

# ESBL-producing organisms

**Matthew E. Falagas, MD, MSc, DSc**

Director, Alfa Institute of Biomedical Sciences (AIBS),  
Athens, Greece

Adjunct Associate Professor of Medicine,  
Tufts University School of Medicine,  
Boston, Massachusetts, USA

# Overview

- Definitions
- Implicated pathogens
- Global epidemiology
- Detection
- Infection control
- Clinical impact
- Treatment options

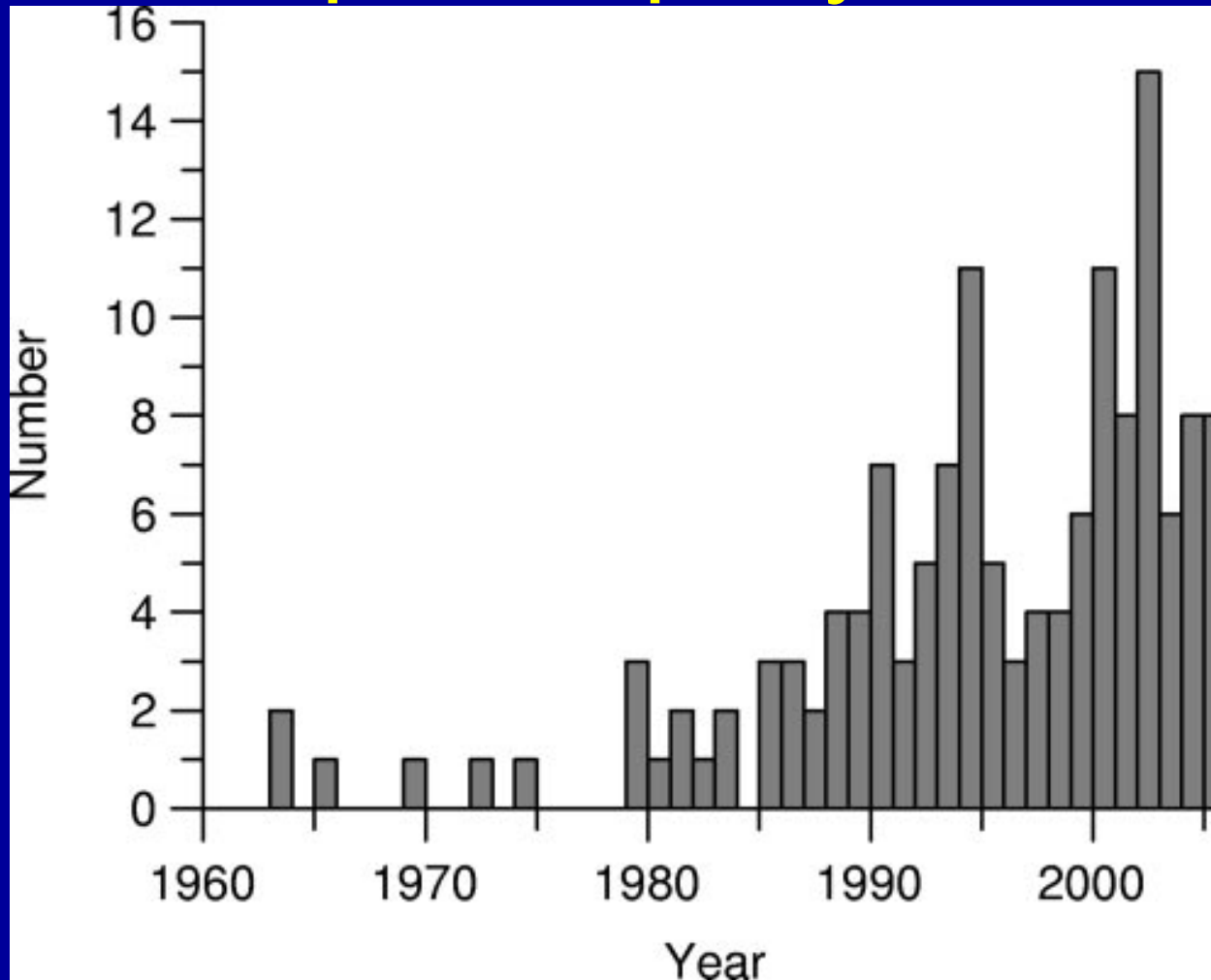
# Definition of ESBLs

- Molecular class A (Ambler)
- Functional group 2be  $\beta$ -lactamases (Bush-Jacoby-Medeiros)
- Ability to hydrolyse an oxyimino-cephalosporin at a rate  $\geq 10\%$  of the hydrolysis rate of benzylpenicillin
- Inhibition by clavulanic acid

Ambler RP, Meadway RJ. *Nature*. 1969;222:24-6

Bush K *et al.* *Antimicrob Agents Chemother* 1995;39:1211–33

# Number of new $\beta$ -lactamases reported per year



# Need for a pragmatic definition

That would include “any  $\beta$ -lactamase, generally acquired rather than inherent to a species, that is either able to confer resistance to oxyimino-cephalosporins (but not carbapenems), or that has an increased ability to do so, as compared with classic members of its genetic family”

# Proposed clinically-oriented classification

- Class A (Ambler) ESBLs (ESBL<sub>A</sub>)
  - Classical, functional class (Bush-Jacoby-Medeiros) 2be  $\beta$ -lactamases
- Miscellaneous ESBLs (ESBL<sub>M</sub>)
  - Plasmid-mediated AmpC (ESBL<sub>M-C</sub>)
  - Plasmid mediated OXA-ESBLs (ESBL<sub>M-D</sub>)
- ESBLs with hydrolytic activity against carbapenems (ESBL<sub>CARBA</sub>)
  - Class A  $\beta$ -lactamases (KPC)
  - Class B (MBL)
  - Class D (OXA-carbapenemases)

