Managements of Infections Caused by MDR Gram-negatives

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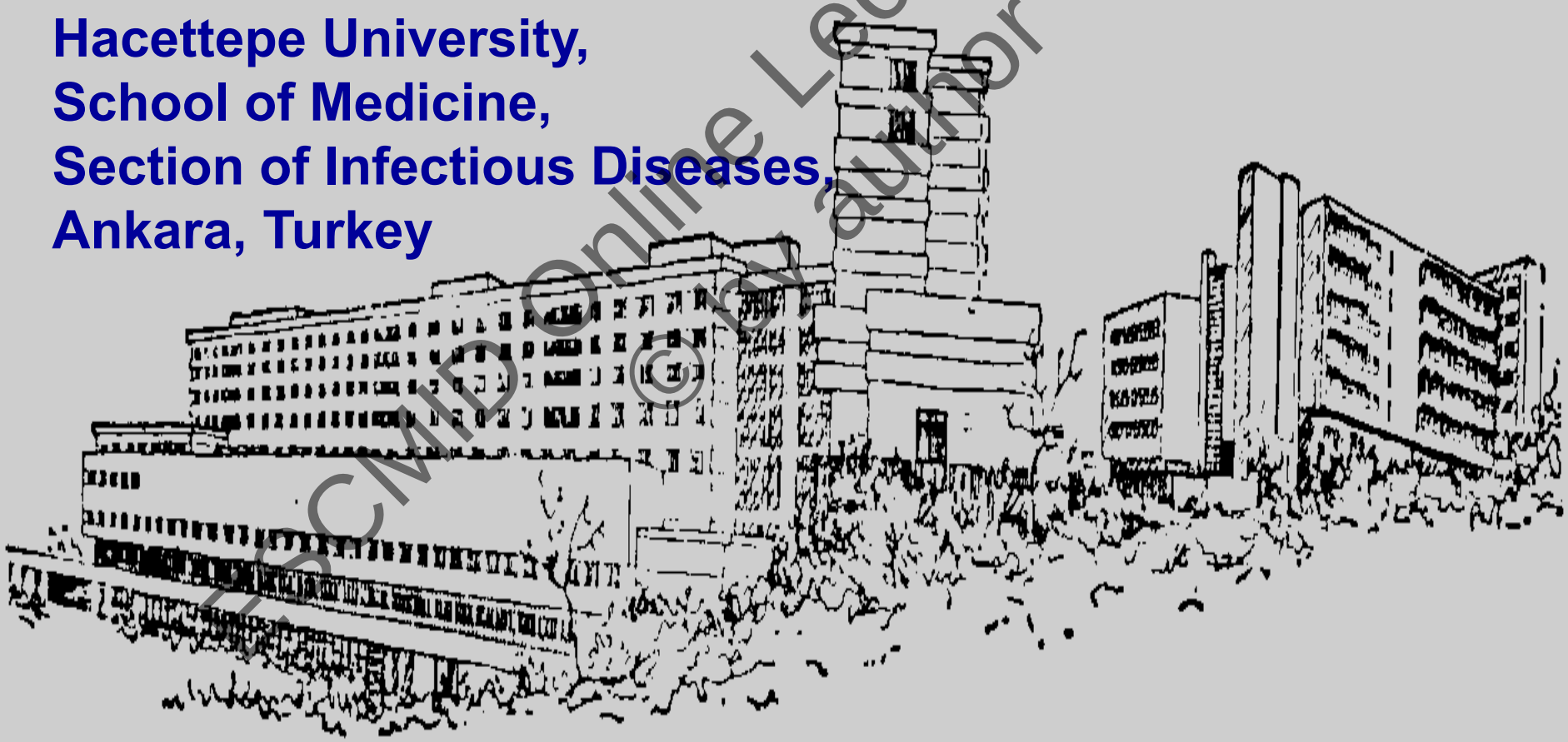


Definitions

- **Multidrug resistance (MDR)**
  - R to 5 out of the following 7 classes of antibiotics
    - Penicillins
    - Cephalosporins
    - Carbapenems
    - Monobactams
    - Quinolones
    - Aminoglycosides
    - Colistin
- **Colistin only sensitive**
  - Resistant to all except colistin
- **Pandrug resistant (PDR)**
  - Resistant to all including colistin

