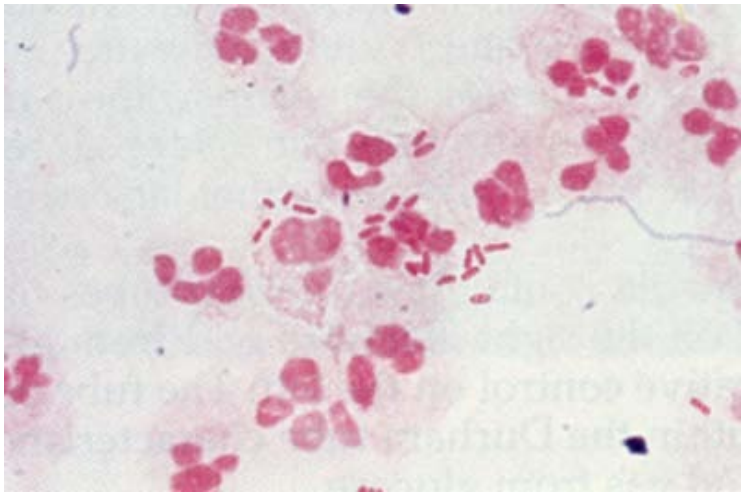
Carbapenem Resistance in *Enterobacteriaceae*