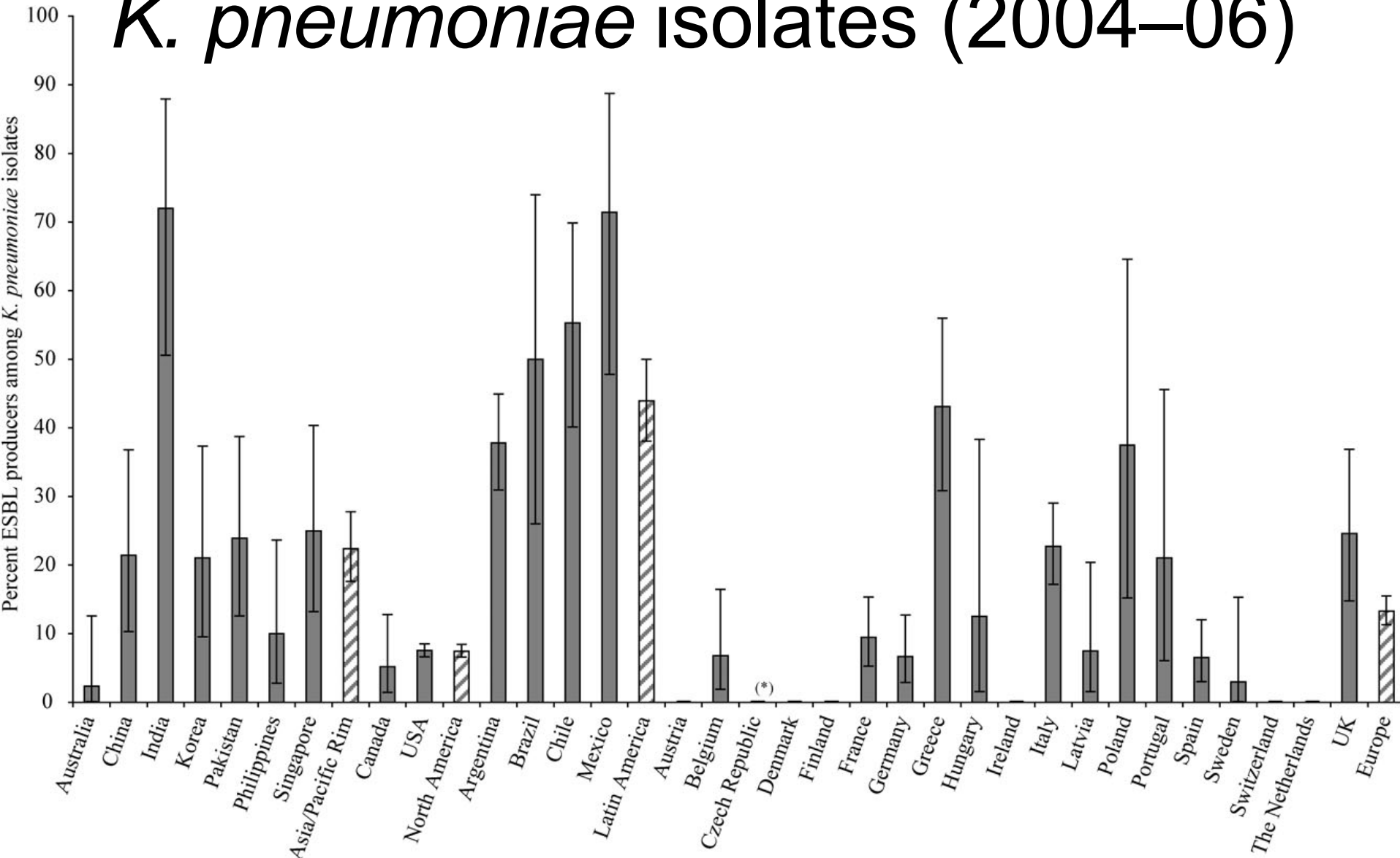
# Main types of ESBLs

- Initially mainly of the TEM and SHV types
  - Derived by point mutations of parent enzymes without ESBL activity
- CTX-M types
- Other types (VEB, PER, GES, TLA, IBC, SFO-1, BES-1, BEL-1)

# Main ESBL-producing pathogens

- Enterobacteriaceae
  - *E. coli*
  - *K. pneumoniae*
  - *K. oxytoca*
  - *P. mirabilis*
  - *Enterobacter*
  - *Salmonella*
- Non-fermentative Gram-negative
  - *A. baumannii*
  - *P. aeruginosa*

