MDR Acinetobacter Infections

Dr. Murat Akova

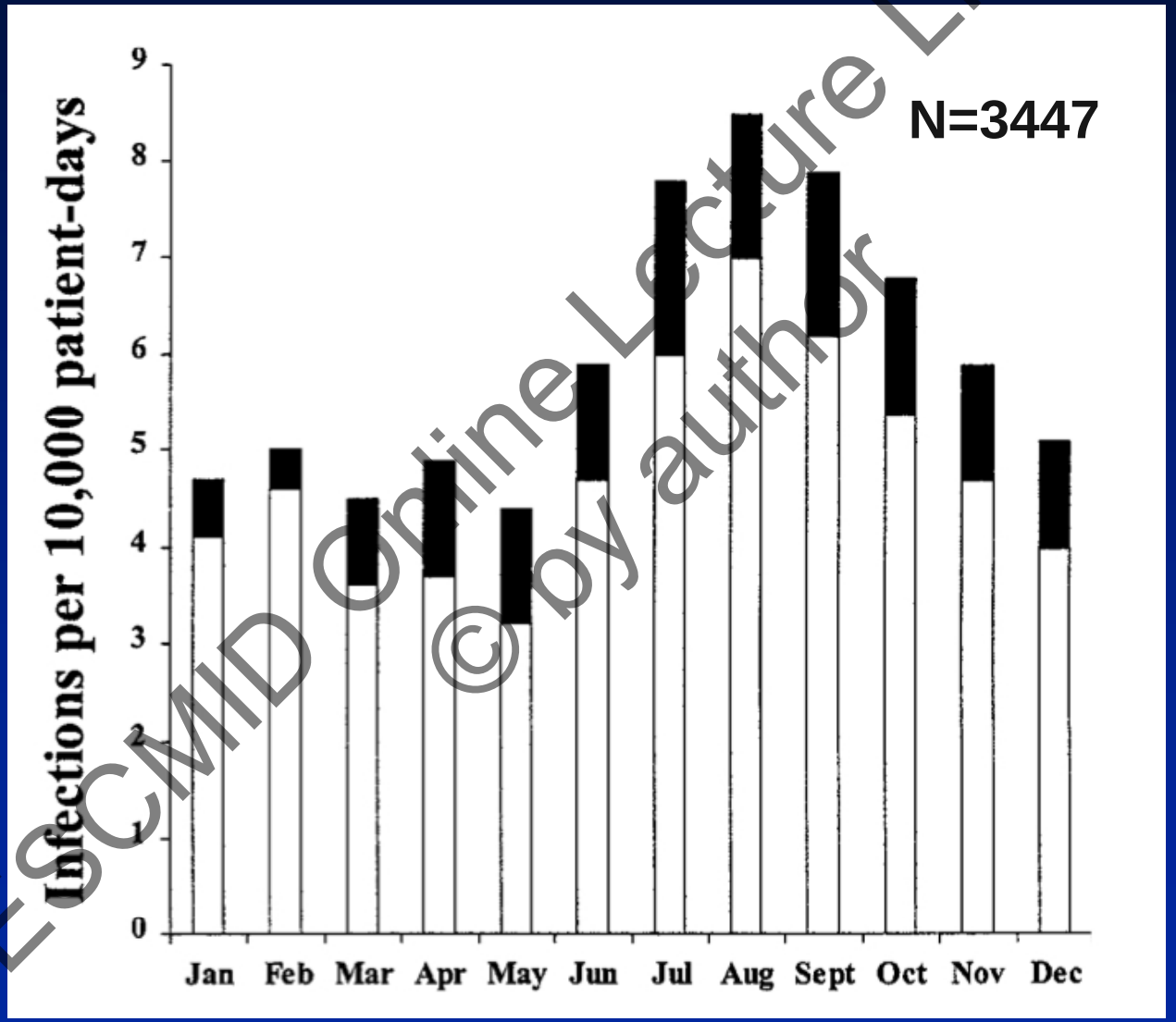
Hacettepe University
School of Medicine
Section of Infectious Diseases
Ankara, Turkey

Acinetobacter spp.

- Gram-negative non-fermenting coccobacillus
- Clinically-related species
  - *A. baumannii*
  - *A. calcoaceticus*
  - *A. lwoffi*
- Widely-distributed in nature (not *A. baumannii*)
  - Prefers aquatic environments
- Colonization is frequent
  - Up to 25% skin colonization in healthy people
  - Up to 45% of tracheostomy sites
- More nosocomial infections in summer

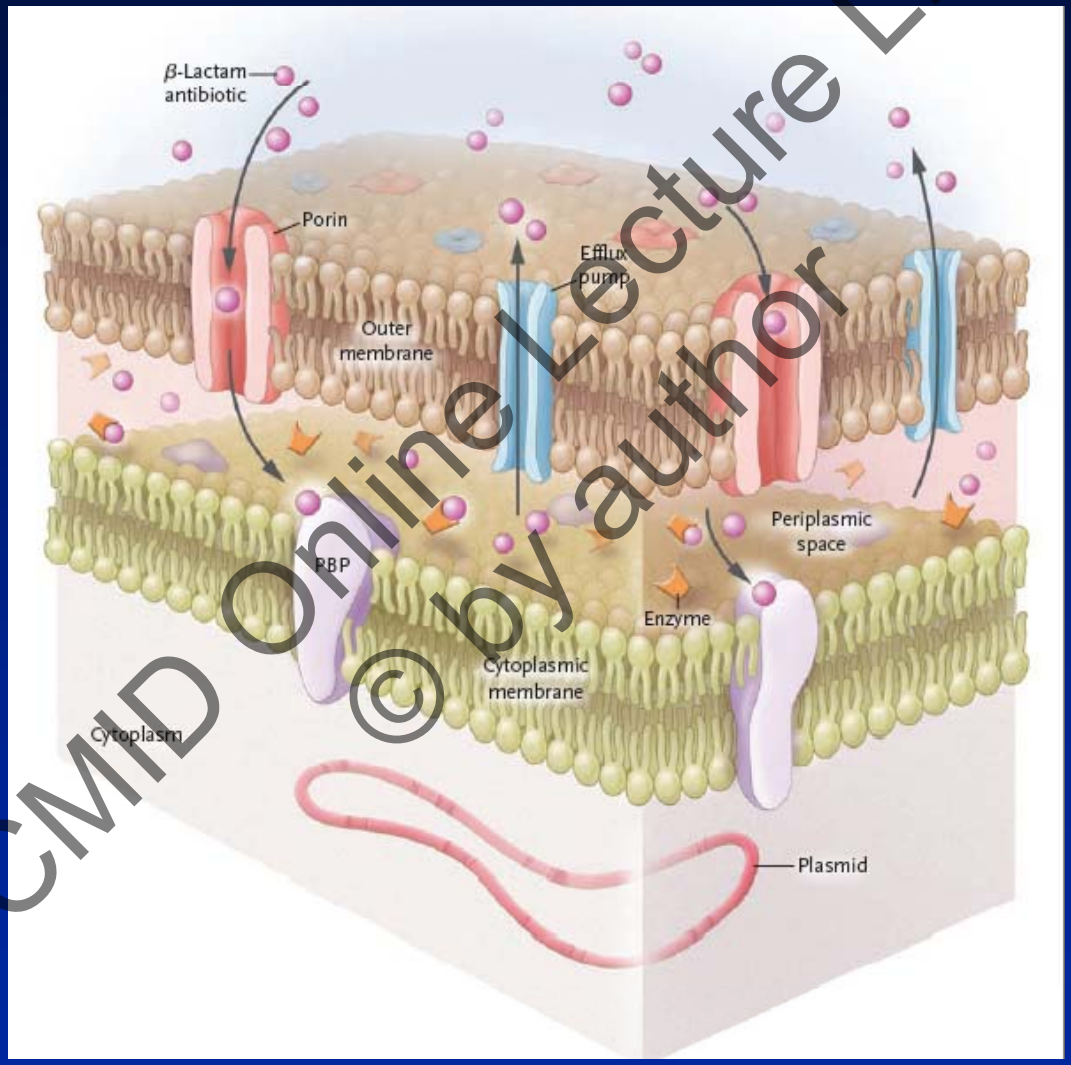
Munoz-Price, L and Weinstein RA. NEJM 2008;358:1271