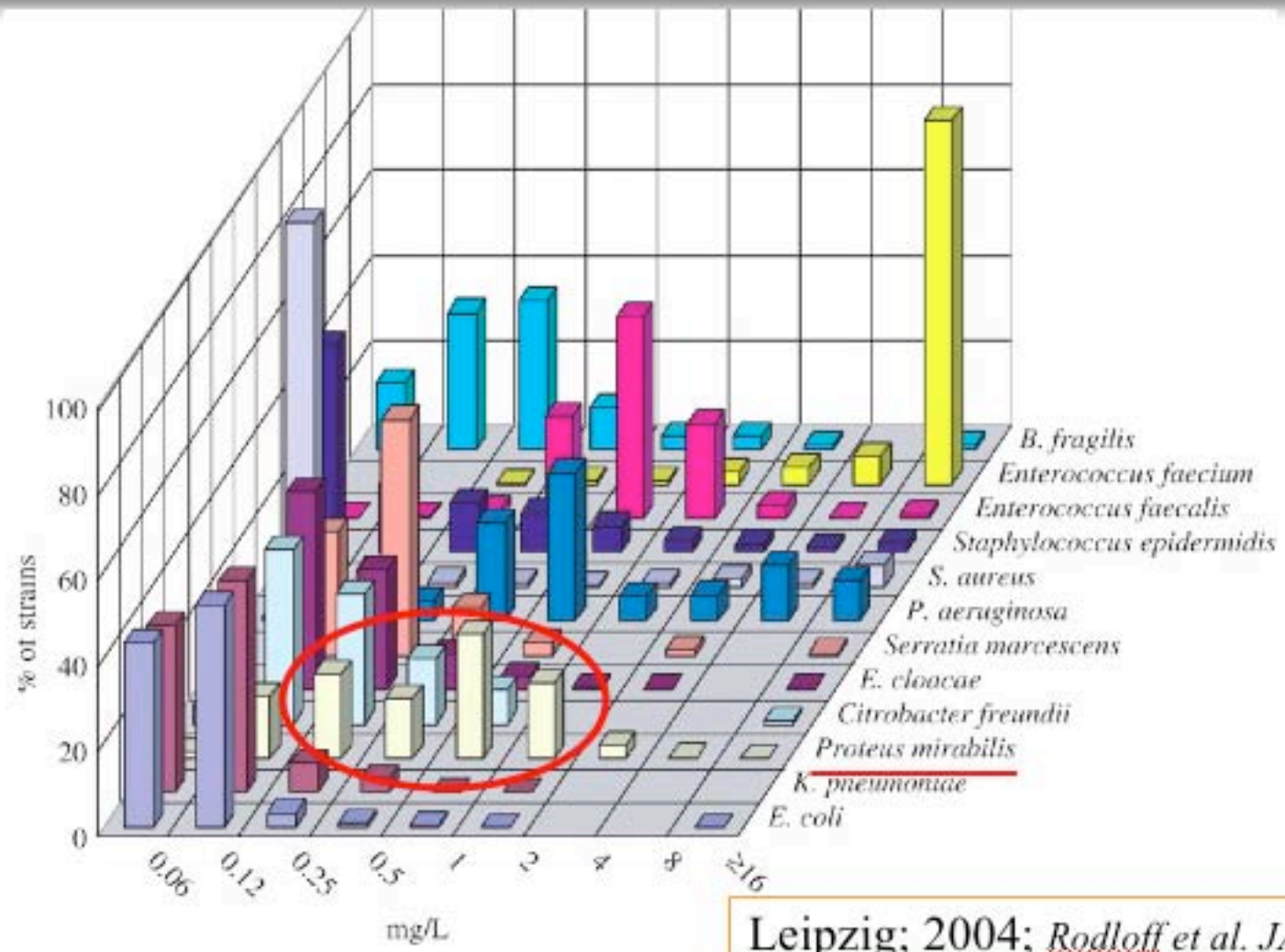
P. Nordmann

CHU de Bicêtre,

Unité EA; Mécanismes Emergents de Résistance

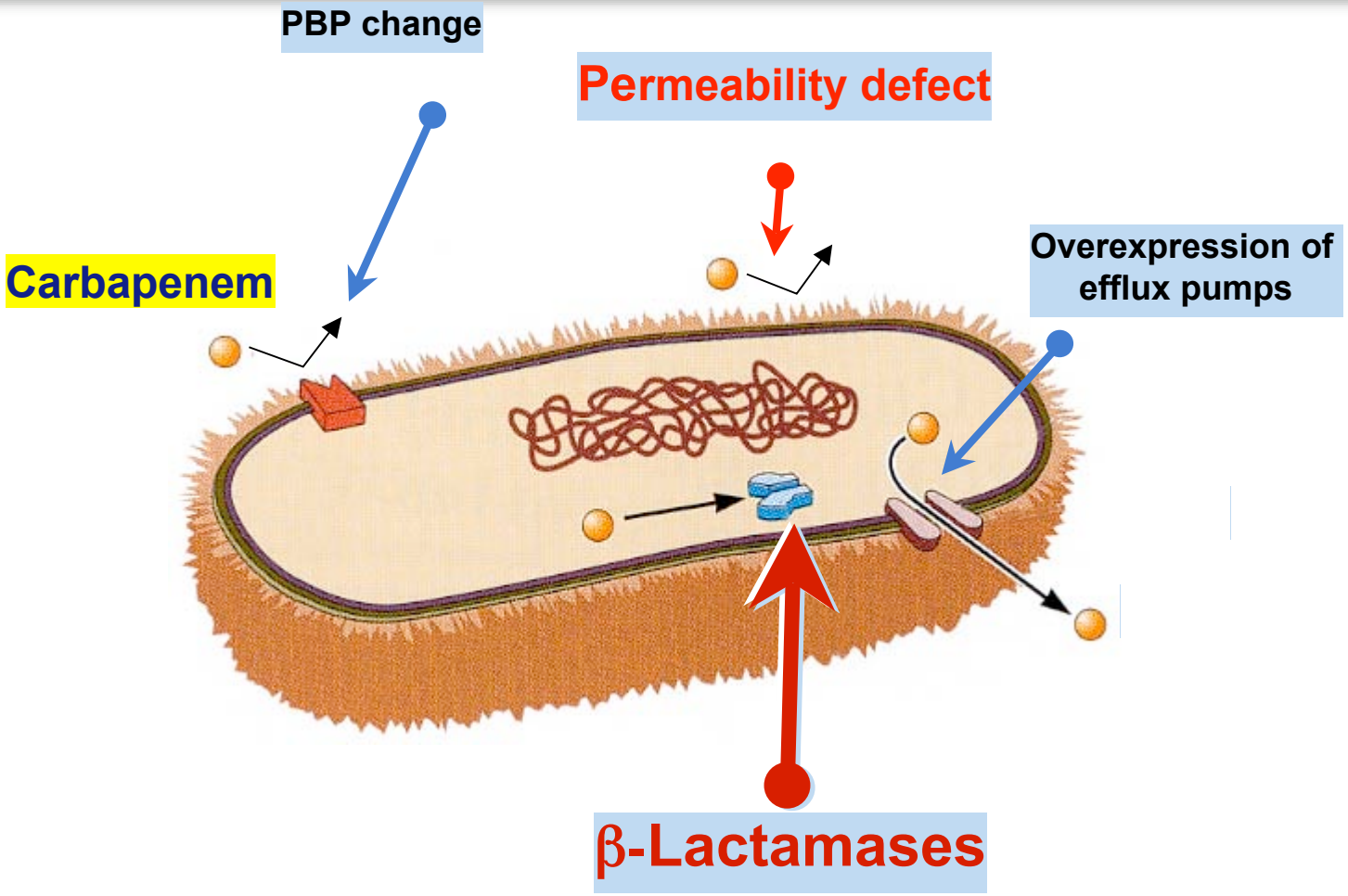
aux antibiotiques

Enterobacteriaceae; wild-type susceptibility to carbapenems

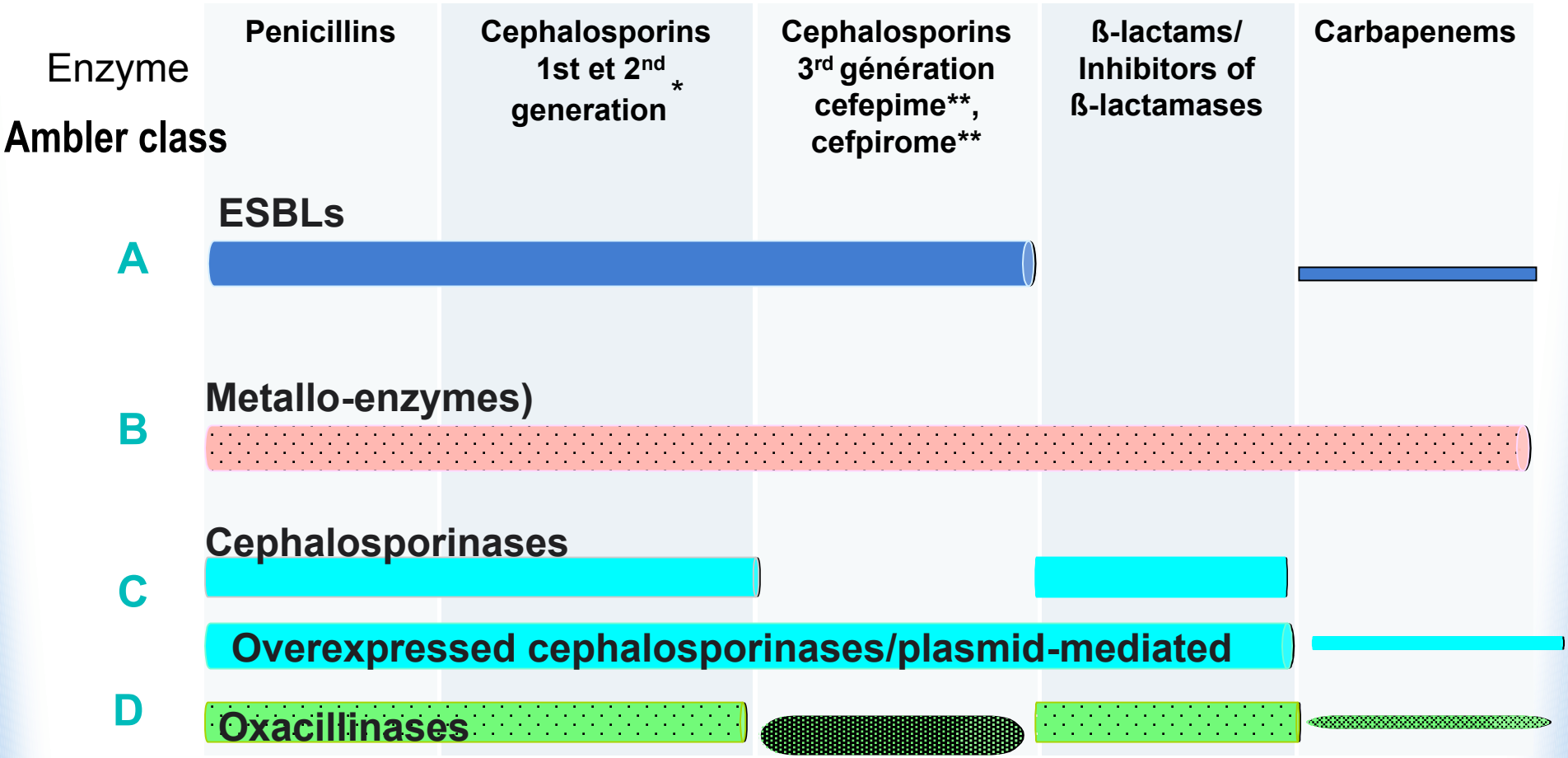


Leipzig; 2004; *Rodloff et al. JAC 2006*

Carbapenem Resistance in *Enterobacteriaceae*



Spectrum of activity of broad-spectrum ß-lactamases



* Cephamycins excluded for ESBLs

** Cefepime, cefpirome excluded for overexpressed cephalosporinase

The carbapenemases in *Enterobacteriaceae*

- **Chromosomally-encoded ESBLs**
- **Plasmid-mediated ESBLs**
- **Plasmid-mediated metallo-enzymes**
- **Rare plasmid-encoded cephalosporinase**
- **Rare oxacillinases**

The class A ESBLs with carbapenemase activity

✓ **Chromosome-encoded**

. NMCA	→	*Enterobacter cloacae*
. IMI-1	→	*Enterobacter cloacae*
. Sme-1, -2	→	*Serratia marcescens*
. SFC-1	→	*Serratia fonticola*
. SHV-38	→	*Klebsiella pneumoniae*