# Rates of ESBL production among *K. pneumoniae* isolates (2004–06)

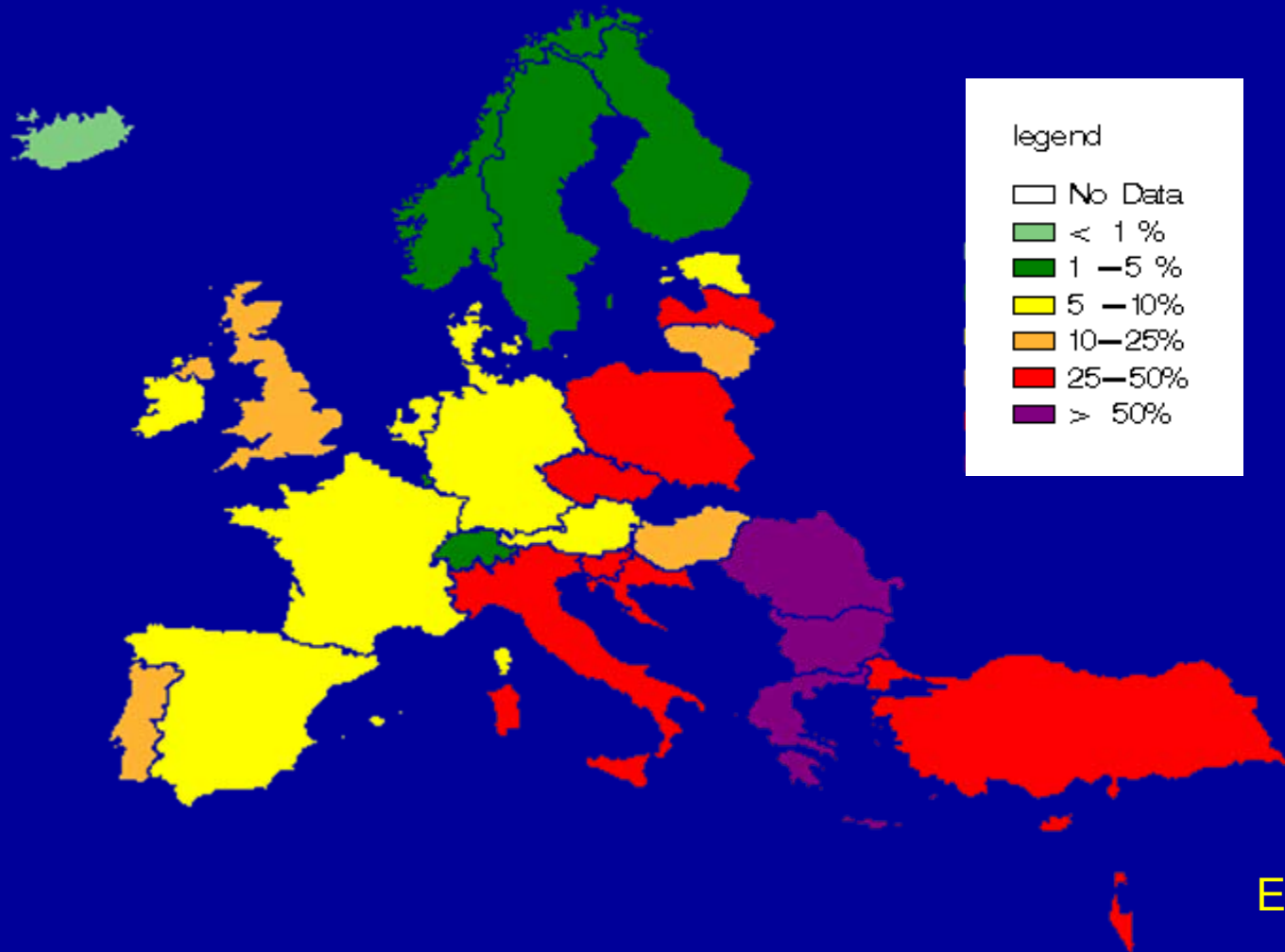


# Prevalence of ESBL-producing Enterobacteriaceae in Europe

- 2007 Tigecycline Evaluation and Surveillance Trial (TEST) database
- 22 European countries (multiple centers)
- Isolates related to both hospital and community acquired infections
- Sites of isolation: blood, respiratory tract, urine, skin, wound, fluids and other defined sources
- ESBL production in:
  - 15.5% among 516 *K. pneumoniae* isolates
  - 9.8% among 794 *E. coli* isolates
- Rates of ESBL production lower in Denmark (2.6%) and higher in Greece (24.2%)

Hackel M *et al.* 18th European Congress of Clinical Microbiology and Infectious Diseases (ECCMID). Abstract P 686. April 2008, Barcelona, Spain

# Percentage of 3<sup>rd</sup> gen. cephalosporin resistant *K. pneumoniae* 2006-08



# Antimicrobial resistance of *Escherichia coli* urinary isolates from primary care patients in Greece

Matthew E. Falagas<sup>1,2ACDEF</sup>, Michael Polemis<sup>3BCDE</sup>, Vangelis G. Alexiou<sup>1BCDEF</sup>,  
Alexandra Marini-Mastrogiannaki<sup>4ACDE</sup>, Jeni Kremastinou<sup>5BCDE</sup>,  
Alkiviadis C. Vatopoulos<sup>3ABCDEG</sup>

# Introduction

- Most of the antimicrobial susceptibility surveillance studies focus on isolates from hospitalized patients
- We performed a retrospective analysis of microbiological data of the antimicrobial susceptibility of *E. coli* urinary isolates from primary care patients in Greece

# Methods

- The in vitro susceptibility to ampicillin, amoxicillin/clavulanate, cefaclor, cefprozil, trimethoprim-sulfamethoxazole (co-trimoxazole), amikacin, and norfloxacin of 2460 *E. coli* isolates (01/2005-06/2005) from urine specimens of patients tested at the laboratories of 3 Greek primary care diagnostic centers were analyzed
- Only the first isolate per patient (2074 females and 386 males) were included in the analysis

**Table 1.** Antimicrobial resistance of urinary *Escherichia coli* isolates from primary care female patients tested in Greek diagnostic centers (01/2005–06/2005).

Age group (years)	Number of resistant isolates among isolates tested (%)								Total	<i>p</i>	
	<15		15–35		35–55		>55				
Ampicillin	68/157	(43.3)	221/639	(34.5)	231/720	(32.1)	253/558	(45.3)	773/2074	(37.3)	<0.001
Amoxicillin-clavulanic acid	6/157	(4.1)	28/639	(4.4)	37/720	(5.1)	51/558	(9.1)	122/2074	(5.9)	0.002
Cefaclor	25/157	(15.7)	21/639	(3.3)	31/720	(4.3)	44/558	(7.9)	121/2074	(5.8)	<0.001
Cefprozil	17/157	(11)	26/639	(4.1)	34/720	(4.7)	46/558	(8.2)	123/2074	(5.9)	<0.001
Cotrimoxazole	59/157	(37.8)	121/639	(18.9)	122/720	(17)	130/558	(23.3)	432/2074	(20.8)	<0.001
Amikacin	3/157	(2.2)	12/639	(1.9)	13/720	(1.8)	13/558	(2.2)	41/2074	(2)	0.918
Norfloxacin	ND		27/639	(4.2)	29/720	(4.1)	50/558	(8.9)	106/1917	(5.5)	<0.001

ND – no data available.

**Table 2.** Antimicrobial resistance of urinary *Escherichia coli* isolates from primary care male patients tested in Greek diagnostic centers (01/2005–06/2005).

Age group (years)	<15		15–35		35–55		>55		Total		<i>P</i>
	Number of resistant isolates among isolates tested (%)										
Ampicillin	42/67	(63)	25/36	(69.1)	45/119	(38)	89/164	(54.2)	201/386	(52.1)	0.001
Amoxicillin-clavulanic acid	10/67	(15.3)	5/36	(14.2)	8/119	(6.6)	17/164	(10.4)	40/386	(10.4)	0.298
Cefaclor	21/67	(31.9)	3/36	(8.3)	6/119	(5)	15/164	(8.9)	45/386	(11.7)	<0.001
Cefprozil	19/67	(25.4)	6/36	(17.8)	8/119	(7)	16/164	(9.7)	49/386	(12.7)	<0.001
Cotrimoxazole	20/67	(29.2)	15/36	(41.5)	23/119	(19.5)	44/164	(26.7)	102/386	(26.4)	0.05
Amikacin	0/67	(0)	1/36	(2.8)	5/119	(4)	7/164	(4.1)	13/386	(3.4)	0.38
Norfloxacin	ND		12/36	(34.1)	15/119	(12.5)	30/164	(18.2)	57/319	(17.8)	0.017

ND – no data available.

# CTX-M ESBLs

- Becoming increasingly more prevalent among Enterobacteriaceae
  - Particularly *E. coli*, and secondly *K. pneumoniae*
- Horizontal transfer of  $bla_{\text{CTX-M}}$  genes, mediated by plasmids and/or mobile elements
- Clonal expansion of epidemic strains