Monthly Incidence of Acinetobacter Infections in ICU, NNIS 1987-1996



McDonald LC, et al. Clin Infect Dis 1999;29:1133

Mechanisms of Beta-lactam Antibiotic Resistance in *Acinetobacter*



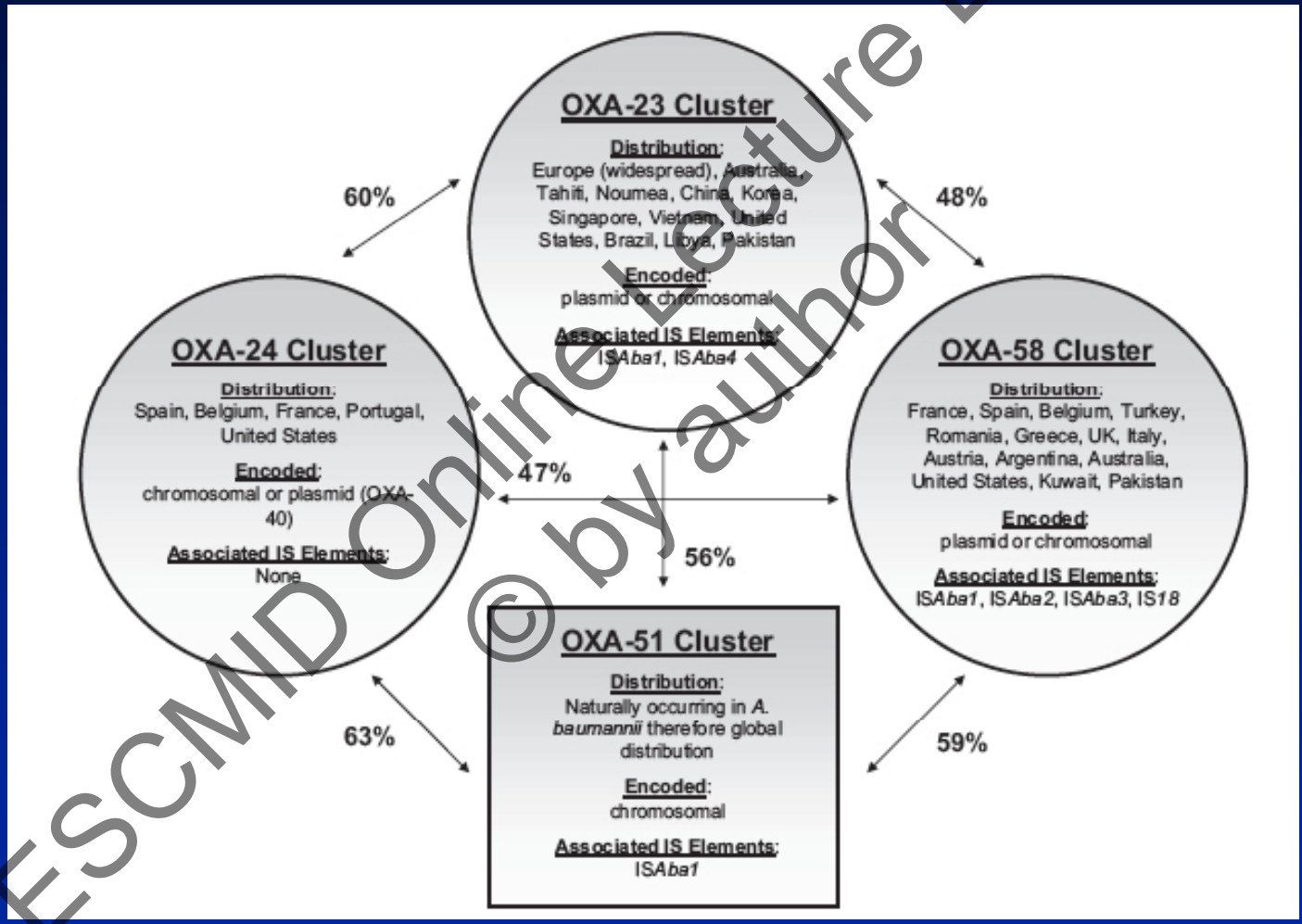
Munoz-Price, L and Weinstein RA. NEJM 2008;358:1271

Mechanisms of Resistance

- Beta-lactam antibiotics
  - Beta-lactamase production
    - » Non-inducible AmpC beta-lactamases
    - » Serin (class D OXA type) & Metallo-beta-lactamases (carbapenemases)
    - » ESBLs (VEB-1, PER-1, PER-2)
  - Overexpression of efflux pomps
  - Reduced expression of porin proteins
- Other antibiotics
  - *gyrA* and *parC* mutations (quinolones)
  - Aminoglycoside-modifying enzymes
  - Efflux pumps

Munoz-Price, L and Weinstein RA. NEJM 2008;358:1271

OXA-type Enzymes in *Acinetobacter baumannni*



Peleg A, et al. Clin Microbiol Rev 2008;21:538

Multidrug Resistance

- Not standardized
- Multidrug resistance
  - Resistance ≥3 drug classes
    - » Antipseudomonal cephalosporins, ampicillin-sulbactam, quinolones, aminoglycosides
- Pandrug resistance
  - Resistance to all antimicrobials except colistin

Paterson DL. Clin Infect Dis 2006;43(Suppl.2):S43
Peleg A, et al. Clin Microbiol Rev 2008;21:538

Countries Reporting Carbapenem-R Outbreaks of *A. baumannii*

Peleg A, et al. Clin Microbiol Rev 2008;21:538

Why is Acinetobacter is a Persistent Hospital Pathogen?

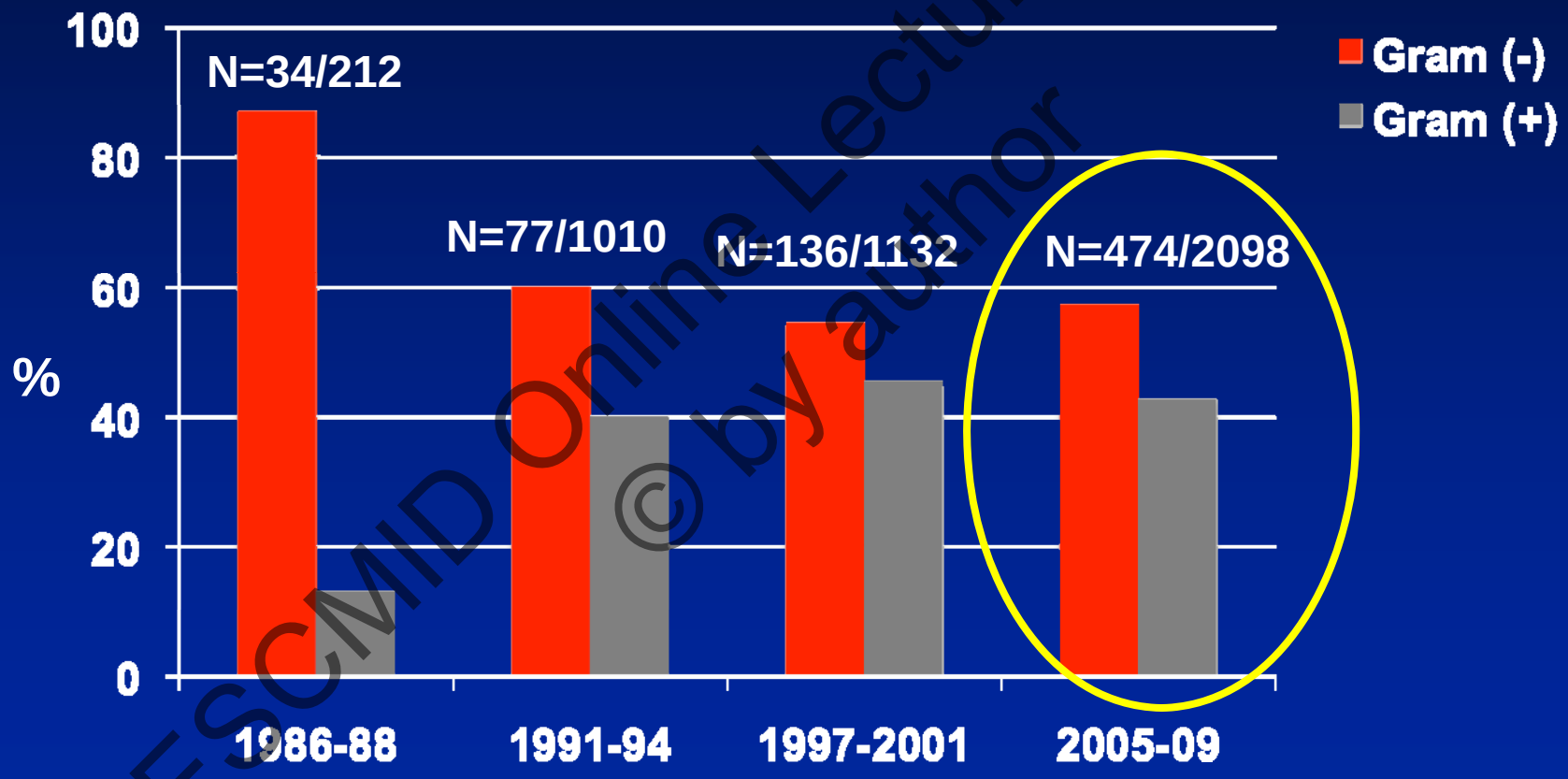
- Resistance to
  - Major antimicrobial classes
  - Desiccation
    - » Long survival time on dry surfaces (up to 33 days)
    - » No difference between outbreak and sporadic strains
    - » Better for *A. baumannii* strains
  - Disinfectants