Falagas M, et al. BMC Infect Dis 2005;5:24

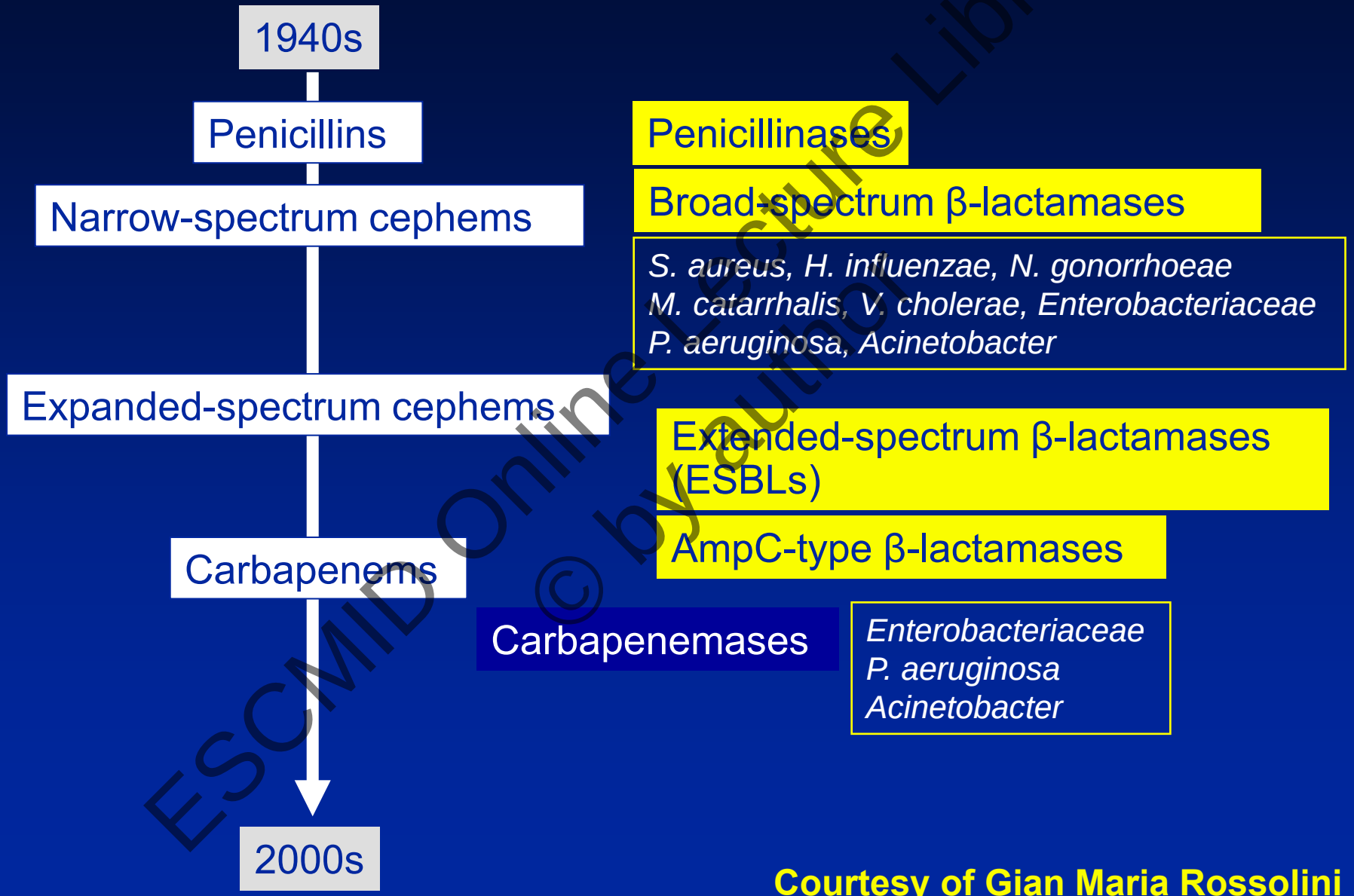
ESKAPE Pathogens

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

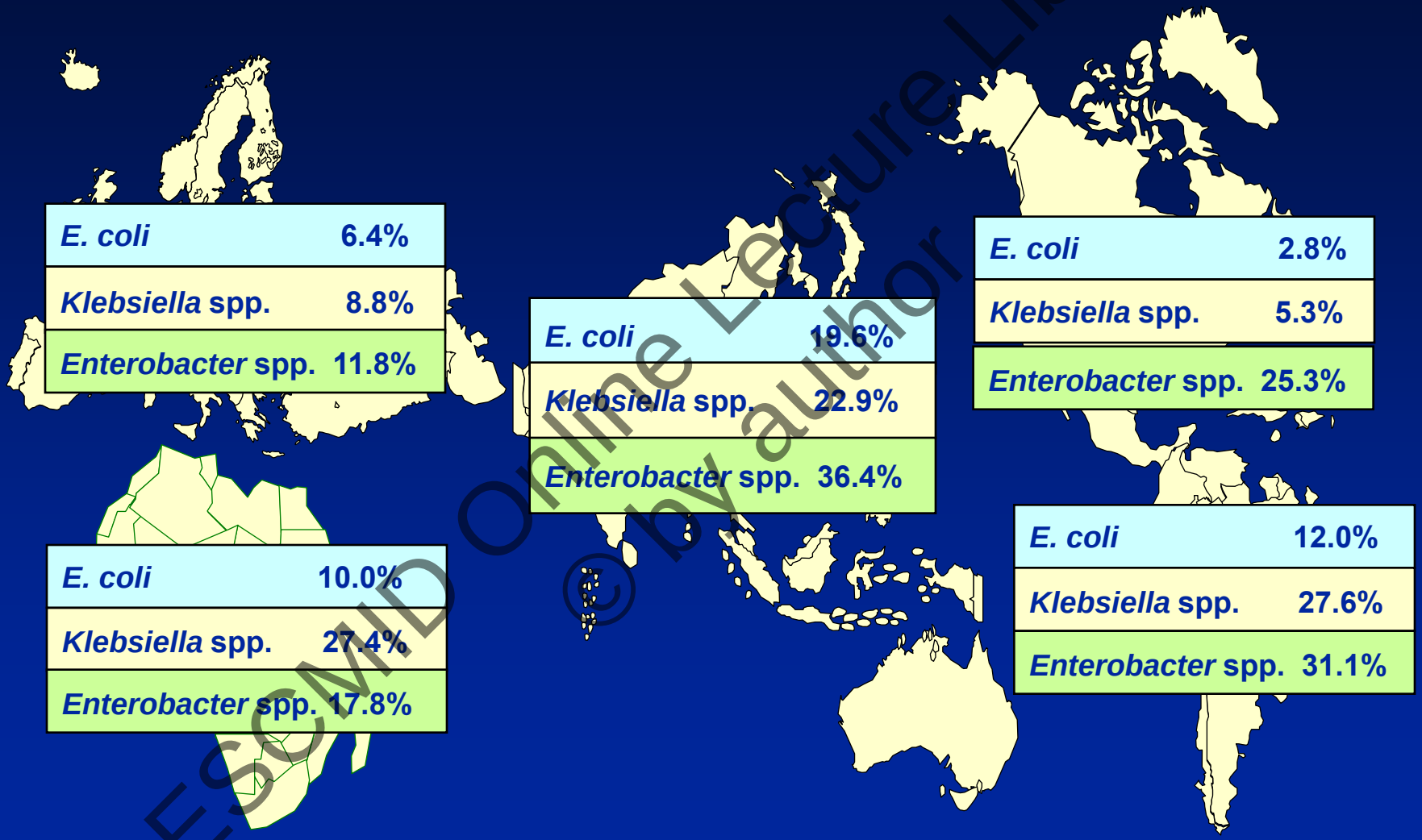
Rice LB. *Infect Control Hosp Epidemiol.* 2010;31(Suppl 1):S7

β-lactamase-mediated Resistance: Evolution in the Clinical Setting



Courtesy of Gian Maria Rossolini

ESBL-Producing Gram-Negative Bacilli: A Global Problem*



* Data from SMART (Study for Monitoring Antimicrobial Resistance Trends) 2004

Rossi F, et al. *J Antimicrob Chemother*. 2006;58:205

Emerging ESBL Producers in the Community

Journal of Antimicrobial Chemotherapy (2005) 56, 52–59
doi:10.1093/jac/dki166
Advance Access publication 25 May 2005

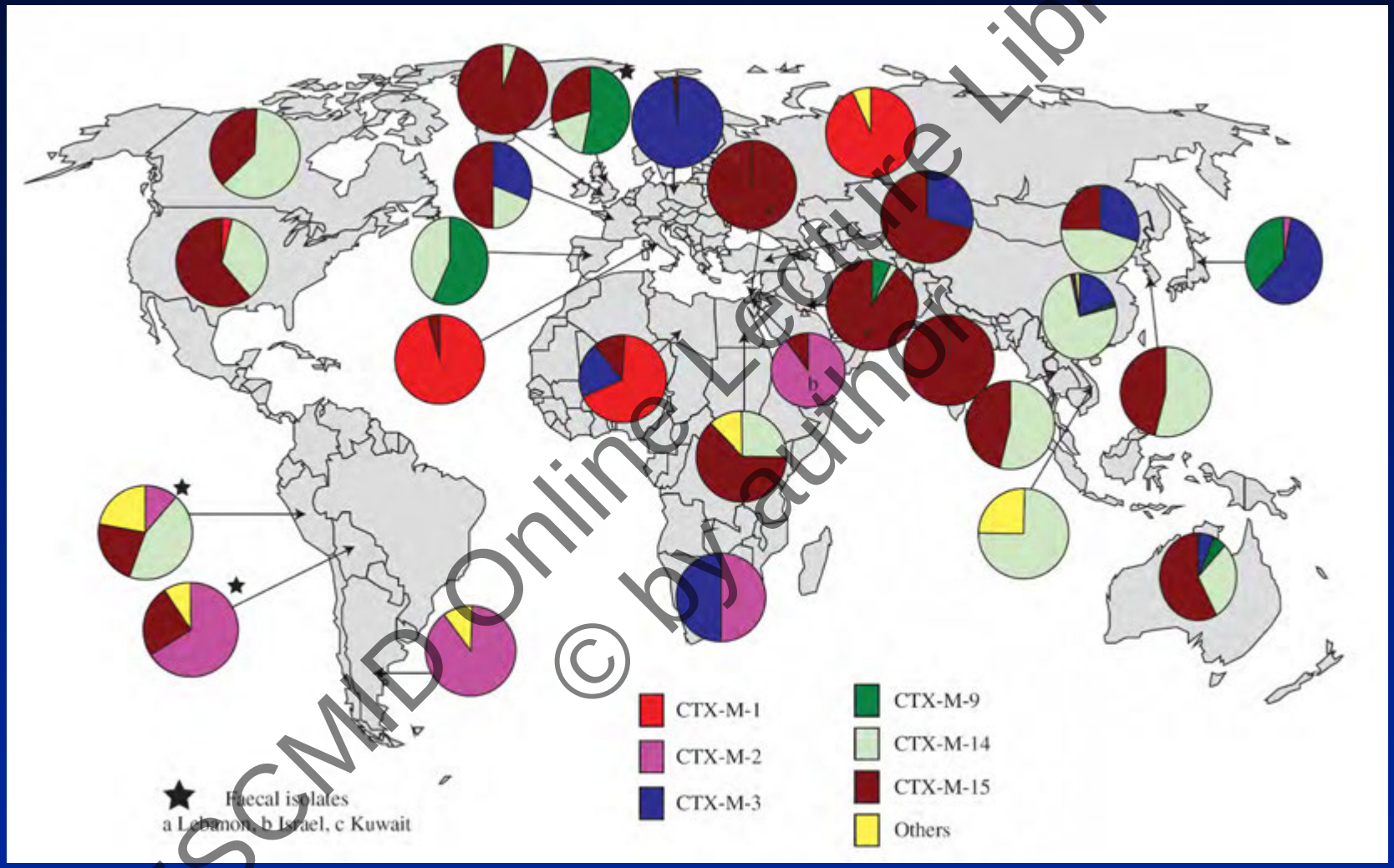
JAC

Emergence of Enterobacteriaceae producing extended-spectrum β-lactamases (ESBLs) in the community

Johann D. D. Pitout[1–3]*, Patrice Nordmann[4], Kevin B. Laupland[2,5,6] and Laurent Poirel[4]

- 0.2 – 1.2% rates in infections
- Up to 5.5% carriage rates
- Mostly *E. coli* producing CTX-M-type ESBLs

Global Distribution of CTX-M Enzymes



Reproduced from Hawkey PM, Jones AM. *J Antimicrob Chemother*. 2009;64(suppl 1):i3

ESBLs: Variable Resistance Phenotypes

	AMP	CTX	CAZ	FEP
E. coli WT	2	≤0.06	0.25	≤0.06
E. coli (TEM-1)	>128	≤0.06	0.25	≤0.06
E. coli (TEM-72)	>64	16	>64	2
E. coli (TEM-87)	>64	1	>64	4
E. coli (SHV-12)	>128	32	32	1
E. coli (CTX-M-1)	>256	>64	6	48
E. coli (CTX-M-15)	>256	>256	256	64

Perilli *et al*. AAC 2000; 44:2537
Perilli *et al*. AAC 2002; 46:925
Nuesch *et al*. AAC 1997; 41:943
Bonnet R. AAC 2004; 48:1
Cartelle *et al*. AAC 2004; 48:2308

Results of Emergence of CTX-M Enzymes

- Considerable morbidity, mortality, and increased cost
- Difficult to manage infections due to resistance
  - Quinolone and TMP-SMX resistance limit outpatient options
  - Extended-spectrum cephalosporin resistance limits options in the hospital
- Delay in appropriate therapy and higher costs
- Increased use of "last resort" antimicrobials (e.g. carbapenems)

Johnson JR, et al. *Clin Infect Dis*. 2010;51:286-294.