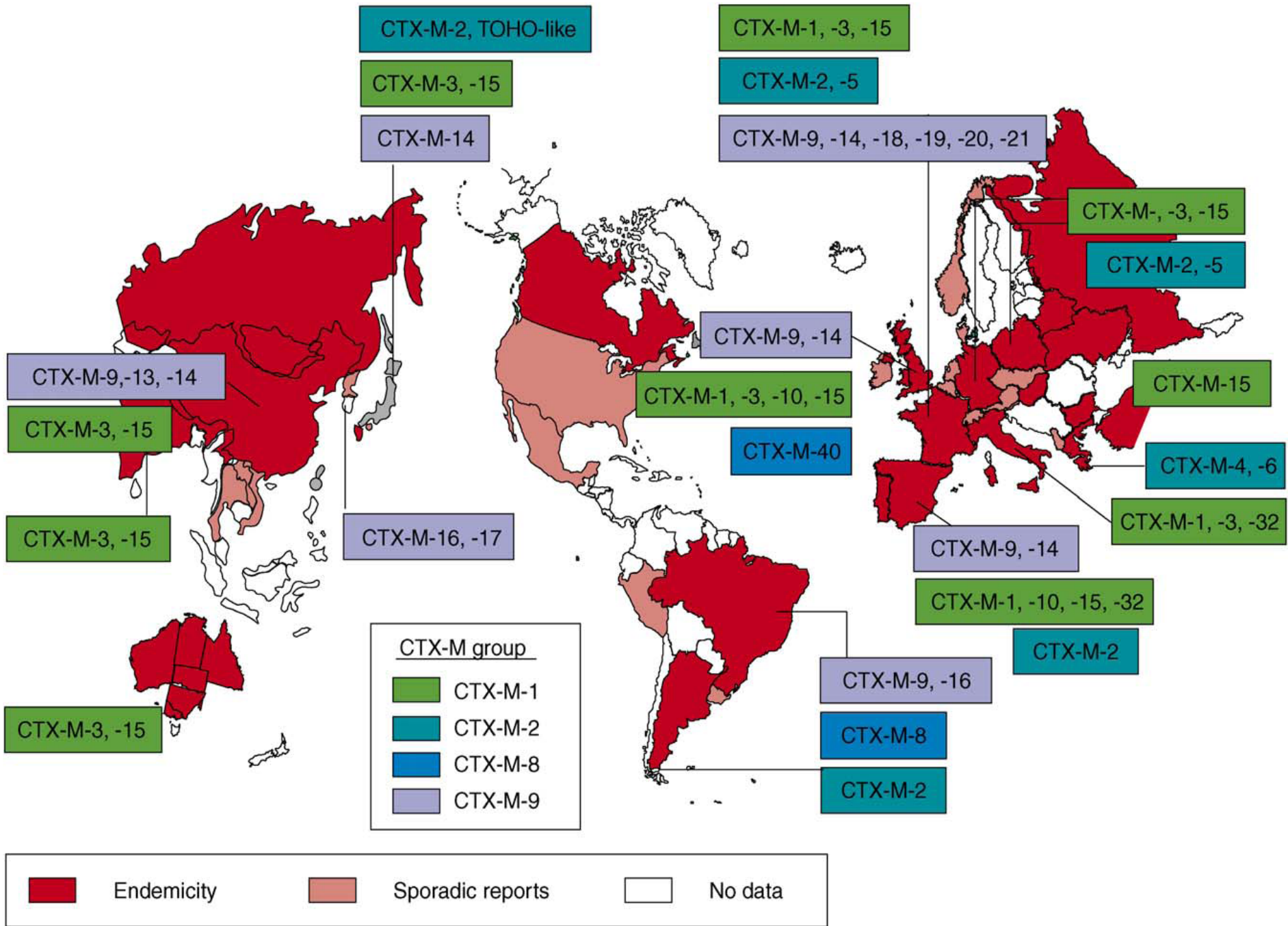
# CTX-M ESBLs

- > 50 enzymes identified to date
- Groups according to aminoacid changes
  - CTX-M1, CTX-M2, CTX-M8, CTX-M9, CTX-M25
  - CTX-M2 and CTX-M8 groups originate from chromosomal enzymes of *Kluyvera* spp (environmental bacteria)

# Worldwide distribution of CTX-M enzymes

- CTX-M1 Italy
- CTX-M2 Israel, Argentina
- CTX-M3 Poland
- CTX-M9 Spain
- CTX-M14 Spain, Canada, China
- CTX-M15 Worldwide (including UK)
- Few reports of CTX-M ESBLs in the US

Pitout JD, Laupland KB. *Lancet Infect Dis.* 2008;8:159-66  
Lewis JS 2<sup>nd</sup> *et al.* *Antimicrob Agents Chemother.* 2007;51:4015-21



# Methods of detection of ESBLs

- Phenotypic methods
  - Used routinely in clinical laboratories
  - The accuracy of semiautomated microbiology systems is not optimal
- Genotypic methods
  - Used in reference laboratories or for research purposes
  - Discriminate between specific types of ESBLs
  - Need shorter time to detection (culture not required)
  - Ability to detect low level resistance