Peleg A, et al. Clin Microbiol Rev 2008;21:538

Major Infections with *Acinetobacter spp.*

- Ventilator associated pneumonia
- Bacteremia
- Urinary tract infection
- Skin and soft tissue infections
- CNS infections
  - Meningitis, ventriculitis
- Community-acquired infections
  - Reported from Australia and Asia
    - Pharyngeal carriage and aggressive pneumonia
  - War, tsunami, earthquake

Agents of Bacteremia in Cancer Patients



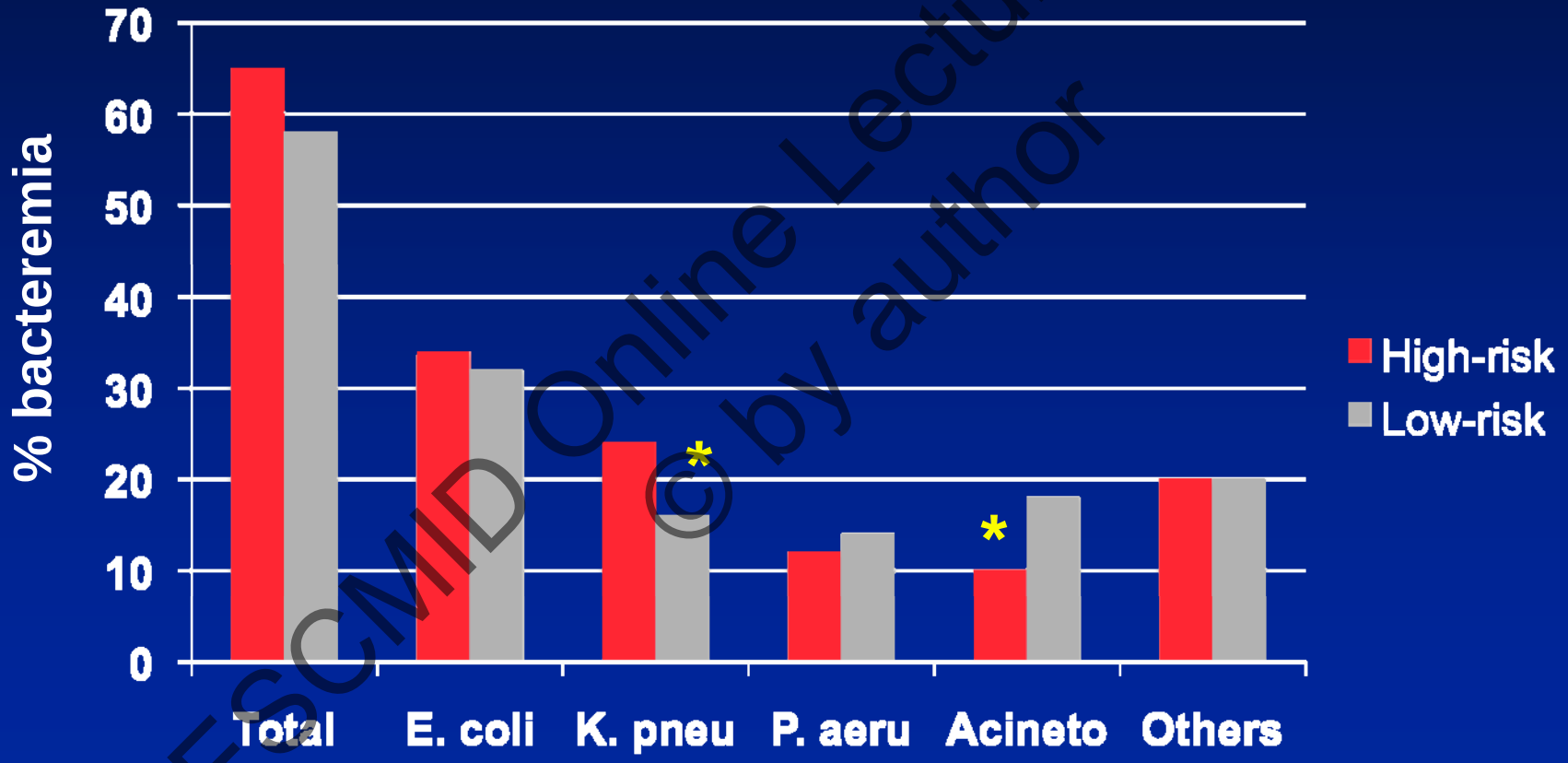
Hacettepe University, unpublished

Bacteremia in Cancer Patients Hacettepe University

- January 2005-October 2009
  - 1000-bed tertiary, cancer center
- 3703 febrile attacks in 2098 neutropenic patients
  - 272 bacteremia in 239 high-risk patients
    - » AML, ALL, MDS, HSCT recipients
  - 202 bacteremia in 189 low-risk patients
    - » Aplastic anemia, lymphoma, CML, CLL, MM

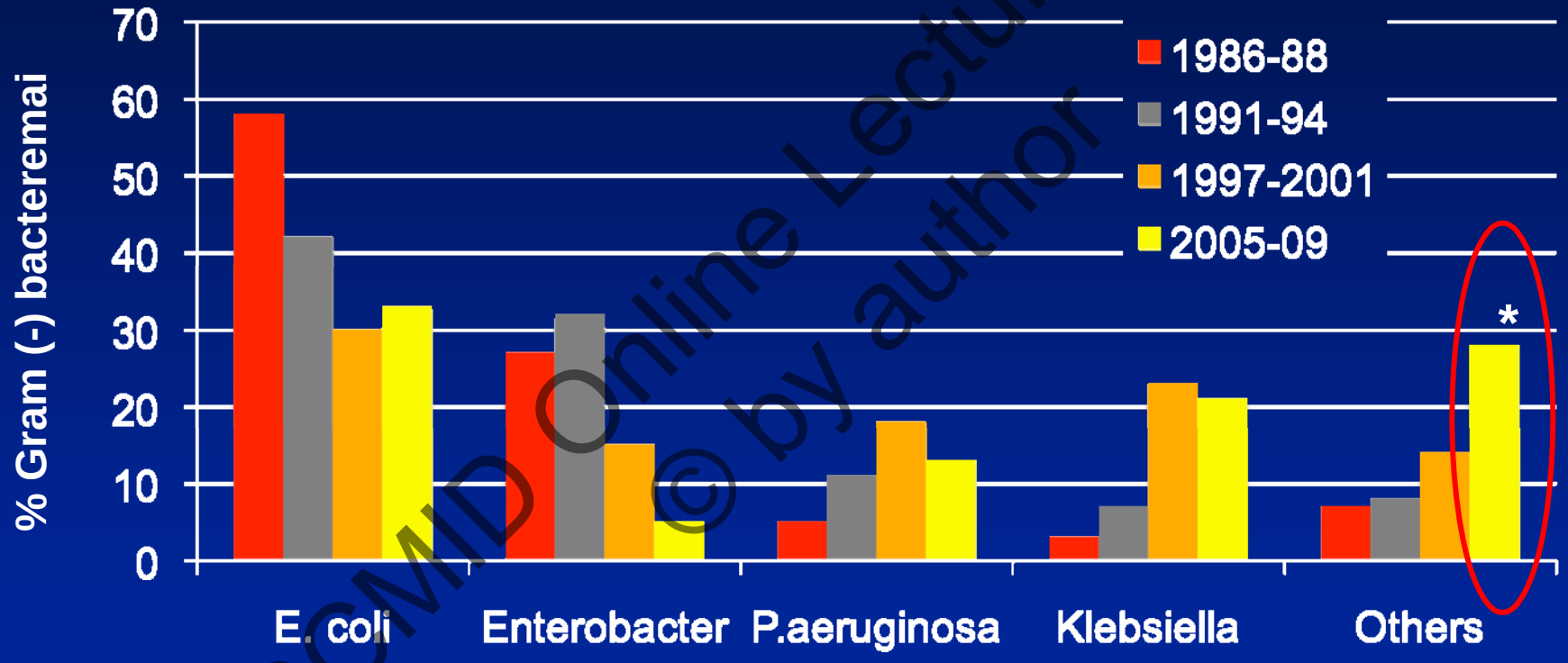
Kara, Ö, et al. Hacettepe University, unpublished