Escherichia coli and *Staphylococcus aureus*: bad news and good news from the European Antimicrobial Resistance Surveillance Network (EARS-Net, formerly EARSS), 2002 to 2009

C Gagliotti[1], A Balode[2], F Baquero[3], J Degener[4], H Grundmann[5], D Gür[6], V Jarlier[7], G Kahlmeter[8], J Monen[5], D L Monnet[1], G M Rossolini[9], C Suetens[1], K Weist[1], O Heuer (ole.heuer@ecdc.europa.eu)[1], the EARS-Net Participants (Disease Specific Contact Points for AMR)[10]

- **Trends described in susceptibility during 2002-09**
  - **198 labs from 22 European countries**
- **During study period BSI increased by**
  - **74% for *E. coli***
    - **Antibiotic R increased**
  - **34% for *S. aureus***
    - **MRSA rates decreased**

Gagliotti C, et al. Euro Surveill 2011;16)11:pII=19819

FIGURE 1

Annual number of bloodstream infections caused by *Escherichia coli* and *Staphylococcus aureus*, EARSS/EARS-Net, 2002-09 (22 countries/198 laboratories)

Gagliotti C, et al. Euro Surveill 2011;16)11:pII=19819

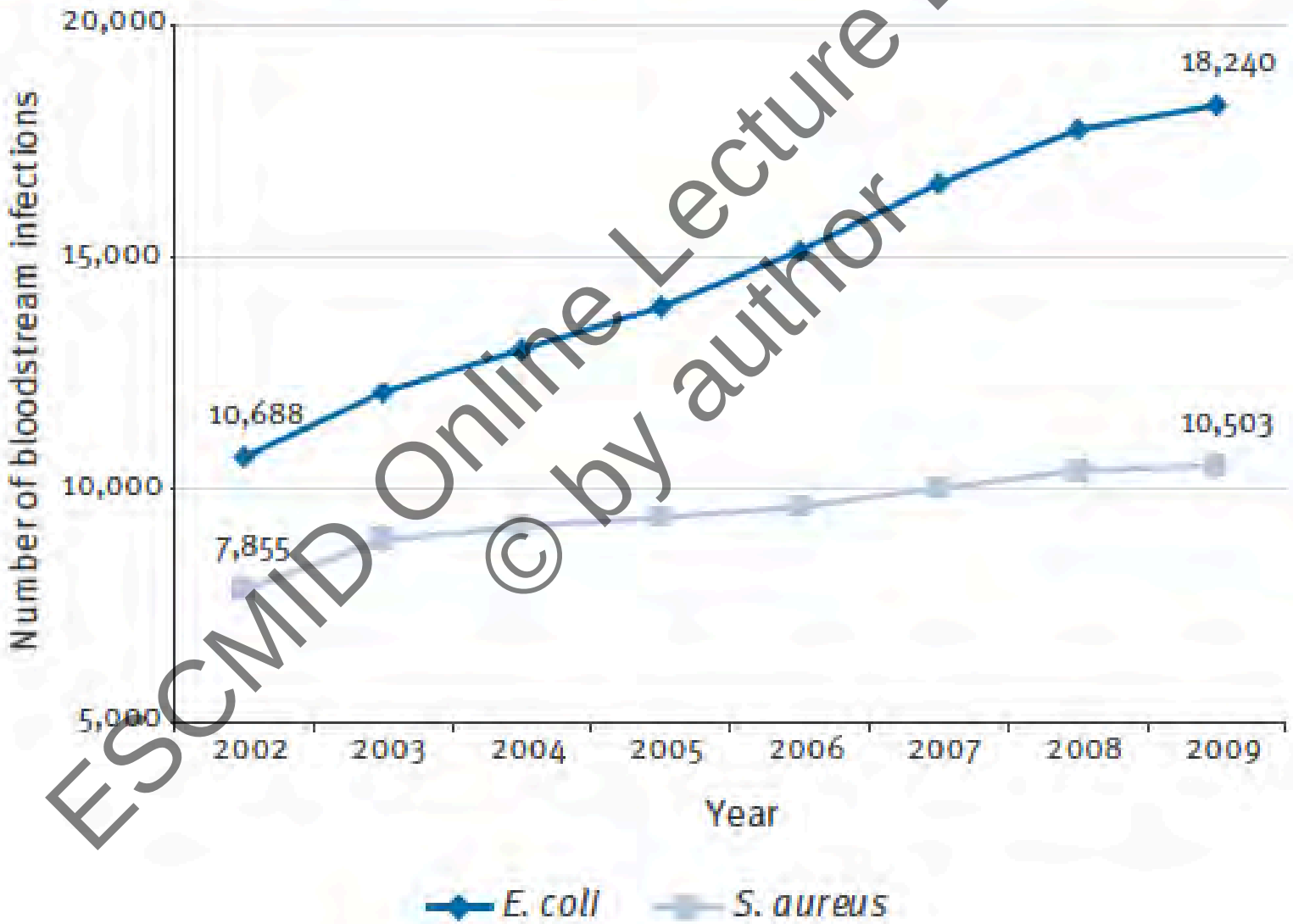
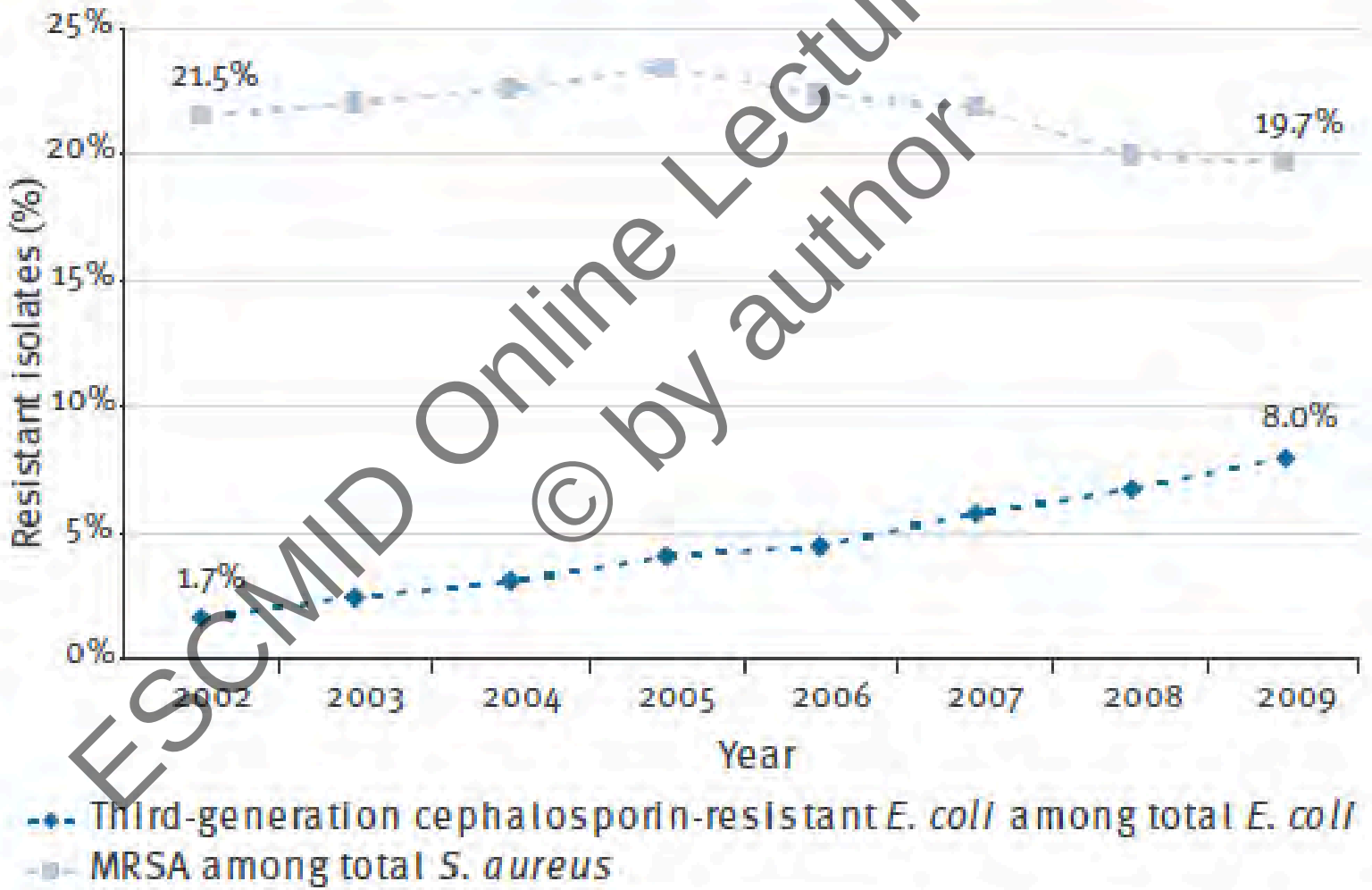


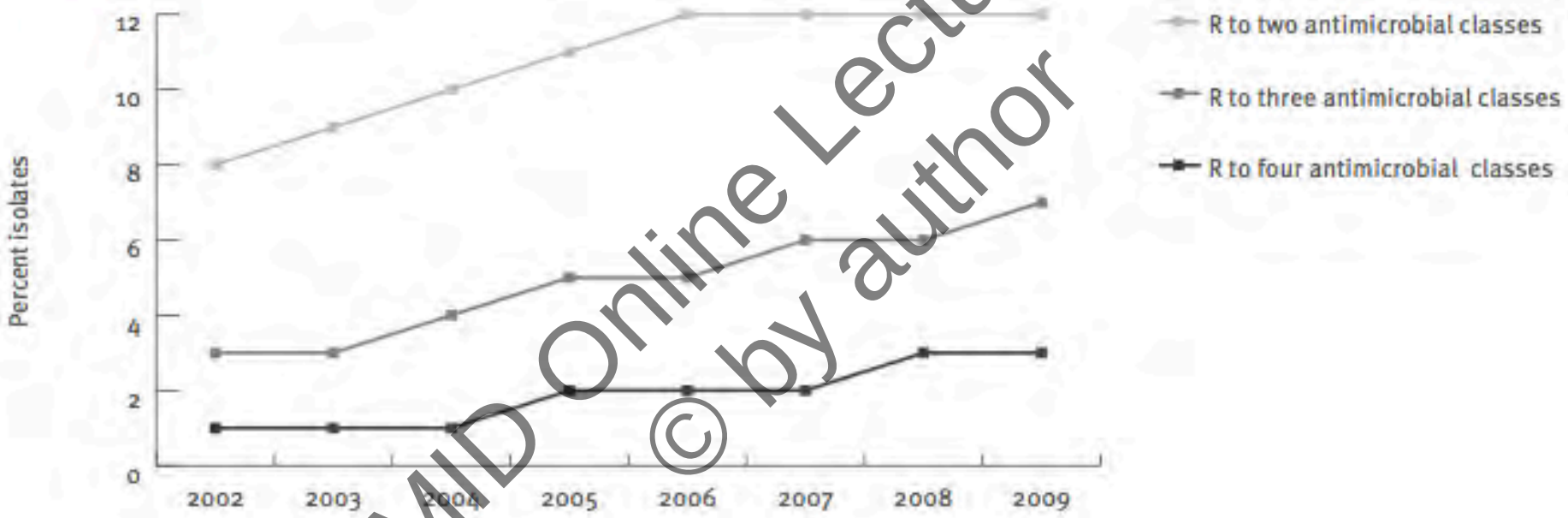
FIGURE 2

Proportion of third-generation cephalosporin-resistant *Escherichia coli* and of meticillin-resistant *Staphylococcus aureus*, EARSS/EARS-Net, 2002-09 (22 countries/198 laboratories)