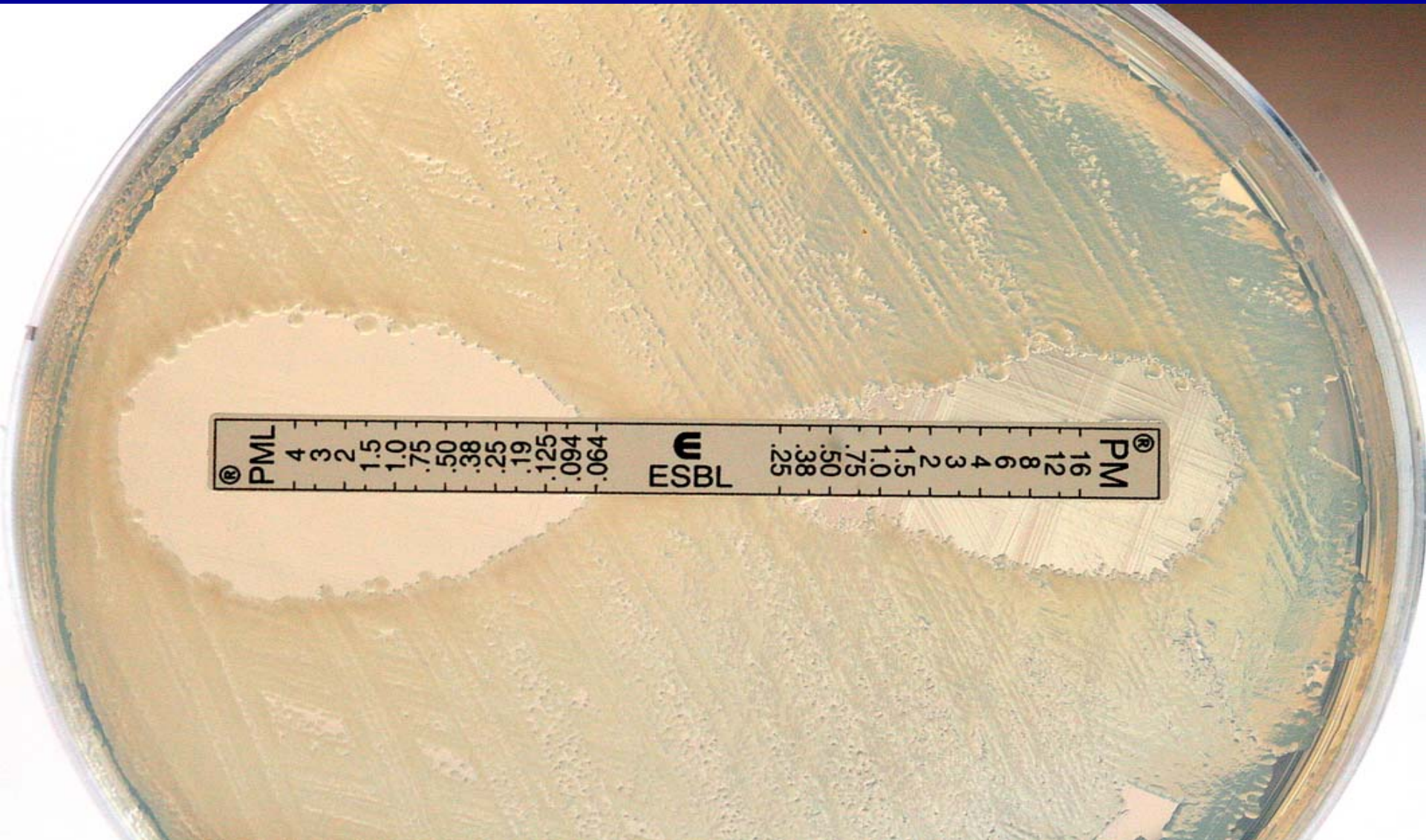
# Phenotypic tests

- Screening
  - Resistance to cefpodoxime
    - Hydrolyzed by TEM, SHV and CTX-M ESBLs
  - Plus resistance to cefotaxime, ceftazidime, ceftriaxone or aztreonam
- Confirmatory tests
  - Inhibition of hydrolytic activity by the addition of clavulanic acid
- Problematic for AmpC  $\beta$ -lactamase producing Enterobacteriaceae (e.g. enterobacter and citrobacter)
  - Induction of AmpC  $\beta$ -lactamase by clavulanic acid
  - Use of cefepime may help

# Ceftazidime – ceftazidime/clavulanic acid combination disk test



# Cefepime – cefepime/clavulanic acid Etest



# Genotypic tests

- PCR-based amplification of specific genes
- Nucleotide sequencing or other molecular methods additionally required for the detection of specific point mutations in *bla*<sub>TEM</sub> and *bla*<sub>SHV</sub> genes that confer ESBL activity

# Type of patients affected by ESBL-associated infections

- Community-acquired infections
  - Non clonally related
  - Mainly *E. coli*
    - CTX-M type
  - Health-care associated?
  - Reports of true community-acquired infections are increasing
    - Fecal carriage of ESBLs in healthy individuals
    - Transmission from animal hosts through the food chain?
- Nosocomial infections
  - Clonal outbreaks
  - Sporadic strains co-exist
  - Mainly *K. pneumoniae*
- Infections in nursing home residents

Rodríguez-Baño J *et al.* Clin Infect Dis. 2006;42:37-45  
Valverde A *et al.* J Antimicrob Chemother. 2008;61:64-72  
Coque TM *et al.* Euro Surveill. 2008;13(47). pii: 19044

# Main clinical syndromes

- Urinary tract infections
- Bloodstream infections
  - Commonly of urinary or, less so, biliary tract origin
- Respiratory tract infections
- Intra-abdominal infections

# Characteristics of community and nosocomial infections

	Community onset	Hospital onset
Organism	<i>Escherichia coli</i>	<i>Klebsiella</i> spp (and others)
Type of ESBL	CTX-M (especially CTX-M15)	SHV (especially SHV2 SHV5) and TEM (especially TEM26, TEM51)
Type of Infection	Most often UTIs, but also bacteraemia and gastroenteritis	Respiratory tract, intra-abdominal, and bloodstream infections
Molecular Epidemiology	Most isolates not clonally related, although clusters have been described	Most often clonally related

# Risk factors for community-acquired ESBL *E. coli* infections

- A case-control study of 122 cases (93% UTIs) in 11 Spanish hospitals identified the following risk factors:
  - Increased age (older than 60 years)
  - Female sex
  - Diabetes mellitus
  - Recurrent urinary tract infections
  - Previous invasive procedures of the urinary tract
  - Follow-up in outpatient clinic
  - Previous receipt of aminopenicillins, cephalosporins, and fluoroquinolones

# Risk factors for infection/colonization by ESBL-producing organisms in the hospital environment

- Increased length of hospital or ICU stay
- Increased severity of illness
- Use of a central venous or arterial catheter or urinary catheter
- Ventilatory support
- Hemodialysis
- Emergency abdominal surgery
- Gastrostomy or jejunostomy
- Gut colonization
- Prior administration of antibiotics, particularly of oxyimino- $\beta$ -lactams

# Hospital epidemiology

- Primarily ICU patients affected
- Complex epidemiology
- Multiple clones may co-exist
- Mobility of genetic material between genotypically unrelated strains (plasmid transfer)

Paterson DL, Bonomo RA. Clin Microbiol Rev. 2005;18:657-86

## **Risk factors of carbapenem-resistant *Klebsiella pneumoniae* infections: a matched case–control study**

**Matthew E. Falagas<sup>1,2,3\*</sup>, Petros I. Rafailidis<sup>1,3</sup>, Diamantis Kofteridis<sup>4</sup>, Simona Vartzili<sup>5</sup>,  
Fotini C. Chelvatzoglou<sup>3</sup>, Vassiliki Papaioannou<sup>6</sup>, Sofia Maraki<sup>7</sup>, George Samonis<sup>4</sup>  
and Argyris Michalopoulos<sup>1,5</sup>**