Gram-negative Bacteremia in High-risk vs Low-risk Patients



Kara, Ö, et al. Hacettepe University, unpublished

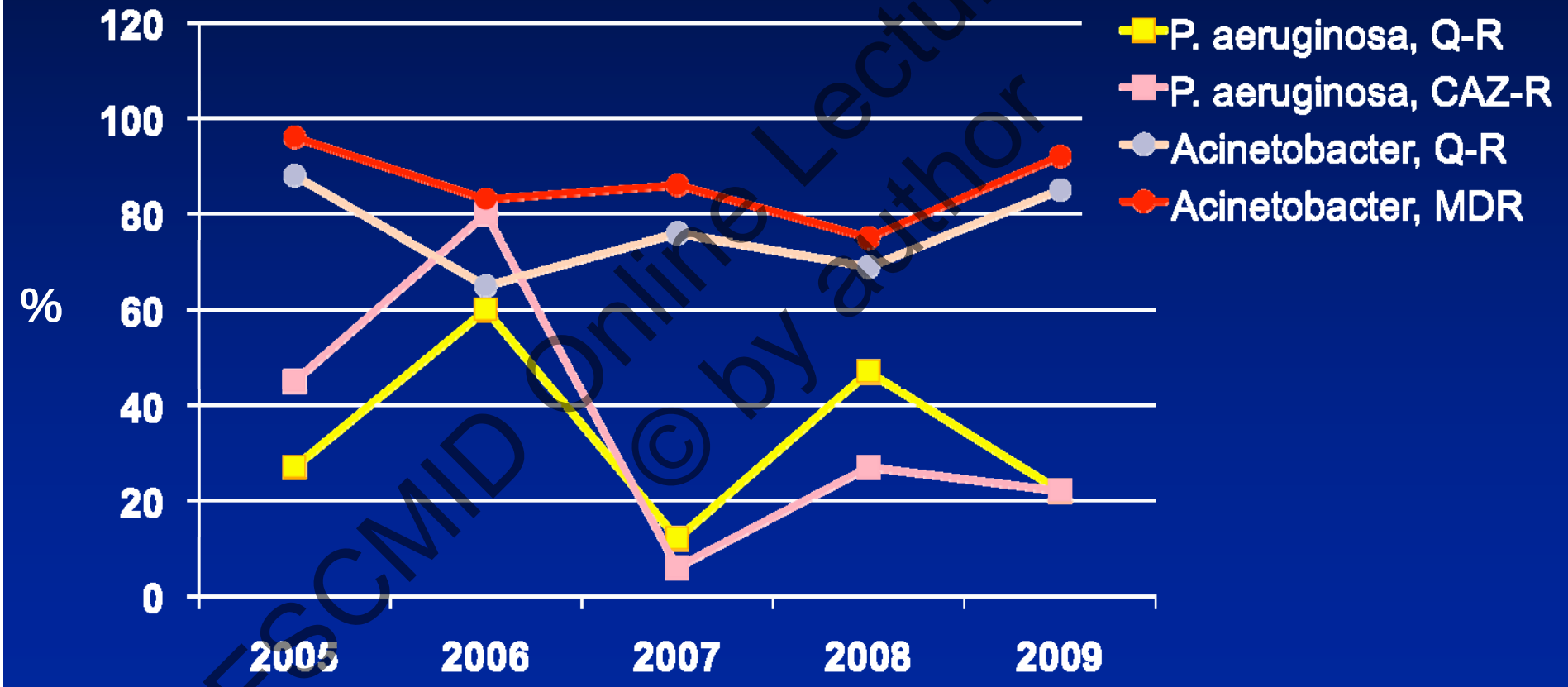
Distribution of Agents of Gram (-) Bacteremia



* 47,5 % were Acinetobacter spp.

Hacettepe University, unpublished

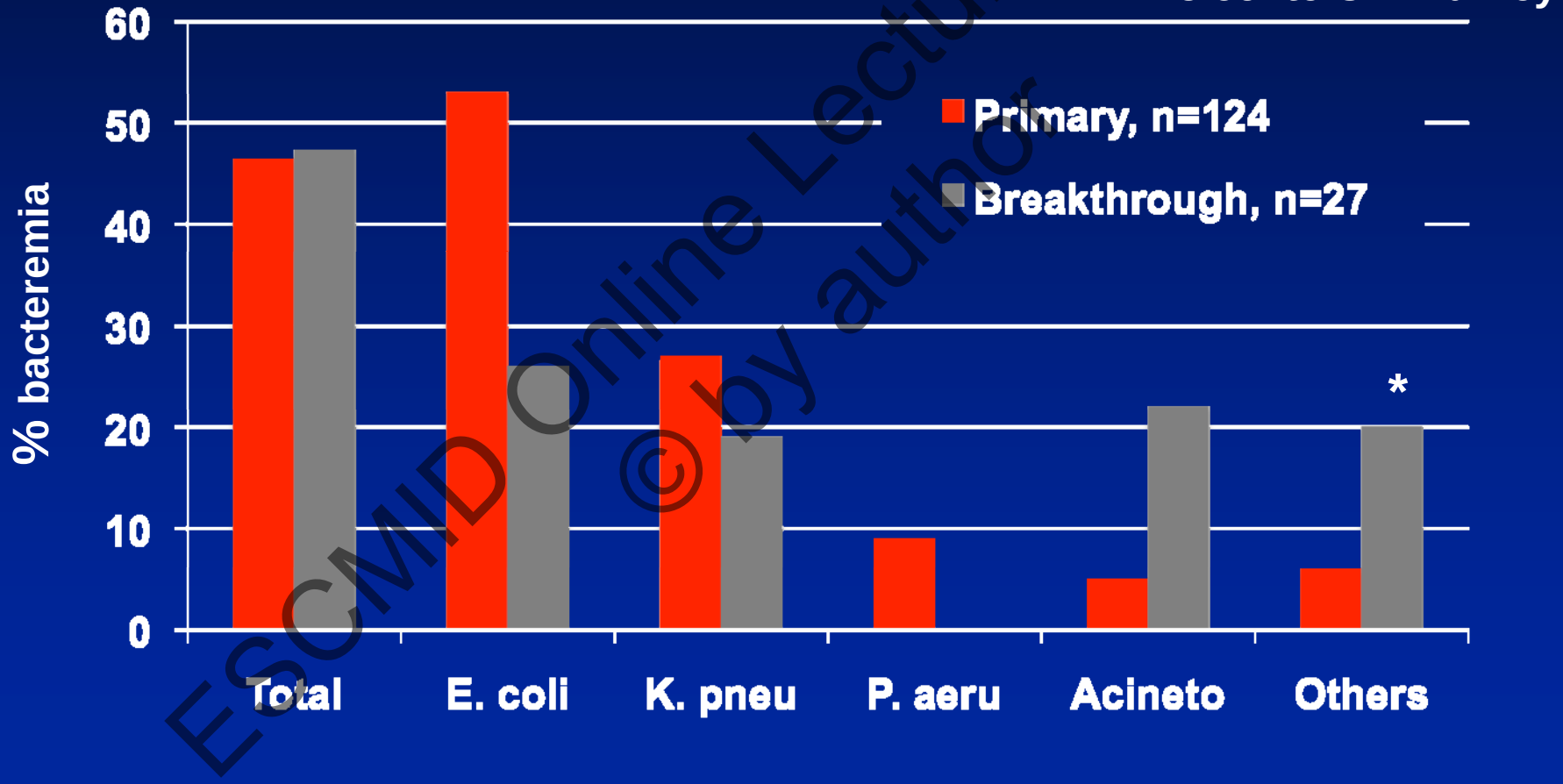
Resistance Patterns in *P. aeruginosa and Acinetobacter spp.* in Cancer Patients



Kara Ö, et al. Hacettepe University, unpublished

Gram-negative Agents in Primary vs Breakthrough Bacteremia in Cancer Patients

2005-2008
5 centers in Turkey



*67% were Enterobacter spp.

