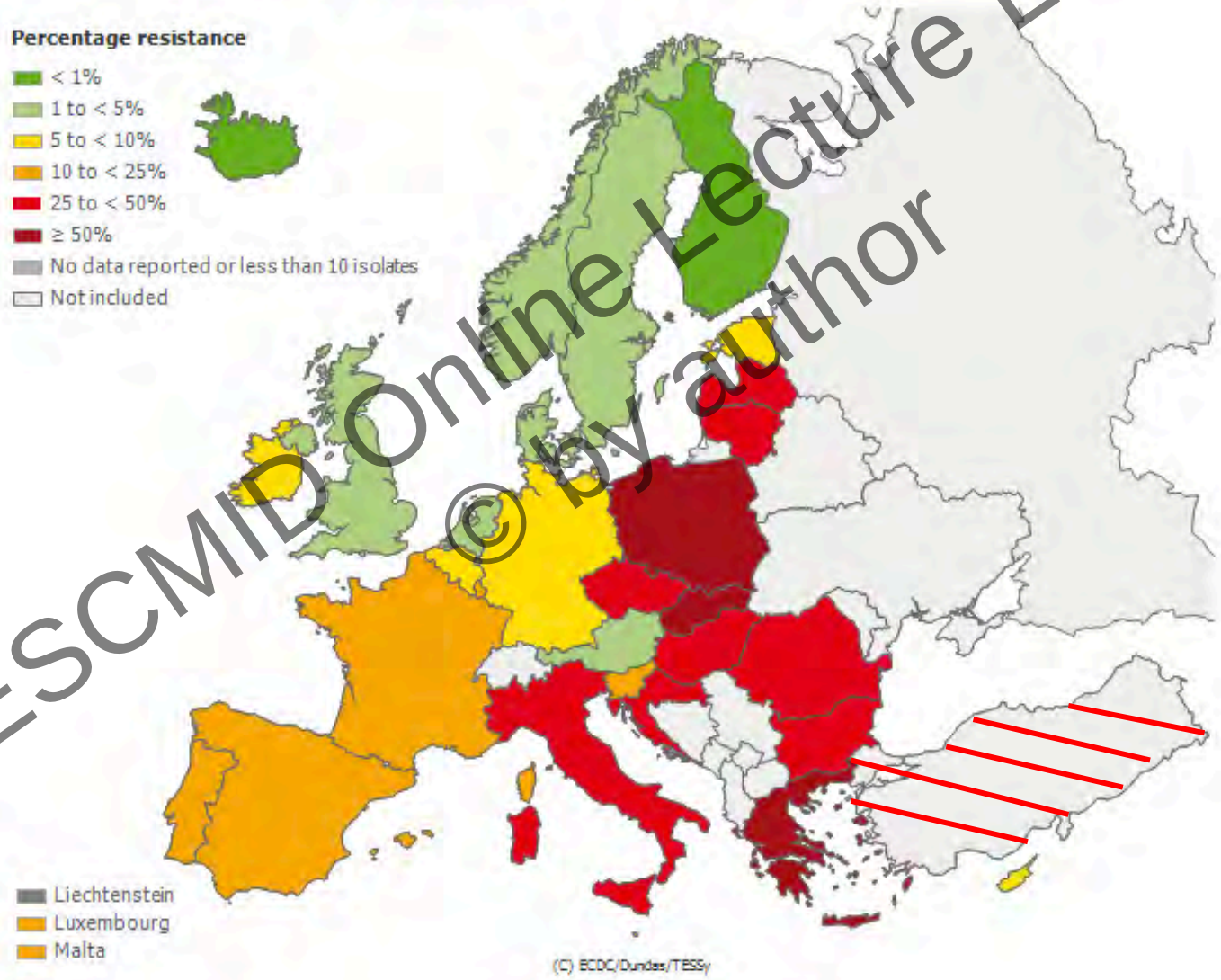
Other countries:
Israel
Luxembourg

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

Back to Table of Contents
Previous
Next

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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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.