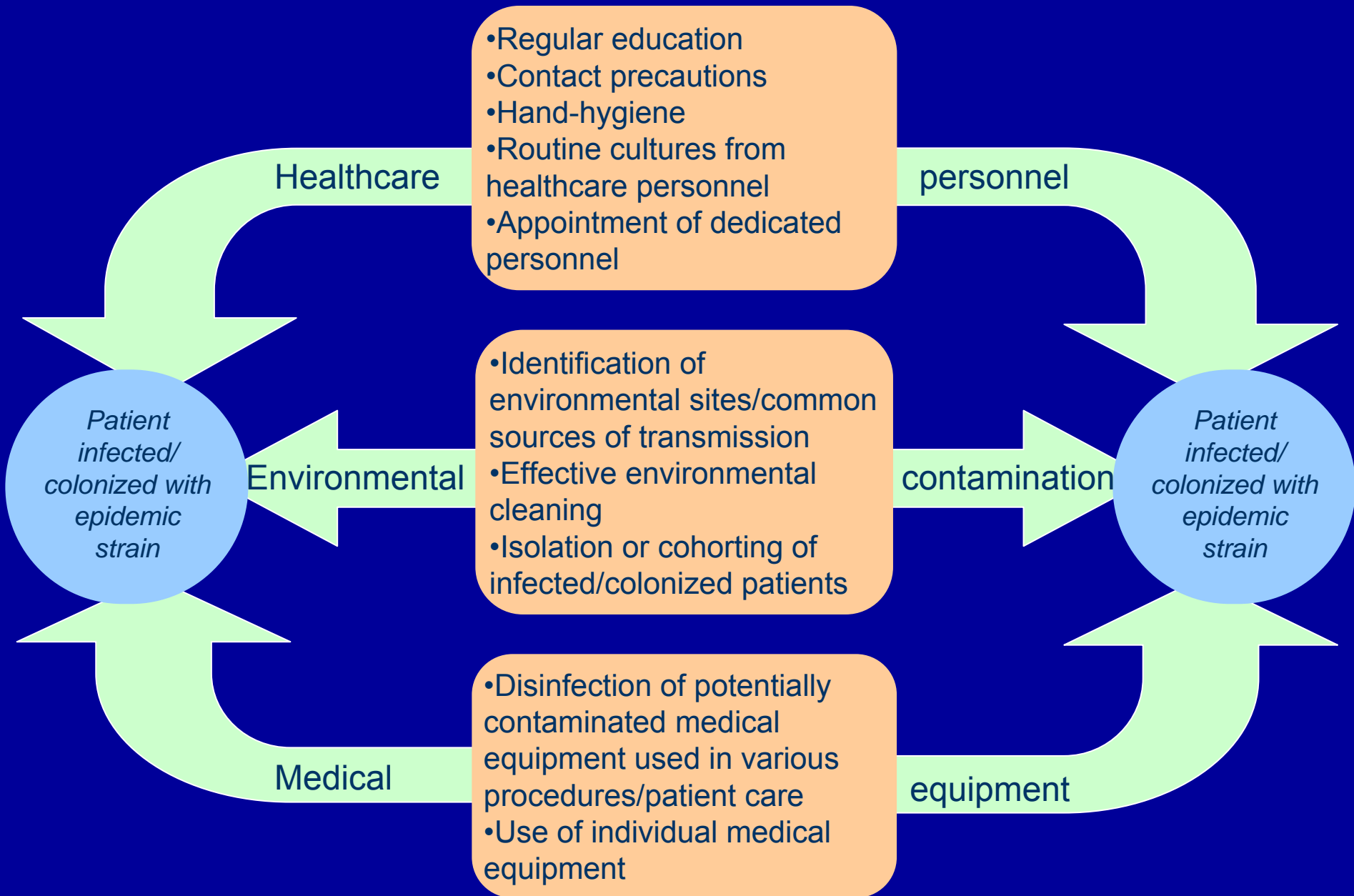
<sup>1</sup>*Alfa Institute of Biomedical Sciences (AIBS), Athens, Greece;* <sup>2</sup>*Department of Medicine, Tufts University School of Medicine, Boston, MA, USA;* <sup>3</sup>*Department of Medicine, Henry Dunant Hospital, Athens, Greece;* <sup>4</sup>*Department of Medicine, University Hospital of Heraklion, Heraklion, Greece;* <sup>5</sup>*Intensive Care Unit, Henry Dunant Hospital, Athens, Greece;* <sup>6</sup>*Department of Microbiology, Henry Dunant Hospital, Athens, Greece;* <sup>7</sup>*Department of Microbiology, University Hospital of Heraklion, Heraklion, Greece*

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- Matched case-control study in 2 hospitals in Greece
- Cases had a carbapenem-resistant *K. pneumoniae* infections
- Controls had a carbapenem-susceptible *K. pneumoniae* infection and were matched for site of infection
- 106 patients (53 cases and 53 controls) were included

- The bivariable analysis found the following risk factors for carbapenem-resistant *K. pneumoniae* infection
  - Anti-pseudomonal penicillins use
  - Carbapenem use
  - Fluoroquinolone use
  - Glucosaminoglycan use
  - Admission to the ICU
  - Tracheostomy
  - COPD
  - Surgery with use of foreign body
  - Mechanical ventilation
- The multivariable analysis identified exposure to fluoroquinolones (OR 4.5, 95% CI 1.8-11.5) and antipseudomonal penicillins (OR 2.6, 95% CI 1.00-6.7) as the only independent risk factors

# Infection control measures



# Key issues in hospital infection control against ESBL pathogens

- Identification of colonized patients
  - Most infected patients have previous colonization of the GI tract
  - Culture of rectal swabs
  - Use of selective media to isolate ESBL-producing Enterobacteriaceae
- Selective decontamination of the GI tract
  - Limited value if there is co-resistance to agents used in this regard
  - Selective pressure for emergence of pathogens with advanced resistance patterns
- Failure to contain ESBL-producing organisms leads to heavier use of carbapenems and potential emergence of carbapenem-resistant pathogens
- Antibiotic restriction (3<sup>rd</sup> generation cephalosporins)
  - Has been shown to decrease the rate of isolation of ESBL-producing Enterobacteriaceae

# Impact

- Empirical antibiotic treatment often inactive
- Delay in institution of appropriate treatment
- Increased mortality
- A meta-analysis of 16 studies comparing bacteremia by ESBL-producers vs non-producers found:
  - pooled RR 1.85, 95% CI 1.39-2.47,  $P < 0.001$  for mortality
  - pooled RR 5.56, 95% CI 2.94-10.51,  $P < 0.001$  for delay in institution of active agents

Schwaber MJ, Carmeli Y. J Antimicrob Chemother. 2007;60:913-20

# Resistance conferred by ESBLs

- Cephalosporins
  - Most CTX-M enzymes confer higher resistance to cefotaxime than ceftazidime
    - Ceftazidime MICs, although elevated, may be in the susceptible range
  - Cephamycins (e.g. cefoxitin, cefotetan) are spared
- Monobactams (aztreonam)
- Level of resistance to  $\beta$ -lactam/ $\beta$ -lactamase inhibitor combinations variable
  - MICs can be in the susceptible or low level resistance range
- Inoculum effect against substrates
  - Clinical relevance not established
  - Laboratory artifact owed to liberation of ESBL enzymes from killed bacteria in the surrounding media

# Commonly associated resistance

- Cephamycins
  - Porin loss mutations
- Fluoroquinolones
- Co-trimoxazole
- Tetracycline
- Aminoglycosides

Lautenbach E *et al.* Clin Infect Dis 2001;33:1288-94

Morosini MI *et al.* Antimicrob Agents Chemother 2006;50:2695-2699

# Treatment options

## Cephalosporins

- Cephalosporins may be ineffective even when routine microbiological methods report susceptibility (low level resistance)

Paterson DL *et al.* J Clin Microbiol 2001;39:2206-12

- Ceftazidime for pathogens with CTX-M enzymes that show susceptibility
  - 15 patients with bacteremia
  - Similar effectiveness with imipenem/cilastatin
  - Worse outcome for intra-abdominal vs urinary tract origin