Gagliotti C, et al. Euro Surveill 2011;16)11:pII=19819



Combined Resistance of *E.coli**



*Resistance to aminopenicillins, 3rd gen. Cephalosporins, quinolones and aminoglycosides

ECDC, EARS-Net 2010

Treatment of ESBL-Producing Pathogens

- No longer nosocomial infections only
  - Presentation from community of MDR urinary or abdominal infection
  - Development of bacteremia or hospital cross-infection
- Antimicrobial stewardship, infection control, and surveillance are crucial

Hunter PA, et al. *J Antimicrob Chemother*. 2010;65(suppl 1):i3

Pitout JDD. *Drugs*. 2010;70:313

Treatment of ESBL-Producing Pathogens

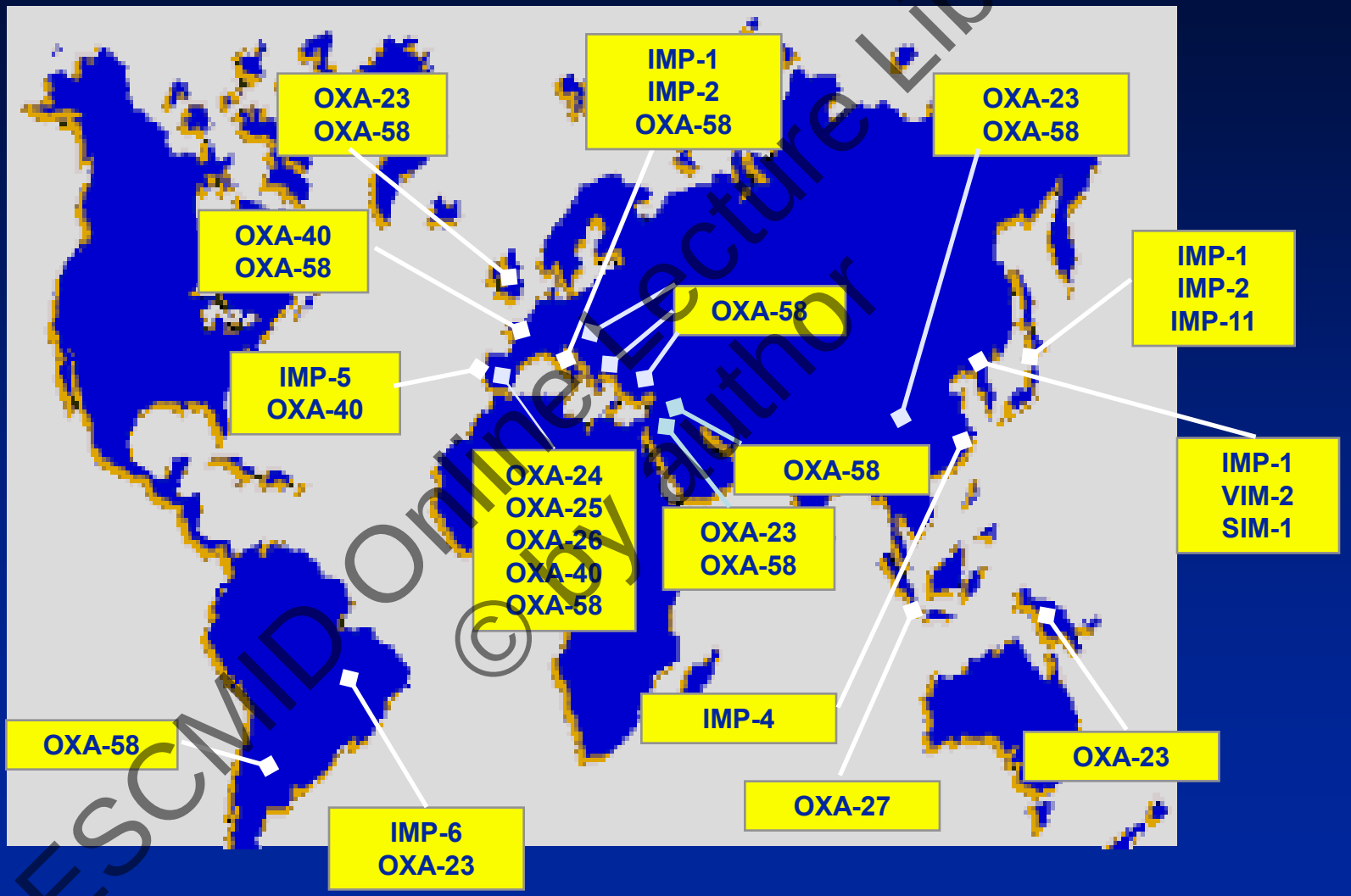
- Reduce use of cephalosporins and fluoroquinolones
- Carbapenems have been the treatment of choice for serious infections
  - Resistance to other antimicrobials, such as aminoglycosides, fluoroquinolones, trimethoprim, sulfonamides, tetracyclines, and chloramphenicol often present in ESBL producers
- Potential for selection of carbapenem-resistant variants

Acquired Carbapenemases: Species Distribution

Organism	MBLs (class B)	Class A KPC (GES)	OXA (class D)
Pseudomonas aeruginosa	++	+	+
Acinetobacter baumannii	+		++
Acinetobacter spp.	+		+
Enterobacteriaceae			
Klebsiella pneumoniae	+	++	+
Escherichia coli	+	+	+
Proteus mirabilis	+		+
Klebsiella oxytoca	+	+	
Enterobacter spp.	+	+	
Citrobacter freundii	+	+	

Miriagou V, et al. Clin Microbiol Infect. 2010:16:112

The Emergence of Carbapenemases in *Acinetobacter baumannii*



Poirel L, et al. *Clin Microbiol Infect.* 2006;12:826-836.

Clinical Importance of MBLs

- MBLs render essentially all β-lactam drugs (except monobactams) useless
- Use of alternative, potentially more toxic classes necessitated

Jones RN, et al. Diagn Microbiol Infect Dis. 2005;51:77

New Delhi Metallo-β-lactamase 1 (NDM-1)

- Most *bla*$_{NDM-1}$ positive plasmids are readily transferable
- Multi-resistant to fluoroquinolones, β-lactams, and aminoglycosides
- The majority of Indian isolates were from community-acquired infections, suggesting that *bla*$_{NDM-1}$ is widespread in the environment
- Potential for worldwide endemicity

Kumarasamy KK, et al. *Lancet Infect Dis.* 2010;10:597

Isolates with NDM-1: Susceptibility

Antibiotic	Proportion susceptible (%) UK (n=37)	Chennai (n=44)	Haryana (n=26)
Meropenem	3	3	3
Aztreonam	11	0	8
Ciprofloxacin	8	8	8
Gentamicin	3	3	3
Tigecycline	64	56	67
Colistin	89	94	100