Predictive Models for Identifying Patients Infected with KPC-producing *K. pneumoniae*

- Retrospective, 1:2 matched case control study in 5 Italian centers
- 657 patients with clinical samples of KPC-Kp
  - 426 patients with KPC-Kp infections

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

Independent Predictors

KPC-Kp Isolation

- Recent admission to the ICU
- Indwell. urinary catheter
- CVC and/or surgical drain
- ≥2 recent hospitalization
- Hematological cancer
- Recent FQ and/or carbapenem tx

Infection with KPC-Kp

- Charlson index ≥3
- CVC
- Recent surgey
- Neutropenia
- ≥2 recent hospitalization
- Recent FQ and/or carbapenem tx

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

KPC-Kp in Hematological Malignancies

	Any Gram (-)		Non-KPC-Kp		KPC-Kp	
Year	BSI, n	Deaths, n (%)	BSI, n	Deaths, n (%)	BSI, n	Deaths, 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

Infections by CRKp in SCT Recipients
Italy 2010-2013

- Retrospective survey in 52 Italian Centers
  - 53.4% centers reported CRKp infections
    - 25 auto-SCT (0.4%) (01.% in 2010 to 0.7% in 2013)
    - 87 allo-SCT (2%) (0.4% in 2010 to 2.9 in 2013)
- Infection followed colonization in
  - 25.8% in auto
  - 39.2% in allo

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

Infections by CRKp in SCT Recipients
Italy 2010-2013

- Infection-related mortality
  - 16% in auto
  - 64.4% in allo
- Independent risk factors for mortality in allo patients
  - Pre-transplant CRKp infection
  - A non-CRKP-targeted 1st line treatment

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

Alternatives to Carbapenems for Infections Caused by ESBL-producers

Antibiotic	Caveats
Colistin	Neprotoxicity, poor outcomes in pneumonia, no activity for *Proteus* and *Serratia*, R in *K. pneumoniae* reported
Tigecycline	No activity for *P. aeruginosa, Proteus, Morganella*. Not effective in VAP
Fosfomycin	Risk of mutational resistance. Few data for iv form.
Nitrofurantoin	Only for lower UTI
Beta-lactamase inhibitors	Many ESBL producers and all carbapenemase producers are resistant
Aminogylcosides, quinolones, TMP-SMX	Many ESBL producers and all carbapenemase producers are resistant

Hawkey & Livermore BMJ 2012;344:e3236

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] Malgorzata Mikulska,[5] Claudio Viscoli,[6] 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

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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

Escalation Approach for Empirical Therapy in High Risk Patients-

- **Indications (BII)**
  - Uncomplicated presentation
  - No colonization or previous infection with R bacteria
  - In centers where R bacteria are rare
- **Options for initial therapy**
  - Anti-pseudomonal cephalosporin (AI)
  - Piperacillin-tazobactam (AI)
  - Ticarcillin-clavulanate, sulbactam-cefoperazon, piperacillin + gentamicin

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

De-escalation Approach

- **Indications (BII)**
  - Complicated presentation
  - Known colonization or previous infection with R bacteria
  - In centers where R bacteria are prevalent
- **Options for initial therapy**
  - Carbapenem monotherapy (BII)
  - Combination therapy including early coverage for R Gram (+)ves

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

When Carbapenems Should be the 1st Choice?

- Patients with septic shock (BII)
- Know colonization or previous infection with (BII)
  - ESBL (+) enterics
  - Gram (-)ves *R* to narrow spectrum B-lactams
  - Centers with high prevalance of infections with ESBL (+)ves

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

When Aminoglycoside Combinations are Indicated? BII

- Seriously ill patients
- If R non-fermenters are likely
  - Local epidemiology
  - Previous colonization or infection
  - Use of carbapenems during the last month

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

A Zen Garden in Kyoto

15 Rocks Surrounded by Gravel

- One cannot see all 15 rocks from any point
- There always will be in need of another perspective

"Zen" Approach to Empirical Therapy in Febrile Neutropenia in an MDR Setting

- Data on local resistance prevalance
- Consider PK/PK parameters
- Consider combination antibiotics where MDR is prevalant
- De-escalate when susceptibility is known
- Do not over treat

Thank you…