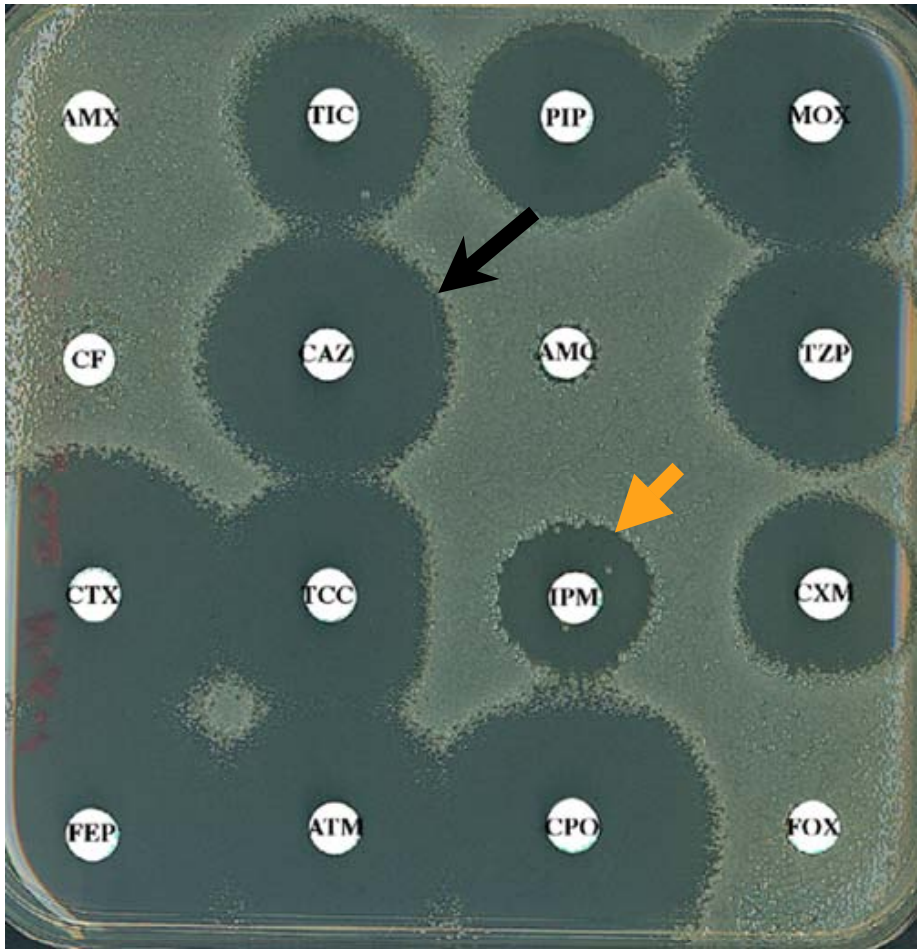
✓ **Plasmid-encoded**

. GES-3,-4,-5	→	*K. pneumoniae, E. coli, E. cloacae*
. IMI-2,-3	→	*Enterobacter asburiae, E. cloacae*
. KPC-1, 2, 3, 4	→	*K. pneumoniae, E. cloacae, Salmonella, E. coli*

The chromosome-encoded class A carbapenemases

Enzymes	Origin	Date of isolation	Bacteria	Number	Clinical specimen	Publication
Sme-1	London (UK)	1982	*S. marcescens*	2	?	Yang et al. 1990, AAC 34 ; 755-758
IMI-1	California (USA)	1984	*E. cloacae*	2	Wound, bile	Rasmussen et al. 1996, AAC : 40 ; 2080-2086
Sme-1	Minnesota (USA)	1985	*S. marcescens*	1	?	Queenan et al. 2000, AAC; 44 ; 3035-3039
NmcA	Paris (France)	1990	*E. cloacae*	1	Subactaneous abscess	Nordmann et al. 1993, AAC ; 37 ; 939-946
Sme-2	UCLA (USA)	1992	*S. marcescens*	5	?	Queenan et al. 2000, AAC; 44 ; 3035-3039
Sme-2	Boston (USA)	1994-1999	*S. marcescens*	19	?	Queenan et al. 2000, AAC; 44 ; 3035-3039
Sme-1	Chicago (USA)	1999	*S. marcescens*	2	Thigh culture ascitis fluid	Gales et al. 2001, DMID, 39 ; 125-127
NmcA	Seattle (USA)	2003	*E. cloacae*	1	Blood	Pottumarth et al. 2003, EID
NmcA	Buenos Aires (Argentina)	2003	*E. cloacae*	1	?	Fernandez et al. 2004, AAC ; 48 : 1068-1069
SFC-1	Vila Real (Portugal)	2000	*S. fonticola*	1	Environment	Henriques et al., 2004, AAC ; 2321-2324

The carbapenemase NmcA - *E. cloacae*



The ß-lactamase SHV-38 from *K. pneumoniae*

- **Reduced susceptibility to 3rd GC and IPM**
- **Chromosomally-encoded *bla*$_{SHV-38}$ gene**
- **SHV-38 (A146V as compared to SHV-1)**