Bin C *et al.* Diagn Microbiol Infect Dis 2006; 56: 351–57

- Outcomes of ceftazidime treatment in patients infected with Enterobacteriaceae expressing SHV or TEM  $\beta$ -lactamases not favorable

Wong-Beringer *et al.* Clin Infect Dis. 2002;34:135-46

# Cefepime

- May be effective against infection with ESBL-producing Enterobacteriaceae that retain susceptibility
  - Typically with TEM and SHV types of ESBLs
- In the context of a randomized trial, 9/13 (69%) patients with nosocomial pneumonia by ESBL pathogens showed cure or improvement with cefepime versus 10/10 (100%) of those treated with imipenem/cilastatin

Ramphal R, Ambrose PG. Clin Infect Dis. 2006;42 Suppl 4:S164-72

Zanetti G *et al.* Antimicrob Agents Chemother 2003; 47: 3442–47

# $\beta$ -lactams/ $\beta$ -lactamase inhibitors

- Tazobactam exhibits an almost 10-fold greater inhibitory activity than clavulanic acid against CTX-M-type – lactamases
- No significant differences against extended-spectrum TEM and SHV enzymes

Bush K *et al.* Antimicrob Agents Chemother 1993;37:851–858  
Payne DJ. Antimicrob Agents Chemother. 1994;38(4):767-72

- They may be effective when isolates are tested susceptible
  - Piperacillin/tazobactam MIC  $\leq$  16 mg/l
  - Amoxicillin/clavulanic acid may be useful particularly for urinary tract infections

Rodríguez-Baño J *et al.* Arch Intern Med. 2008;168:1897-902

# Cephameycins

- Relevant clinical data are limited

Lee CH *et al.* J Antimicrob Chemother 2006; 58: 1074–77

- Porin loss mutations limit their value

Pangon B *et al.* J Infect Dis 1989;159:1005-6

Martinez-Martinez L *et al.* Antimicrob Agents Chemother  
1996;40:342-8

# Carbapenems

- Meropenem, imipenem, ertapenem
- Few studies have assessed their clinical effectiveness for ESBL infections
- Regarded as the treatment of choice
  - Carbapenem use was associated with lower mortality in 85 cases of *K. pneumoniae* bacteremia evaluated in a prospective, multicenter study

Paterson DL *et al.* *Clin Infect Dis* 2004; **39**: 31–37

# Fluoroquinolones

- For infections by susceptible pathogens
- Mortality rate 3/29 (10.3%) in patients with *E. coli* or *K. pneumoniae* bloodstream infections treated with ciprofloxacin vs 8/62 (12.9%) in those treated with a carbapenem

Kang CI *et al.* Antimicrob Agents Chemother. 2004;48:4574-81

- Ciprofloxacin was less effective than imipenem in a study evaluated 17 patients with ESBL *K. pneumoniae* bacteremia

Endimiani A *et al.* Clin Infect Dis 2004;38:243-51

- Fluoroquinolones constitute a reasonable choice for the treatment of UTIs by ESBL-producing, susceptible organisms

# Tigecycline

- The first marketed member of glycyclines
- 9-t-butylglycylamido derivative of minocycline
- Evades common tetracycline efflux pumps and ribosomal protection mechanisms
- Bacteriostatic mode of activity

## Tigecycline for the treatment of multidrug-resistant Enterobacteriaceae: a systematic review of the evidence from microbiological and clinical studies

Theodoros Kelesidis<sup>1,2</sup>, Drosos E. Karageorgopoulos<sup>1</sup>, Iosif Kelesidis<sup>1,3</sup> and Matthew E. Falagas<sup>1,4,5\*</sup>

<sup>1</sup>*Alfa Institute of Biomedical Sciences (AIBS), Athens, Greece;* <sup>2</sup>*Department of Medicine, Caritas St Elizabeth's Medical Center, Tufts University School of Medicine, Boston, MA, USA;* <sup>3</sup>*Department of Medicine, Montefiore Medical Center, Albert Einstein College of Medicine, NY, USA;* <sup>4</sup>*Department of Medicine, Henry Dunant Hospital, Athens, Greece;* <sup>5</sup>*Department of Medicine, Tufts University School of Medicine, Boston, MA, USA*

*Received 4 April 2008; returned 8 May 2008; revised 2 July 2008; accepted 6 July 2008*

- PubMed was searched for articles that evaluated the *in vitro* activity of tigecycline against Enterobacteriaceae with MDR or other clinically significant resistance patterns, as well as the clinical effectiveness of tigecycline against infections caused by such pathogens
- We included 26 studies that evaluated the *in vitro* susceptibility to tigecycline of MDR Enterobacteriaceae (including ESBL-producing)
- The evaluated pathogens were isolated in:  
North or Latin America (8 studies), Europe (7 studies), Asia (3 studies), Australia (1 study), or multiple continents (7 studies)
- Interpretative MIC breakpoints of susceptibility
  - FDA:  $\leq 2$  mg/l
  - EUCAST:  $\leq 1$  mg/l

# ***In vitro* susceptibility data to tigecycline per type of ESBL-producing organism**

<b>Pathogens</b>	<b>No. of studies</b>	<b>Cumulative susceptibility, % (No. of isolates)</b>	
		<b>FDA</b>	<b>EUCAST</b>
<b><i>E. coli</i></b>	16	99.8% (1636)	99.7% (737)
<b><i>Klebsiella spp</i></b>	17	92.3% (2030)	72.3% (1284)
<b><i>Enterobacter spp</i></b>	4	91.3% (69)	77.6% (49)

# Clinical effectiveness of tigecycline for infections by ESBL-producing organisms

Infection type	Pathogens	Favorable clinical outcome	Concomitant therapy
Respiratory tract infections	<i>K. pneumoniae</i>	1/2 cases	Amino-glycosides
Bloodstream infections	<i>K. pneumoniae</i>	1/2 cases	Colistin and/or meropenem
Intra-abdominal infections	<i>K. pneumoniae</i> or <i>E. coli</i>	12/15 cases	None
Urinary tract infections	<i>K. pneumoniae</i> or <i>E. coli</i>	1/2 cases	None

# Polymyxins

- Good antimicrobial activity against *E. coli* and *K. pneumoniae* (including ESBL-producing isolates)

Sader HS *et al.* Diagn Microbiol Infect Dis. 2005;52:181-6

Gales AC *et al.* Clin Microbiol Infect. 2006;12:315-21

- Rare clinical reports for use against ESBL producing Enterobacteriaceae

Karabinis A *et al.* Clin Infect Dis. 2004;38:e7-9

- Favorable effectiveness and safety profile against multidrug resistant *A. baumannii* and *P. aeruginosa* infections

Falagas ME, Kasiakou SK. Clin Infect Dis. 2005;40-1333.