0% Susceptible

Imipenem

Pip-taz

Cefotaxime

Ceftazidime

Cefpirome

Tobramycin

Amikacin

Minocycline

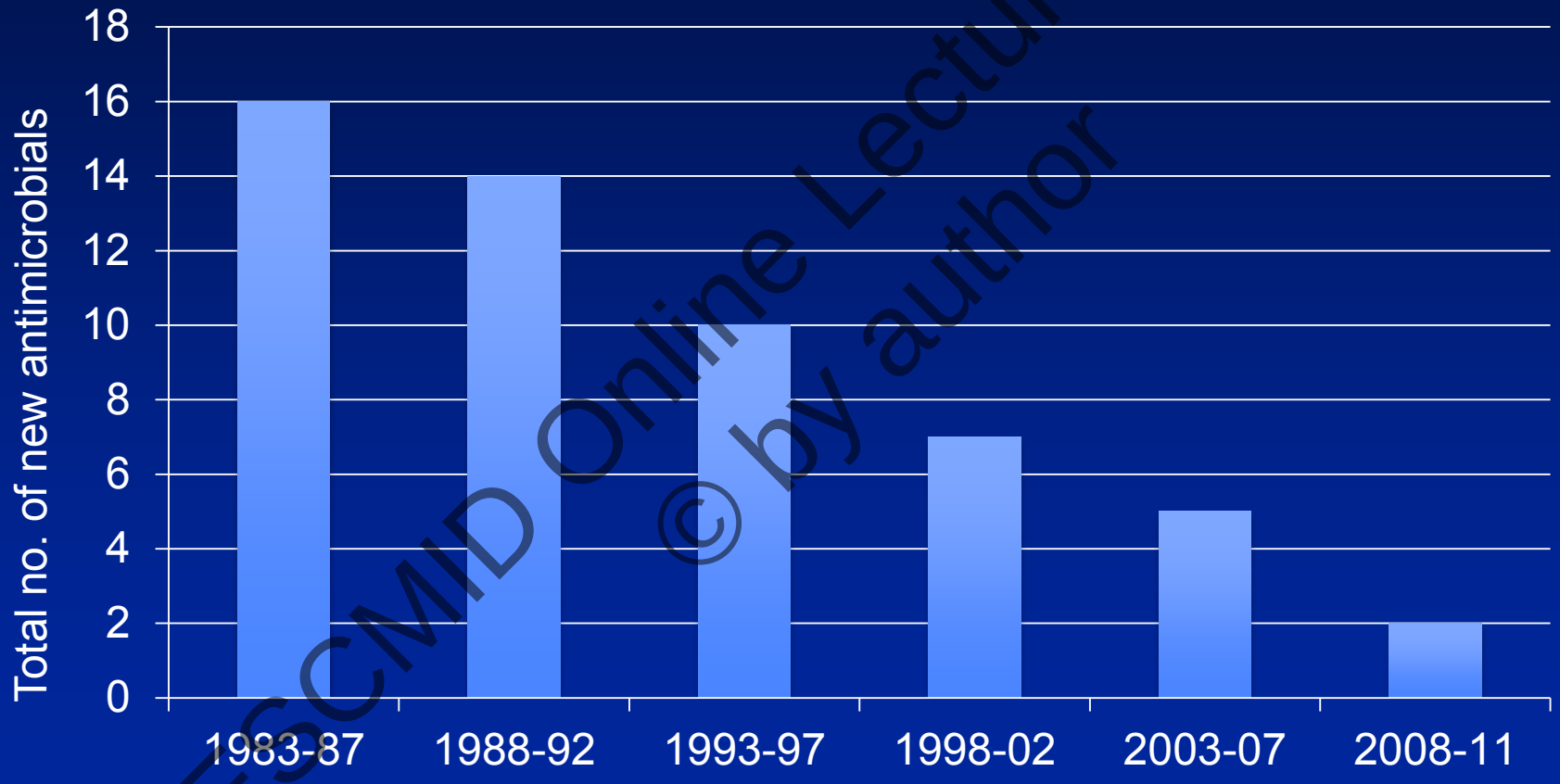
Kumarasamy KK, et al. *Lancet Infect Dis.* 2010;10:597

Factors Affecting to Choose Empirical Antibiotic Therapy

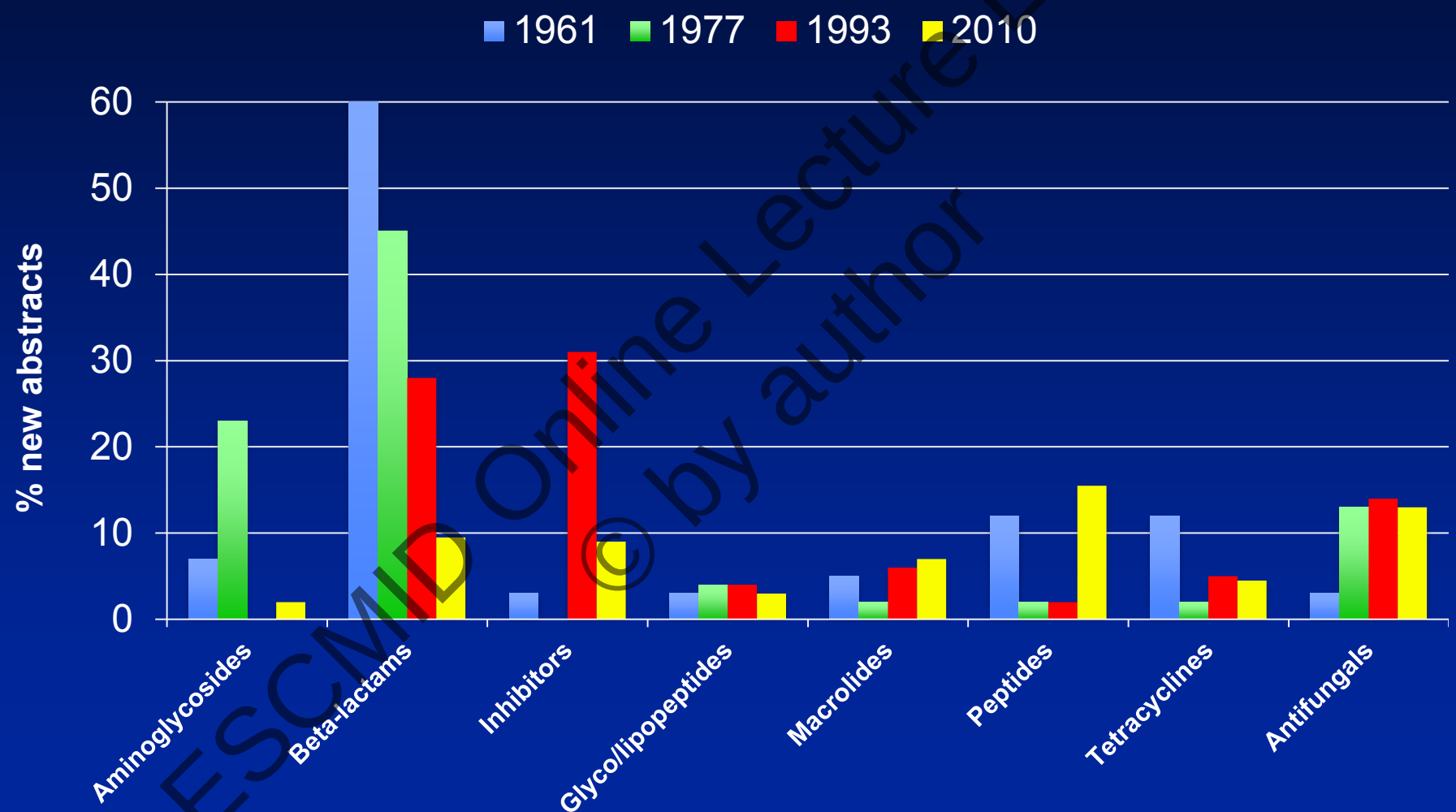
- Patients with risk factors for MDR pathogens
  - Underlying disease
  - Age of patient
  - Prior exposure to antibiotics
  - Severity of infection
  - Increased LOS in hospital
- Local resistance patterns
- Collateral damage