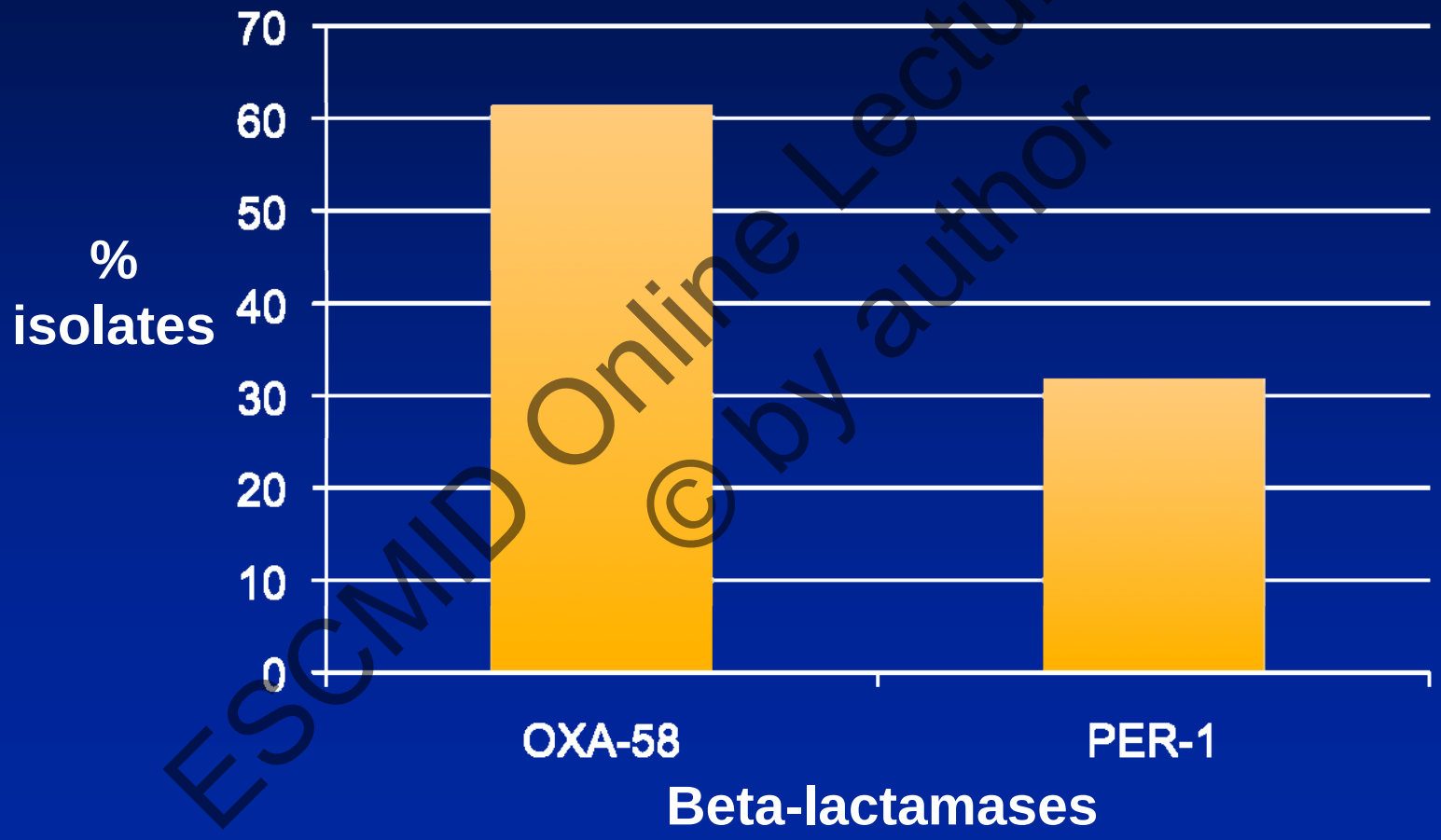
Korten V, et al., unpublished

Risk Factors for Acinetobacter Bacteremia and Mortality

- Retrospective case-control study
- Between 1997-2008, 88 cases w Acinetobacter bacteremia
  - 180 cases w/o bactermia as controls
- 68.4% *A. baumannii*, 18.2% *A. lwoffi*
  - 91% of *A. baumannii* had MDR pattern
    - » 67% R to carbapenems
    - » No R to colistin

Bitik B, et al. Hacettepe University, unpublished

Type of Beta-lactamases in Acinetobacter Isolates



Bitik B, et al. Hacettepe University, unpublished

Multivariate Analysis of Risk Factors for Acinetobacter Bacteremia

Risk factors	Odds ratio	p	95% CI
Intubation	13,64	<.001	5,52-33,69
Accompanying culture positivity	5,46	<.001	2,07-14,36
Previous antibiotic use	17,09	<.001	6,49-45,00

Bitik B, et al. Hacettepe University, unpublished

Multivariate Analysis of Risk Factors for Mortality

Risk factors	Odds ratio	p	95% CI
Intubation	7,34	0.0001	2,06-26,14
Staying in ICU	3,92	0.03	1,13-13,60

Bitik B, et al. Hacettepe University, unpublished

Available Antibiotics for the Treatment of *Acinetobacter* Infections

- Beta-lactams
  - Sulbactam and its combinations
  - Antipseudomonal
    - » Penicillins
    - » Cephalosporins
    - » Carbapenems
    - » Monobactams
- Aminoglycosides
- Fluoroquinolones
- Tetracyclines
- Glycylcylines
- Polymyxins

Lancet Infect Dis 2008;8:751

Data in Literature is a Mixed Bag for Combination Therapy

- Imipenem plus sulbactam
  - Synergistic in vitro
  - Effective in four clinical MDR cases

Pharmacotherapy 2007;27:1506

- Imipenem plus rifampin
  - Synergistic in vitro
  - In a study with 10 patients
    - » 50% mortality
    - » Those survived were required drainage, catheter removal

J Antimicrob Chemother 2006;58:697

Data on Combination of Antimicrobials-cont…

- Imipenem + amikacin
  - In a guinea pig pneumonia model
    - » was inferior to imipenem for imipenem-S strain
    - » was inferior to amikacin for imipenem-R strain

Clin Microbiol Inf 2005;11:315

- Imipenem + tigecycline is not synergistic

Antimicrob Agents Chemother 2007;51:1621

- Meropenem + aztreonam is indifferent against MBL-producing Acinetobacter

J Chemother 2005; 17: 622

Adaptive Resistance to *A. baumannii*

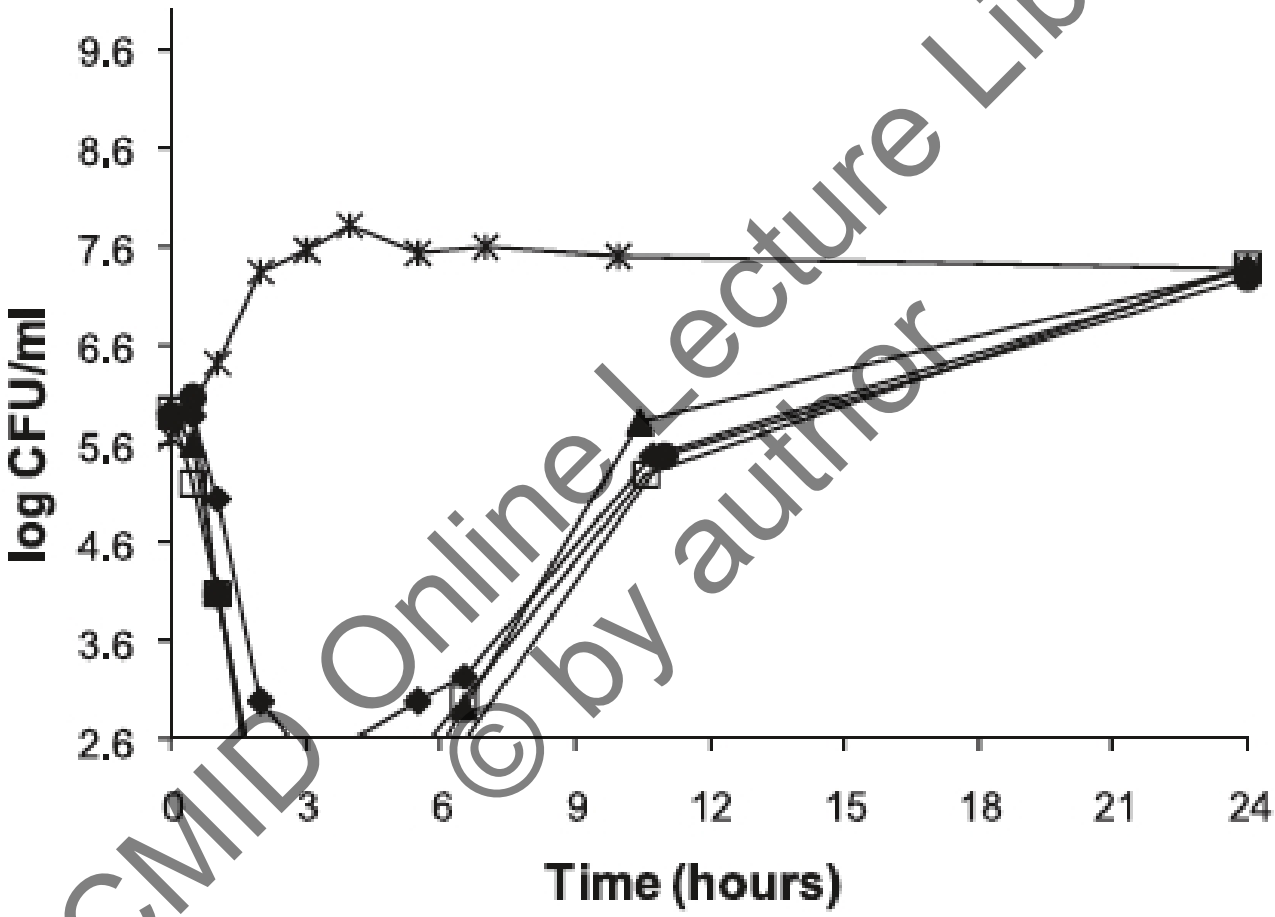


FIG. 1. Time-kill curves of CMS against *A. baumannii* at maximum serum drug concentrations of 3 μg/ml (◆), 6 μg/ml (●), 12 μg/ml (▲), and 24 μg/ml (□). The growth control (×) is also depicted.