Falagas ME, Michalopoulos A. Lancet. 2006;367:633

# **Antimicrobial susceptibility of multidrug-resistant Gram negative bacteria to fosfomycin**

**M. E. Falagas • M. D. Kanellopoulou •  
D. E. Karageorgopoulos • G. Dimopoulos •  
P. I. Rafailidis • N. D. Skarmoutsou • E. A. Papafrangas**

- We evaluated the antimicrobial activity of fosfomycin against MDR clinical isolates from patients in a general tertiary care hospital in Athens, Greece
- A randomly selected sample of 30 *Klebsiella pneumoniae*, 30 *Pseudomonas aeruginosa*, and 30 *Acinetobacter baumannii*
- The MIC of fosfomycin for each isolate was determined by the agar dilution method
- Provisional breakpoint of susceptibility  $\leq 64$   $\mu\text{g/ml}$

- *K. pneumoniae* isolates
  - All isolates were both ESBL and MBL (*bla*<sub>VIM-1</sub>) producers
  - MIC range: 8-64 µg/ml
  - MIC<sub>50</sub> 16 µg/ml and MIC<sub>90</sub> 32 µg/ml
  - None of the isolates was resistant
- *P. aeruginosa* isolates
  - All isolates were ESBL producers
  - MIC range: 4 to >512 µg/ml
  - MIC<sub>50</sub> 32 µg/ml and MIC<sub>90</sub> 128 µg/ml
  - 20% of the isolates were resistant to fosfomycin
- *A. baumannii* isolates
  - MIC range: 64 to >512 µg/ml
  - MIC<sub>50</sub> 256 µg/ml and MIC<sub>90</sub> >512 µg/ml

# Fosfomicin

- Among the few active agents that can be given orally
- Retains activity against ESBL isolates
- Has been proven effective for the treatment of cystitis caused by ESBL-producing pathogens

Rodríguez-Baño J *et al.* Arch Intern Med. 2008;168:1897-902

# Fosfomycin: Use Beyond Urinary Tract and Gastrointestinal Infections

**Matthew E. Falagas,<sup>1,2</sup> Konstantina P. Giannopoulou,<sup>1</sup> George N. Kokolakis,<sup>1</sup> and Petros I. Rafailidis<sup>1</sup>**

<sup>1</sup>Alfa Institute of Biomedical Sciences, Athens, Greece; and <sup>2</sup>Department of Medicine, Tufts University School of Medicine, Boston, Massachusetts

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**CID 2008:46 (1 April) • 1069**

- Aim: to compile the relevant evidence regarding the effectiveness and safety of fosfomycin against Gram-positive and/or Gram-negative bacterial infections
- We searched PubMed and Scopus (11/1971-01/2007)
- We excluded urinary tract and gastrointestinal infections
- From 1,311 potentially relevant studies, 62 studies were reviewed in detail (31 cohort studies, 17 case-reports and 9 case-series)

- 1604 patients with various Gram-positive and Gram-negative infections in various body sites being treated with fosfomycin alone or in combination with other antibiotics
- Wide range of infections: pneumonia/respiratory infections, osteomyelitis, meningitis, ear-nose-throat infections, surgical infections, obstetric and gynaecological infections, arthritis, septicemia, peritonitis, cervical lymphadenitis, eye infections, diabetic foot infections, and typhoid fever
- Most commonly isolated pathogens: staphylococci, streptococci, *P. aeruginosa*, *Enterobacter*, *Klebsiella*, *E. coli*, *Proteus*, *S. typhi*

- Cure was achieved in 1,302 (81.1%) patients
- Fosfomycin was administered alone or in combination with other antibiotics such as cefotaxime, ceftriaxone, penicillin, ampicillin, amoxicillin, clindamycin, gentamicin, or ciprofloxacin
- More than 192 patients required surgical operations or manipulations along with fosfomycin treatment

# Nitrofurantoin

- Low resistance of *E. coli* isolated from the urinary tract in this agent
- However, susceptibility of ESBL isolates appear to be moderate

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## ICU, Henry Dunant Hospital, Athens, Greece

Michalopoulos A, MD, Director, ICU, Henry Dunant Hospital

Rellos K, MD, Associate Director, ICU, Henry Dunant Hospital

Rizos M, MD, Attending Physician, ICU, Henry Dunant  
Hospital

Mastora Z, MD, Attending Physician, ICU, Henry Dunant Hospital

Virgili S, MD, Attending Physician, ICU, Henry Dunant Hospital

## University Hospital, Heraklion, Athens, Greece

Samonis G, MD, Chairman, Department of Medicine, Univ.  
Hospital, Heraklion

Kofterides D, MD, Lecturer, Univ. Hospital, Heraklion

Mantadakis E, MD, Attending Physician, Univ. Hospital,  
Heraklion

## ICU, Henry Dunant Hospital, Athens, Greece

Michalopoulos A, MD, Director, ICU, Henry Dunant Hospital

Rellos K, MD, Associate Director, ICU, Henry Dunant Hospital

Rizos M, MD, Attending Physician, ICU, Henry Dunant  
Hospital

Mastora Z, MD, Attending Physician, ICU, Henry Dunant Hospital

Virgili S, MD, Attending Physician, ICU, Henry Dunant Hospital

## University Hospital, Heraklion, Athens, Greece

Samonis G, MD, Chairman, Department of Medicine, Univ.  
Hospital, Heraklion

Kofterides D, MD, Lecturer, Univ. Hospital, Heraklion

Mantadakis E, MD, Attending Physician, Univ. Hospital,  
Heraklion

Study group on Gram-negative bacterial infections  
Alfa Institute of Biomedical Sciences (AIBS),  
Athens, Greece ([www.aibs.gr](http://www.aibs.gr))

Falagas M, MD, Director, AIBS

Rafailidis P, MD, Researcher, AIBS

Kapaskelis A, MD, Researcher, AIBS

Karageorgopoulos D, MD, Researcher, AIBS

Kopterides P, MD, Researcher, AIBS

Kasiakou S, MD, Research Fellow, AIBS

Bliziotis I, MD, Research Fellow, AIBS

Siempos I, MD, Research Fellow, AIBS

Vardakas K, MD, Research Fellow, AIBS

Matthaiou D, MD, Research Fellow, AIBS

Vouloumanou E, MD, Research Fellow, AIBS

Korbila I, MD, Research Fellow, AIBS

Alexiou MD, Research Fellow, AIBS ,

Kastoris A, MD, Research Fellow, AIBS

Ioannidou E, MD, Research Fellow, AIBS

Sermaides G, Statistician, AIBS

Chelvatzoglou F, RN, Clinical Research Co-ordinator, AIBS

Nenti A, RN, Data Manager, AIBS