Maragakis LL. Crit Care Med 2010;38(8 Suppl):S345

New Antimicrobials

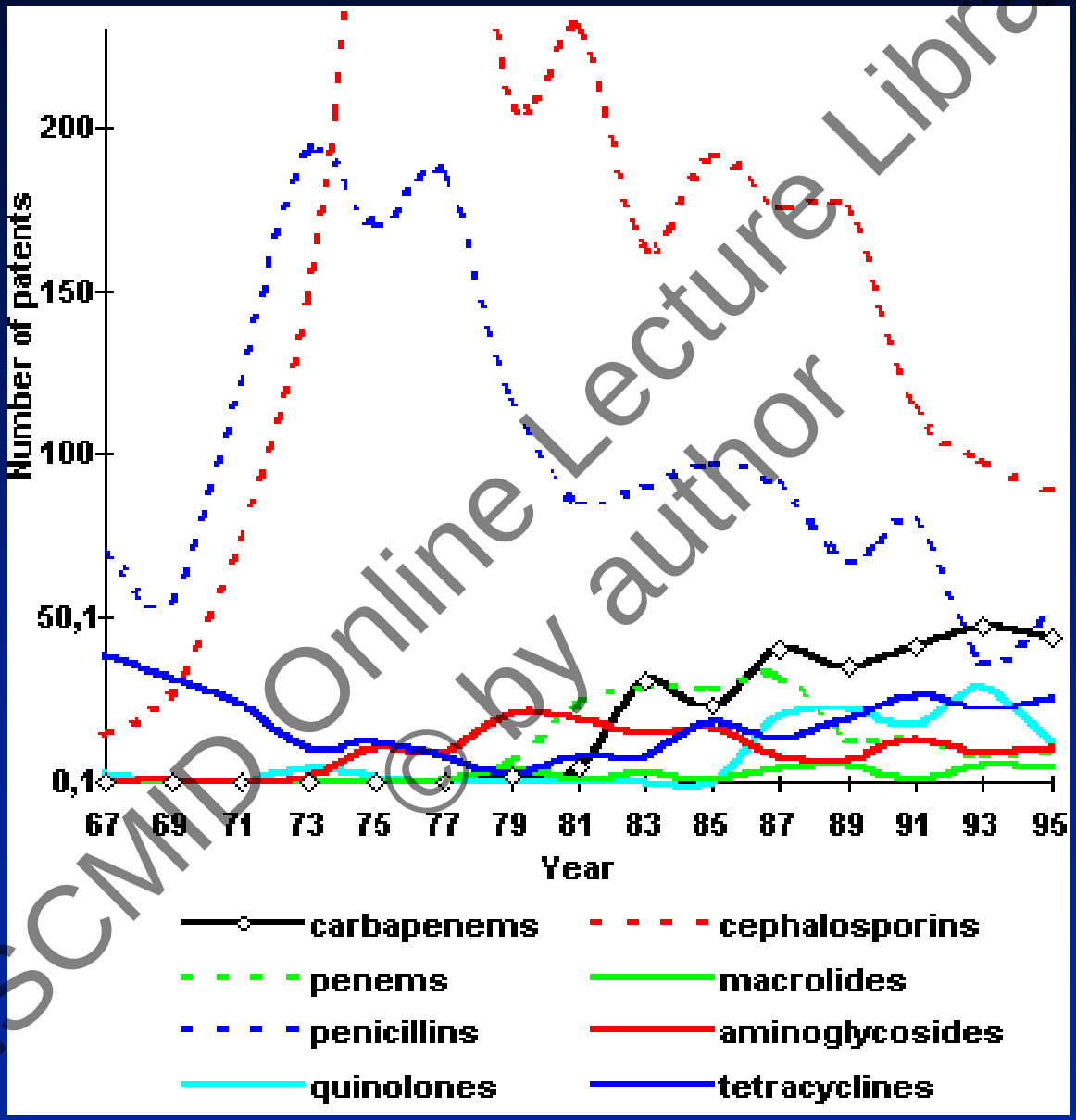


% of New Agent Abstracts in ICAAC



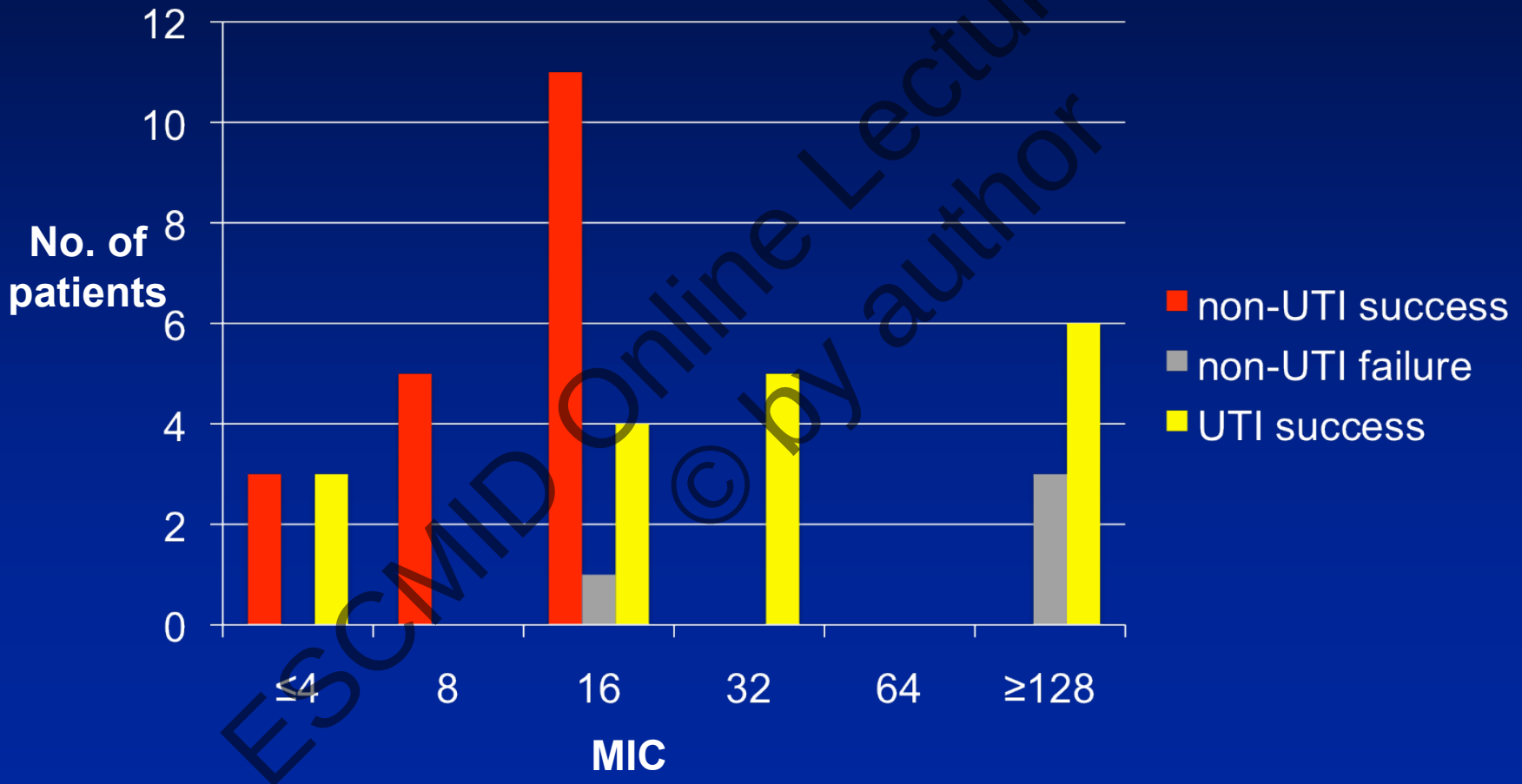
Courtesy of G. Cornaglia

New Antibiotic Patent Publications



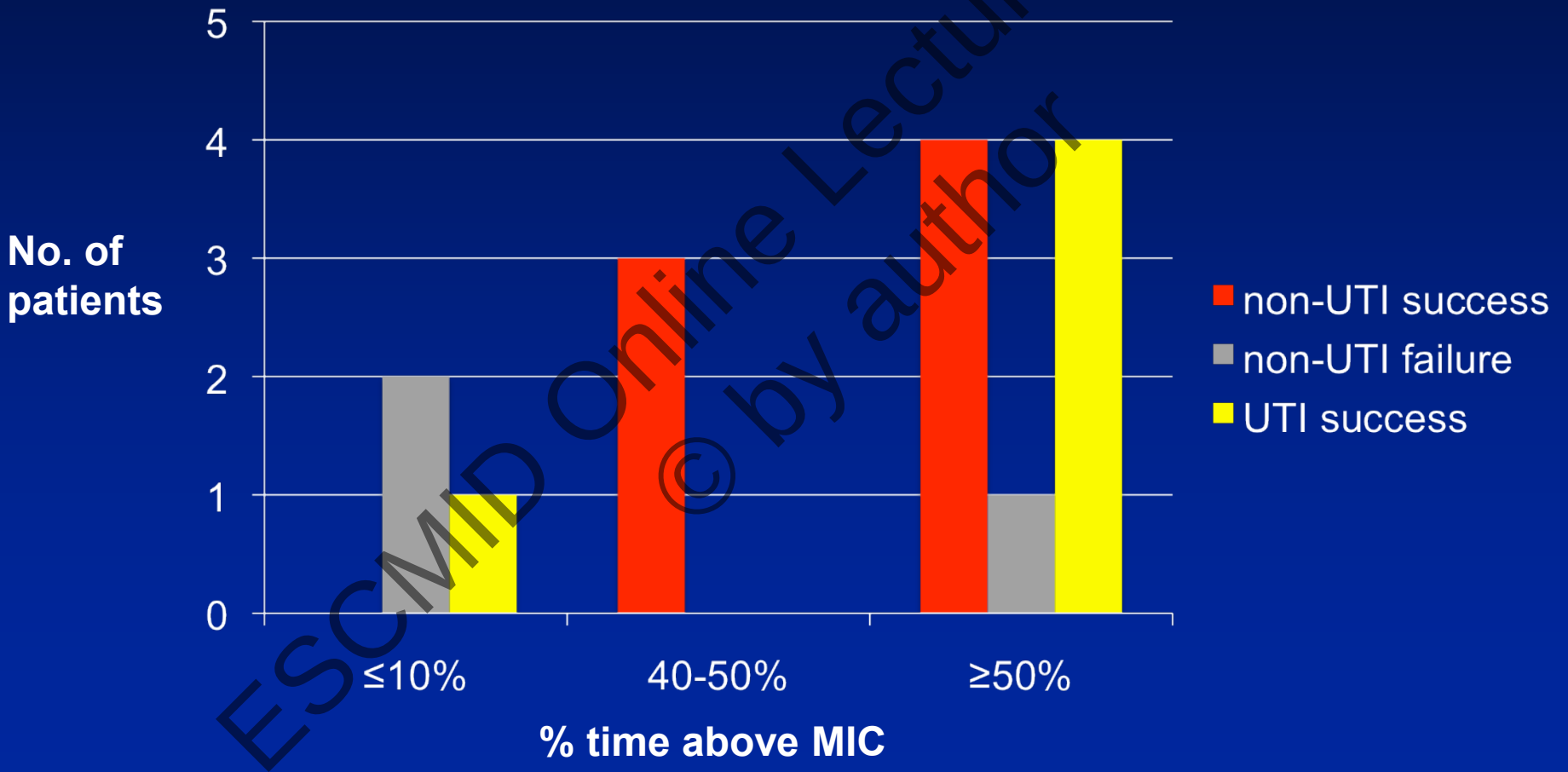
Courtesy of G. Cornaglia

Piperacillin-Tazobactam Against ESBL-producing *E. coli* and *Klebsiella spp.*



Gavin PJ, et al. Antimicrob Agents Chemother 2006; 50: 2244

Piperacillin-Tazobactam Against ESBL-producing *E. coli* and *Klebsiella spp.*



Gavin PJ, et al. Antimicrob Agents Chemother 2006; 50: 2244

Resistance to Beta-lactamase Inhibitors

- Increased production of an ESBL or a classical penicillinase
- >1 beta-lactamases produced
  - CTX-M15 (+) isolates producing OXA-1 penicillinase (clavulanate resistant)
- Mutants with decreased permeability and/or upregulated efflux

Unorthodox Clavulanate Combinations Against ESBL Producers

- **Reasons for a search of new combinations**
  - Amoxycillin and ticarcillin are good substrates for ESBLs
    - Difficult to protect
  - Producers of OXA-15, dominant CTX-M in Europe, usually co-produce OXA-1
    - OXA-1 is resistant to clavulanate