Antimicrobial Agents Chemother 2007;51:3431

Colistin and Ceftazidime MICs

	MIC	mcg/ml
	Colistin	Ceftazidime
A. baumanni preexposure	0.5	≥64
A. baumannii postexposure		
3 mcg/ml CMS	64-128	
6 mcg/ml	64->128	
12 mcg/ml	128	
24 mcg/ml	32->128	
24 mcg/ml (bolus dose at 0 and 12 h)	≥128	
24 mcg/ml CMS and 50 mcg/ml ceftazidime	0.5	32-64
50 mcg/ml ceftazidime and 24 mcg/ml CMS	0.06	32-64

Antimicrobial Agents Chemother 2007;51:3431

Ceftazidime Prevents Adaptive Resistance to CMS

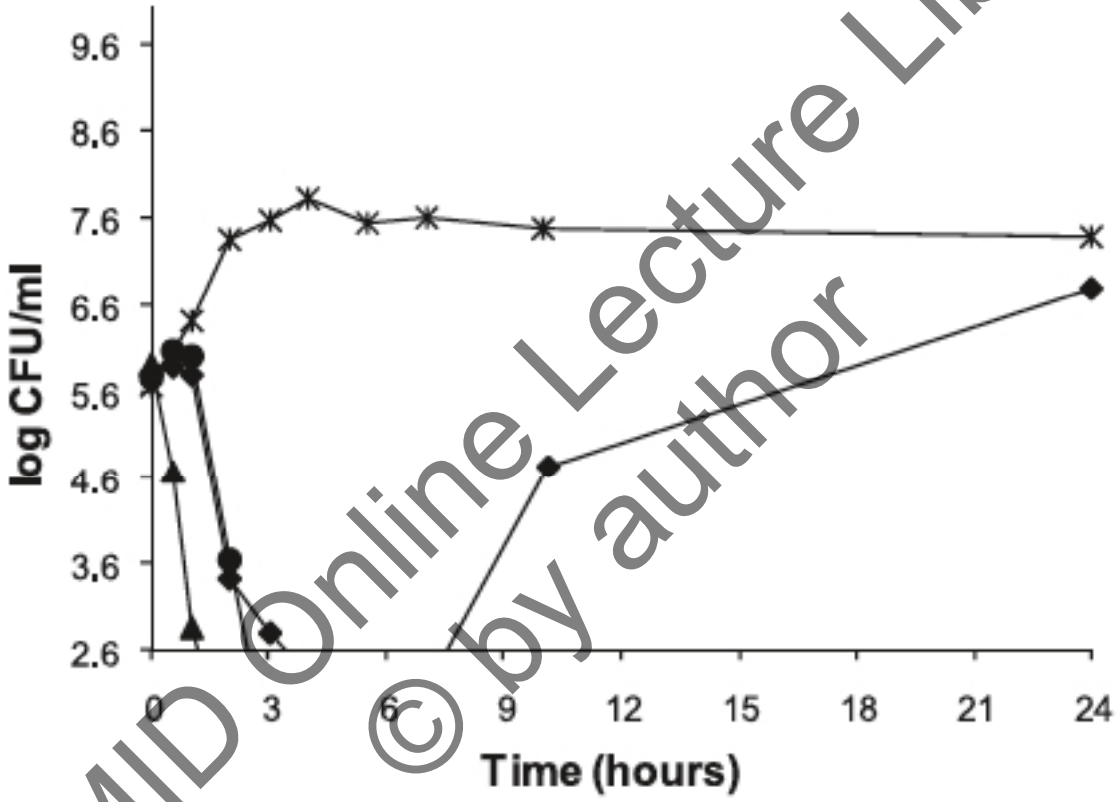


FIG. 2. Time-kill curves of CMS given at time zero plus the addition of continuous-infusion ceftazidime started at 2 h (▲) and continuous-infusion ceftazidime started at time zero plus a CMS bolus given at 2 h (●) against *A. baumannii*. Continuous-infusion ceftazidime given alone (◆) and the growth control (×) are also depicted.

Antimicrobial Agents Chemother 2007;51:3431

Colistin + Rifampin

- Synergistic in vitro in most studies against MDR *Acinetobacter*
- Clinical trials
  - 29 patients (19 pneumonia, 10 bacteremia)
  - 76% success, 21% inf.-related mortality

J Antimicrob Chemother 2008;61:417

  - 26 patients (16 pneumonia, 9 bacteremia, 1 meningitis)
  - Aerosolized and intrathecal use
  - Favorable for all

J Infection 2006;53:274

Colistin Combinations vs Monotherapy in Clinical Trials

- Several prospective and retrospective studies
  - No prospectively controlled trials
  - Colistin monotherapy is less effective in pneumonia
  - IN VAP, similar efficacy with imipenem for imipenem-S *Acinetobacter* vs colistin for MDR *Acinetobacter*
  - One retrospective trial indicates colistin monotherapy had better survival rates than combination with imipenem

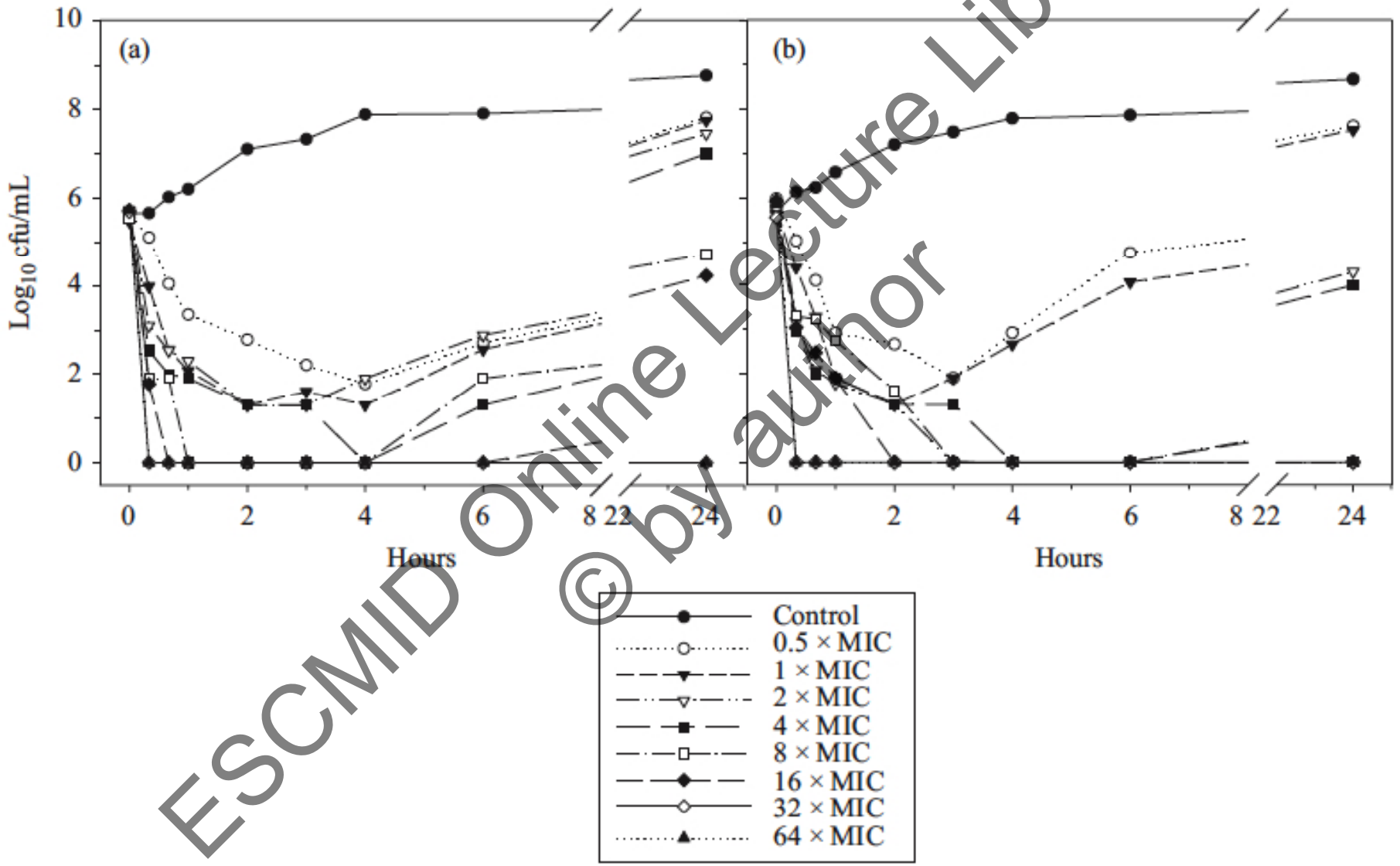
Clin Microbiol Infect 2006;12:1221
Clin Microbiol Infect 2008;14:816
Lancet Infcet Dis 2008;8:751