Livermore DM, et al. Clin Microbiol Infect 2008;14 (suppl 1):189

Combinations of Clavulanate plus an Oxyimino-Cephalosporin

- **Advantages**
  - Oxyimino-cephalosporins
    - Weaker substrates for ESBLs
    - Higher affinity for PBPs
    - Stable to OXA-1
  - Active >95% *E.coli* and *Klebsiella spp.* producing ESBLs
  - Pharmacokinetics of clavulanate, cefotaxime and ceftazidime are compatible

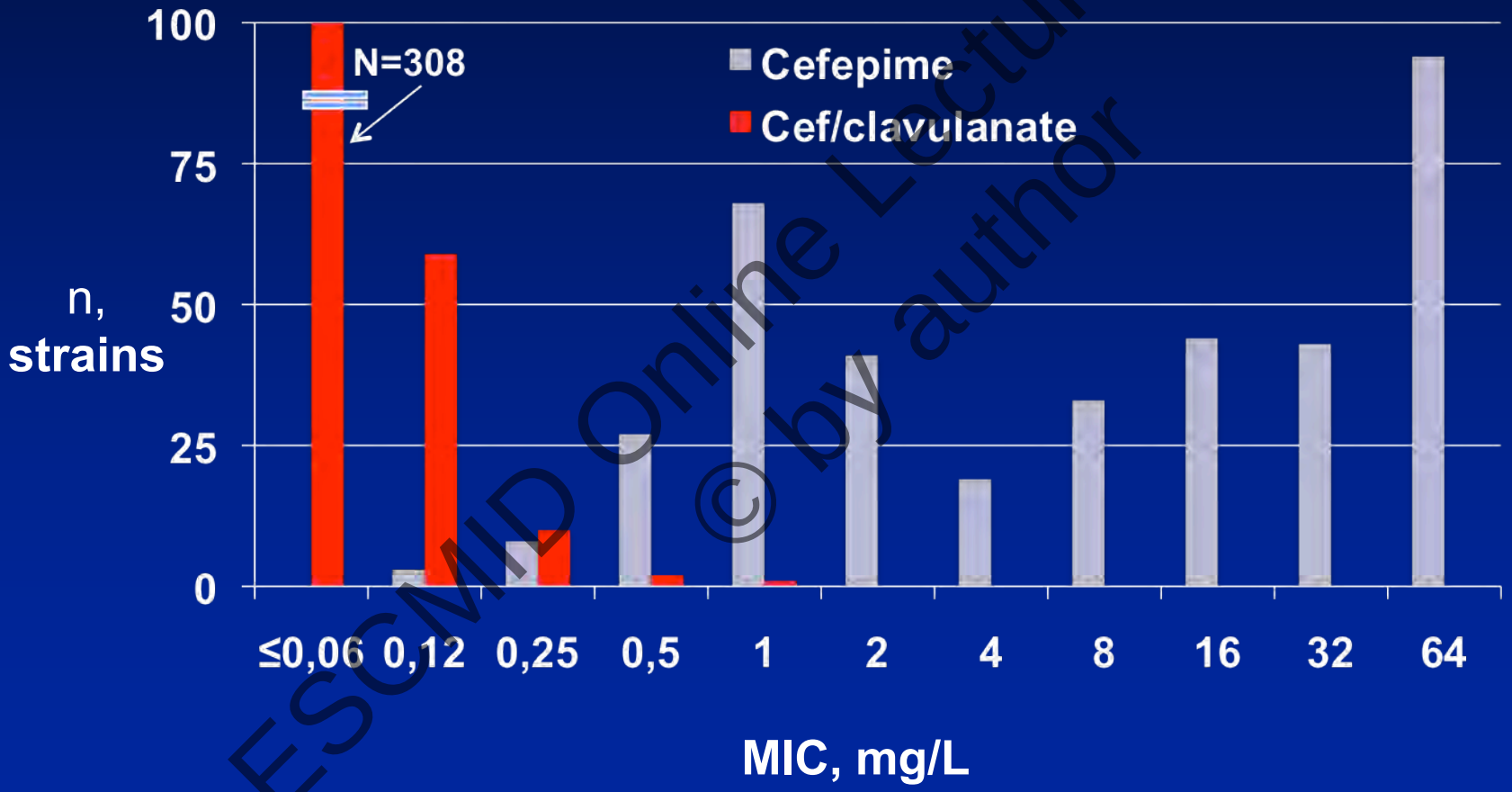
Livermore DM, et al. Clin Microbiol Infect 2008;14 (suppl 1):189

Combinations of Clavulanate plus an Oxyimino-Cephalosporin

- **Disadvantages**
  - AmpC producers
    - Derepressed strains resistant to cephalosporins
    - Clavulanate can stimulate AmpC synthesis
      - 3rd gen cephalosporin combinations may be antagonistic against ESBL-negative *Enterobacter spp.* and *C. freundii*

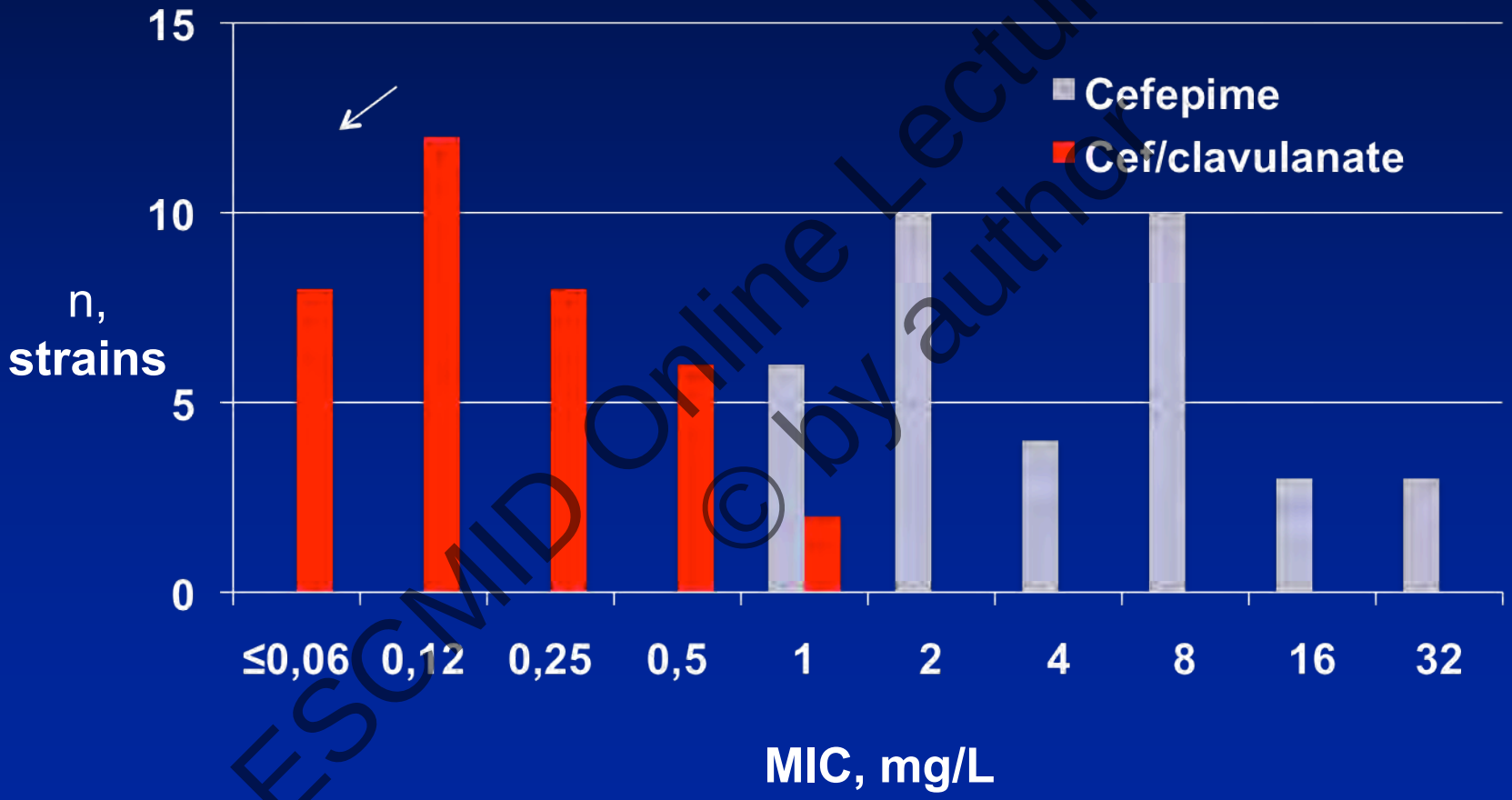
Livermore DM, et al. Clin Microbiol Infect 2008;14 (suppl 1):189