Colistin + Rifampin, cont…

- 14 patients w VAP caused by IMP-R *Acinetobacter*
- Five patients also received ampicillin-sulbactam
- Seven patients (50%) died
- Three relapsed and received 2nd course tx, 2 died
- Microbiological clearence occurred in 9 patients

Clin Microbiol Inf 2005;11:682

Colistin Heteroresistance



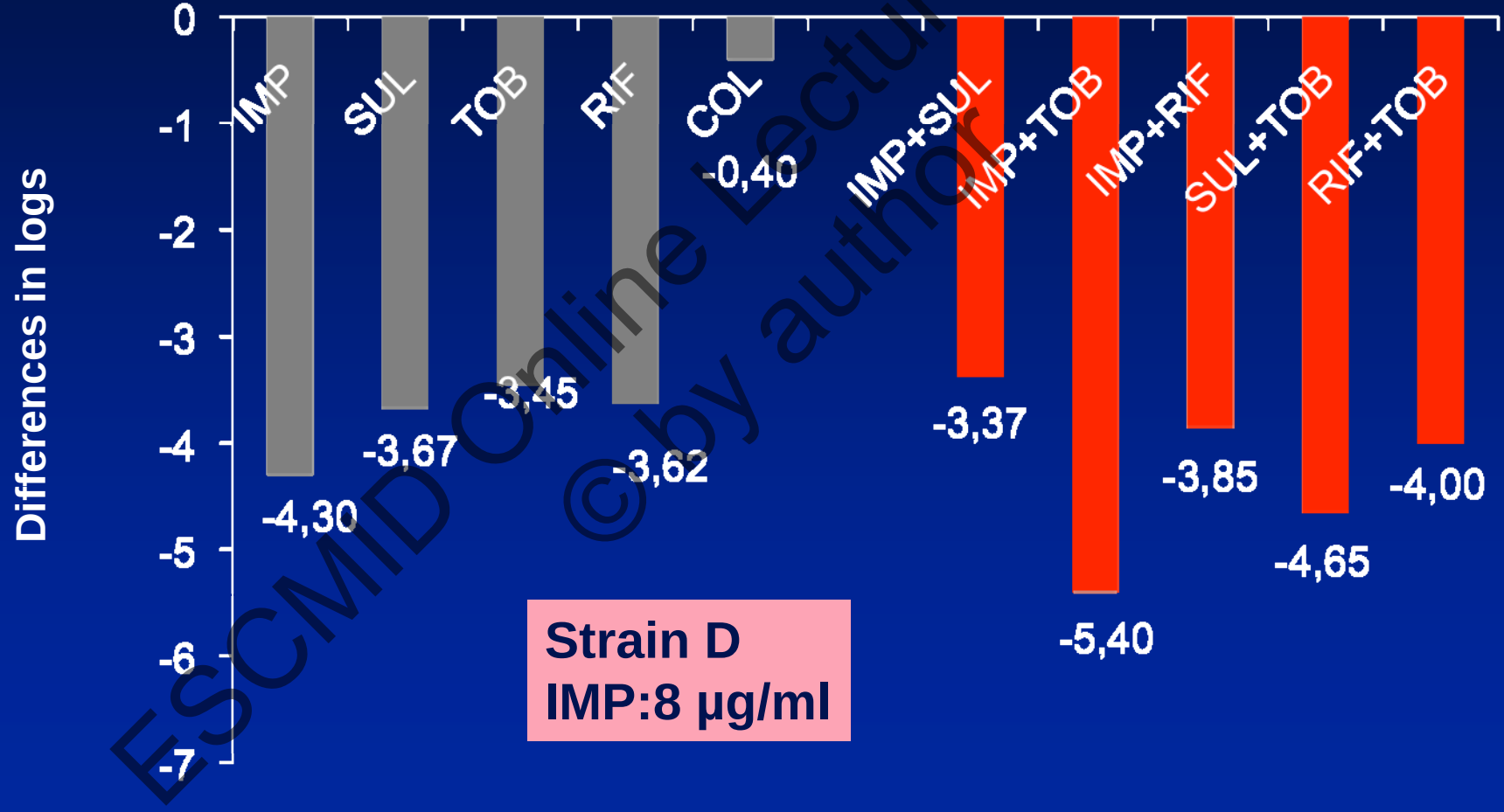
J Antimicrob Chemother 2007;59:473

Colistin Heteroresistance

- A colistin-susceptible isolate with an MIC 2 mg/L, but where subpopulations growing in the presence of >2 mg/L colistin were detected
- Reported 10^{-7} - 10^{-8} frequency in sensitive populations
- 23-100% of the studied strains
  - Cannot be detected by traditional MIC measurment
  - Population analysis profiles (PAPs) are required
- Increased in those previously exposed colistin

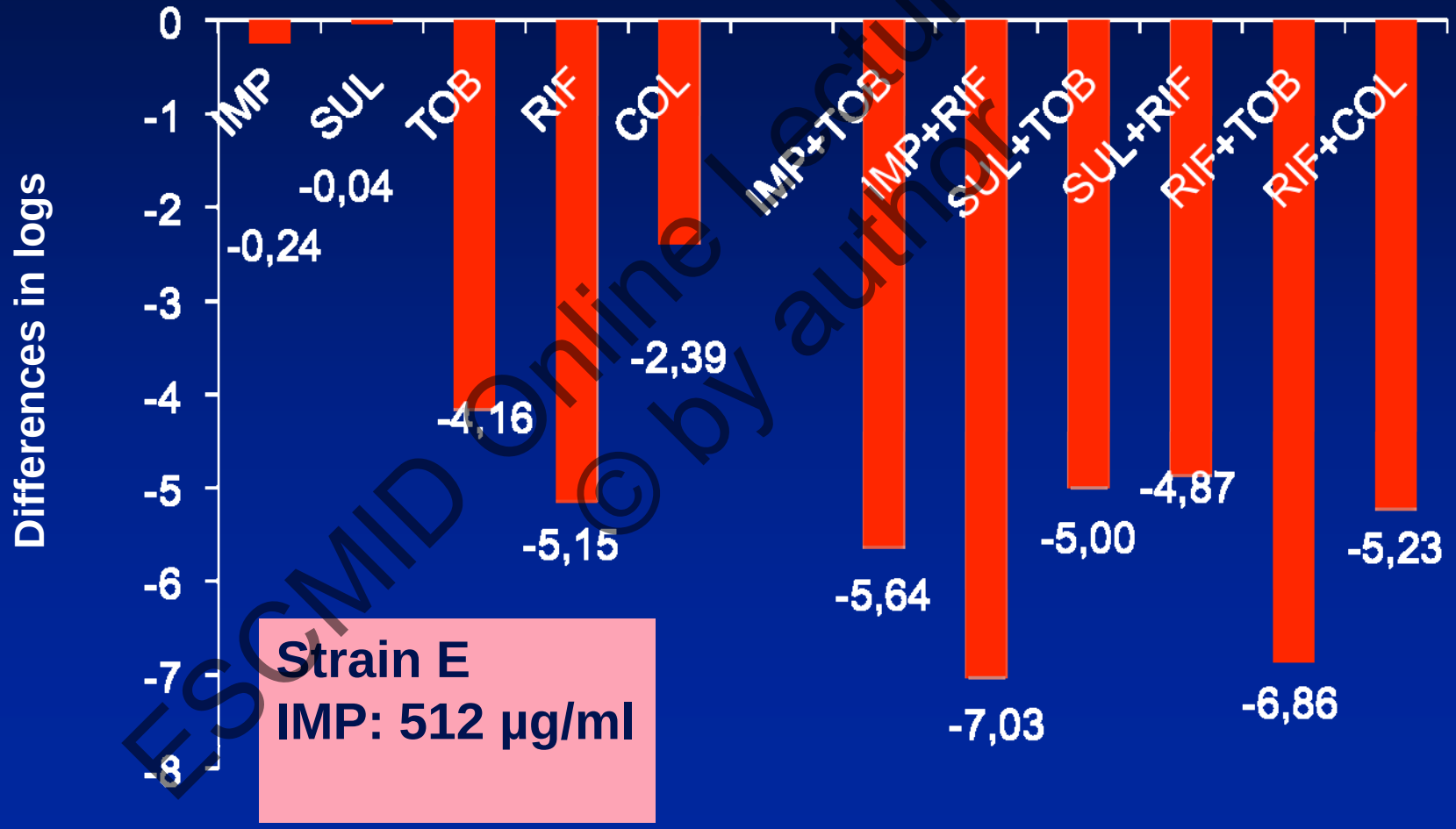
Antimicrob Agents Chemother 2006; 50:2946
Antimicrob Agents Chemother 2008;52:351
J Infection 2009;58:138

Efficacy of Antibiotic Combinations in Carbapenem-R *A. baumannii* Mouse Pneumonia



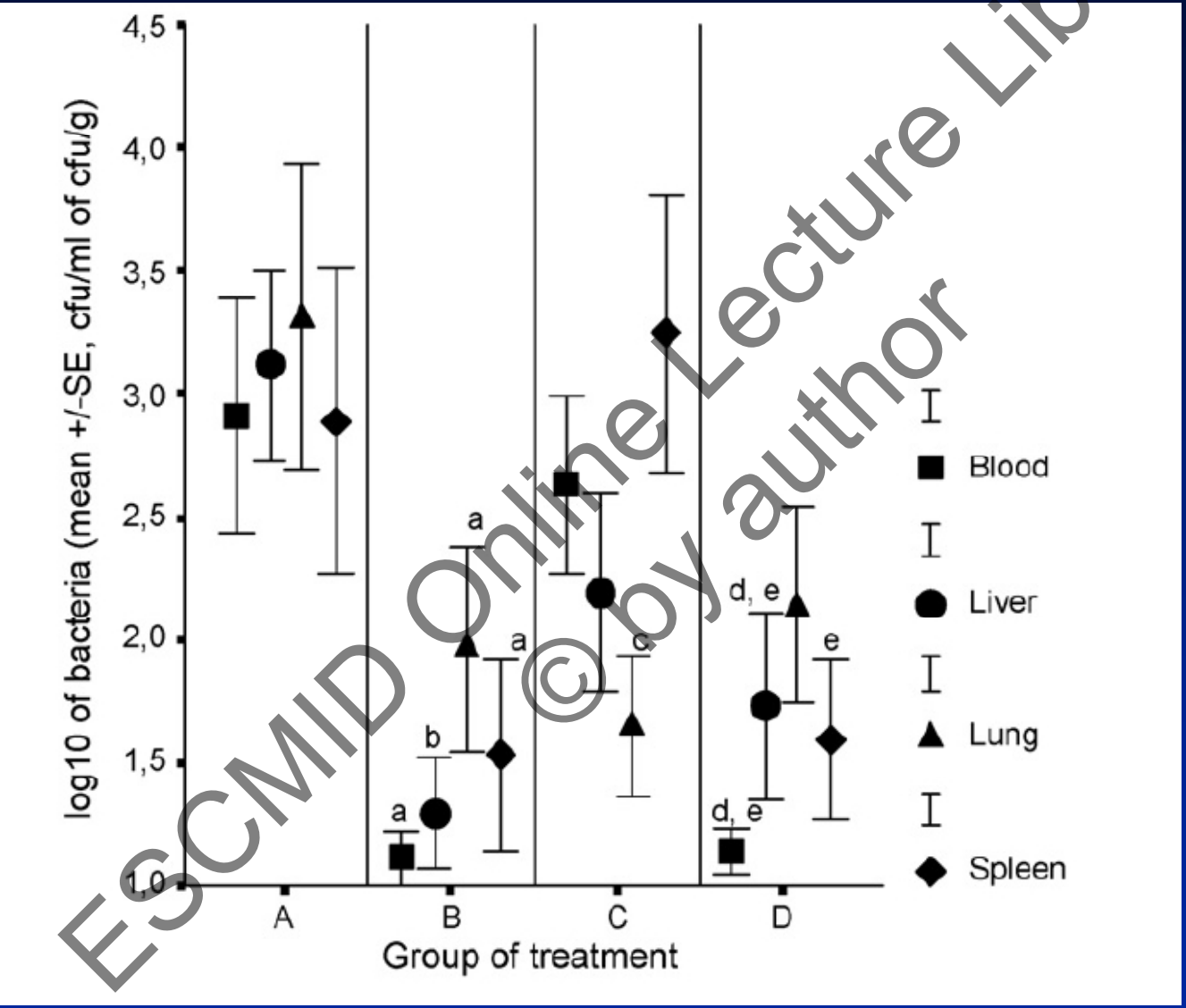
J Antimicrob Chemother 2002;54:1085

Efficacy of Antibiotic Combinations in Carbapenem-R *A. baumannii* Mouse Pneumonia



J Antimicrob Chemother 2002;54:1085

Colistin plus Rifampin for MDR *A. baumannii* in a Mouse Thigh Model

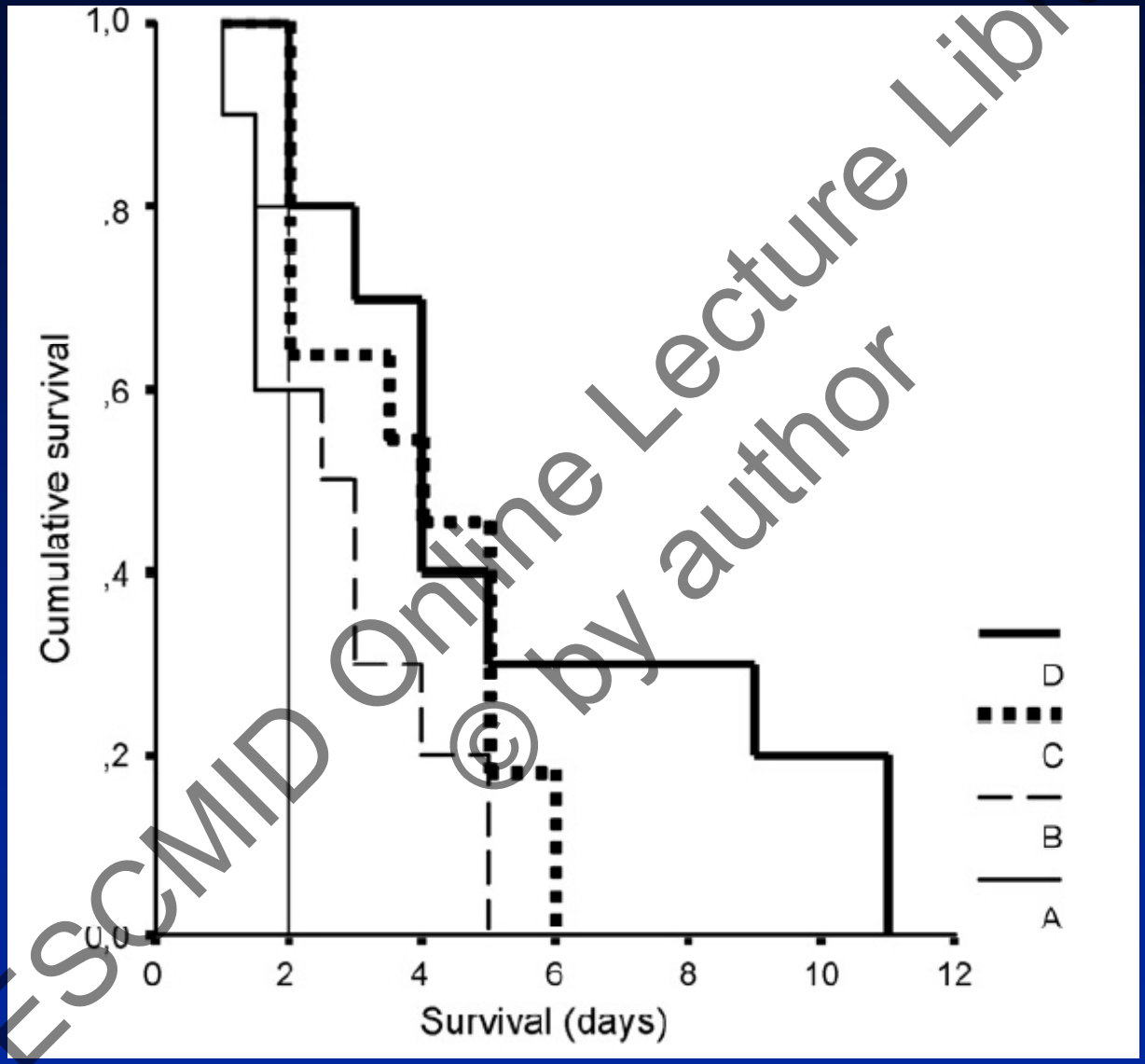


A : Control
B: Rifampin
C: Colistin
D: Rif + Col

Statistical significance
B vs A
B vs C
C vs A
D vs A
D vs C

Int J Antimicrob Agents 2007;29:51

Survival



A : Control
B: Rifampin
C: Colistin
D: Rif + Col

Statistical significance
A vs C
A vs D

Int J Antimicrob Agents 2007;29:51

Conclusions

- MDR *Acinetobacter* infections have become a global challenge
- Patients in ICU are at significant risk developing infections caused by *A. baumannii*
  - Intubation and previous antimicrobial use are independent risk factors
- Therapeutic choices are limited and usually require polymyxins, sometimes in combination with other antimicrobials
  - Controlled trails are urgently needed

THANK YOU...