Activity *vs* ESBL-producing *E.coli*



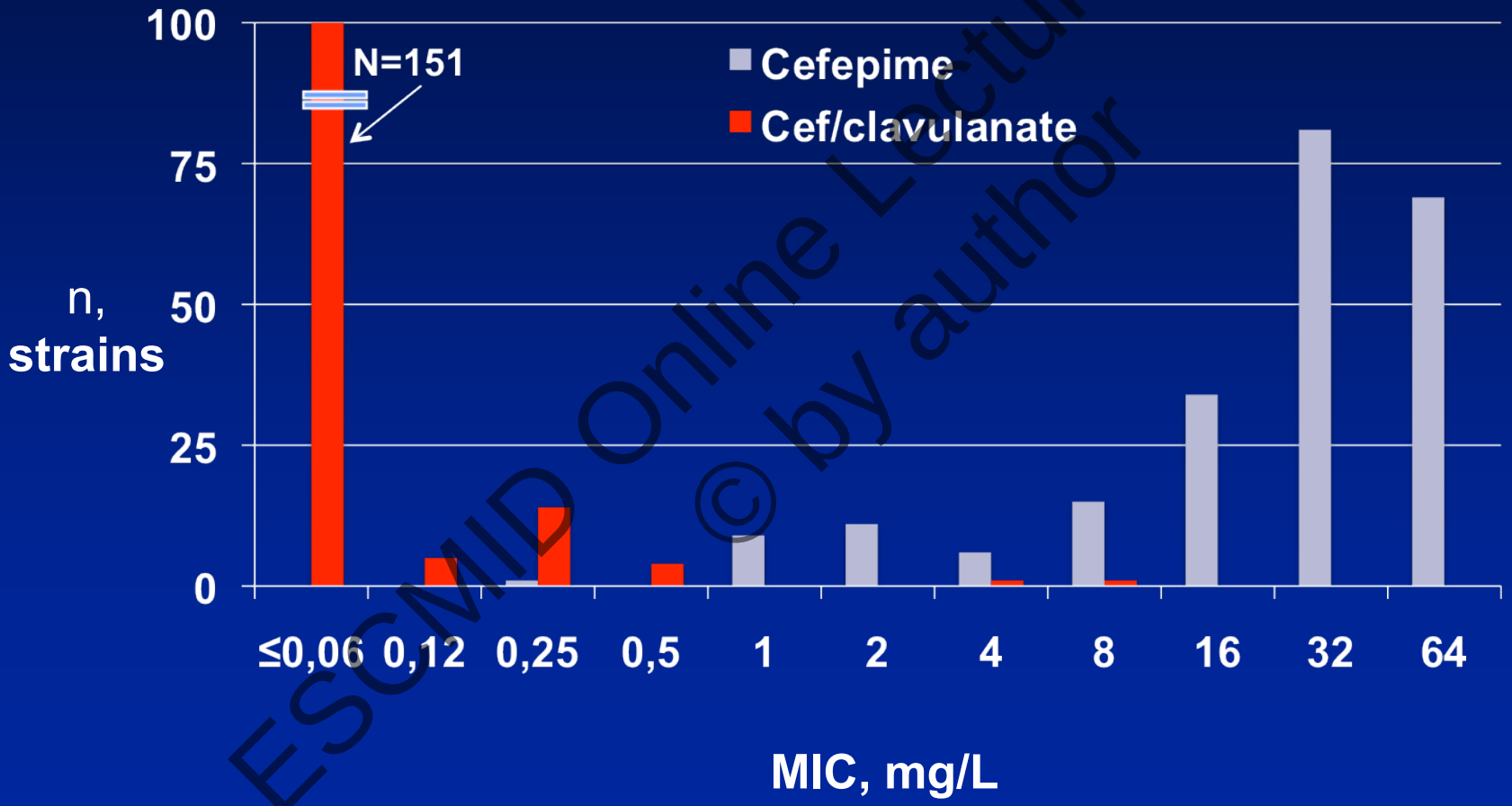
Livermore DM, et al. Clin Microbiol Infect 2008;14 (suppl 1):189

Activity *vs* ESBL-producing *Enterobacter spp.*



Livermore DM, et al. Clin Microbiol Infect 2008;14 (suppl 1):189

Activity *vs* ESBL-producing *Klebsiella spp.*



Livermore DM, et al. Clin Microbiol Infect 2008;14 (suppl 1):189

Carbapenemase-producing Enterobacteriaceae (CPE)

- Most active agents in vitro
  - Colistin
  - Tigecycline
  - Fosfomycin
- Colistin, tigecycline resistant mutants on rise
- Clinical experience with fosfomycin is limited for CPE
  - Drug readily select for resistance

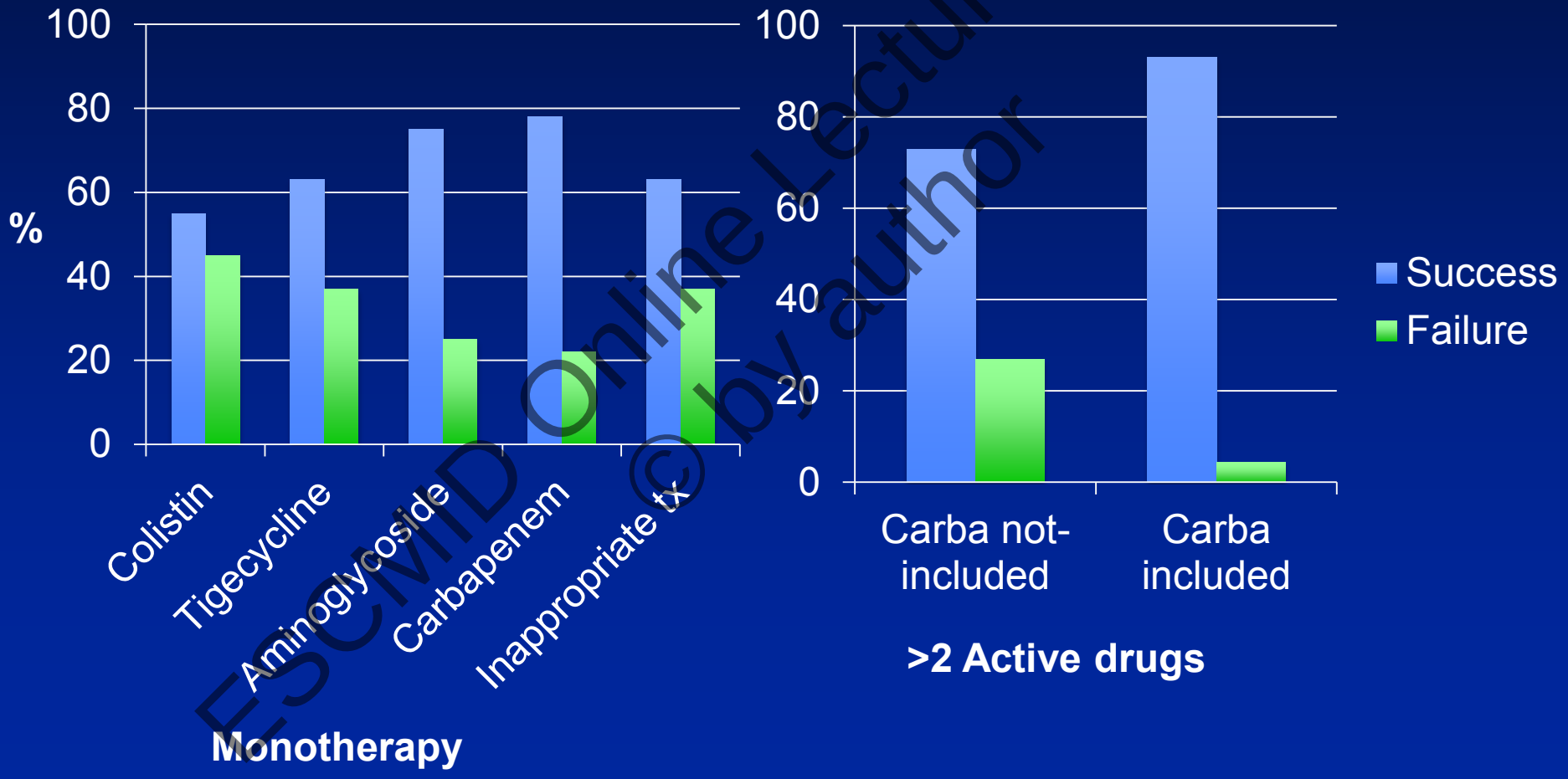
Akova M, Daikos GL, et al. Submitted to Clin Microbiol Infect 2012

In vitro Activity of Antibiotics Against Carbapenem R Enterobacteriaceae

- 81 isolates from UK
  - Include strains w combinations of carbapenemases, ESBL, AmpC and impermeability
- Inhibition rates
  - Chlora, cipro, nitrofurantion >25%
  - Colistin 92,6%
  - Fosfomycin 60,5%
  - Tigecycline, 47% plus 33,3% intermediate
  - Temocillin 5%

Livermore DM, et al. Int J Antimicrob Agents 2011;37:415

Efficacy of Antibiotics for CPKP Infections (n=234)



Akova M, Daikos GL, et al. Submitted to Clin Microbiol Infect 2012

New Alternatives on the Horizon

- **Avibactam (NXL-104), Astra Zeneca**
  - Beta-lactamase inhibitor
  - Inhibits class A (many ESBLs), class C, some class D, not active against class B
  - Combined with ceftazidim or ceftaroline
  - Phase II trials ongoing
- **CXA-101, Cubist**
  - I.v. antipseudomonal cephalosporin
  - Combination with tazobactam (CXA-201) covers most class A and class c enzymes
  - Currently Phase I-III trials ongoing

Conclusions

- Among MDR Enterobacteriaceae most important resistance mechanism is ESBL production
- Prevalence has been on rise
  - In hospital
  - Community
- Treatment options are limited

Conclusions-II

- Beta-lactamase inhibitor combinations should be used cautiously in severe infections caused by ESBL producers
  - CTX-M and OXA-1 co-producers
  - Inoculum effect (??)
- Limited clinical data indicate that *in vitro* susceptility may favor clinical success
- Combinations with more stable cephalosporins might be potentially useful

Conclusions-III

- Antimicrobial stewardship, infection control, and surveillance are crucial
- Consider reduced use of cephalosporins and fluoroquinolones
- Carbapenems are the treatment of choice for serious infections
  - Emerging of carbapenem resistance as collateral damage

Conclusions-IV

- Options limited for Carbapenemase-producing enterics
- Colistin monotherapy not successful
  - May be related with pK/pD issues
- If active in vitro, carbapenem combinations more effective

Thank you…