Poirel & Nordmann AAC, 2003

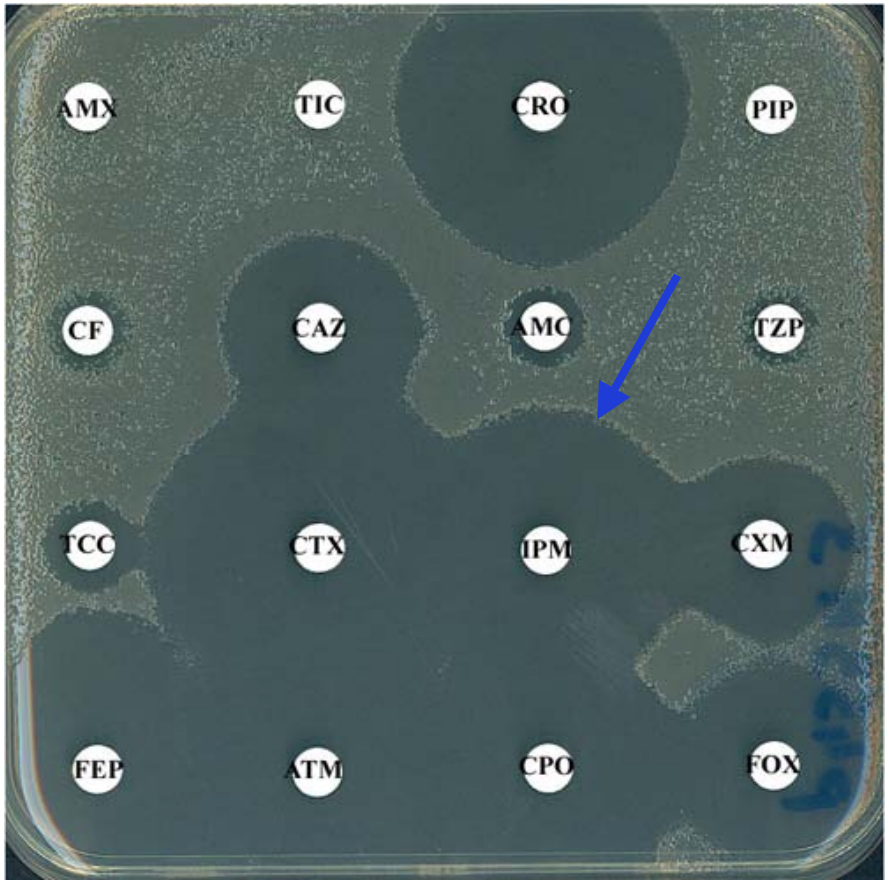
TABLE 1. MICs of β-lactams for *K. pneumoniae* Lor-1, *E. coli* DH10B(pLP-1), *E. coli* DH10B(pLP-2), and *E. coli* DH10B (reference strain)

β-Lactam(s)*	MIC (μg/ml) for:			
	K. pneumoniae Lor-1 (SHV-38)	*E. coli* DH10B (pLP-1) (SHV-38)	*E. coli* DH10B (pLP-2) (SHV-1)	*E. coli* DH10B
SHV-38	SHV-1			
Amoxicillin	>512	>512	>512	4
Amoxicillin + CLA	>512	>512	64	4
Ticarcillin	>512	>512	>512	4
Ticarcillin + CLA	>512	>512	128	4
Piperacillin	>512	>512	>512	2
Piperacillin + TZB	>512	>512	256	2
Cephalothin	128	512	32	4
Cefuroxime	4	16	8	4
Cefoxitin	4	8	8	8
Ceftazidime	16	64	2	0.25
Ceftazidime + CLA	2	8	1	0.25
Cefotaxime	0.25	0.5	0.12	0.06
Ceftriaxone	0.12	0.25	0.06	0.06
Cefepime	2	4	0.25	0.03
Cefpirome	2	4	0.5	0.03
Cefpirome + CLA	0.12	0.5	0.06	0.03
Aztreonam	2	4	0.25	0.12
Moxalactam	1	2	0.25	0.06
Moxalactam + CLA	0.25	0.5	0.12	0.12
Imipenem	0.25	0.5	0.06	0.06
Meropenem	0.06	0.12	0.06	0.06

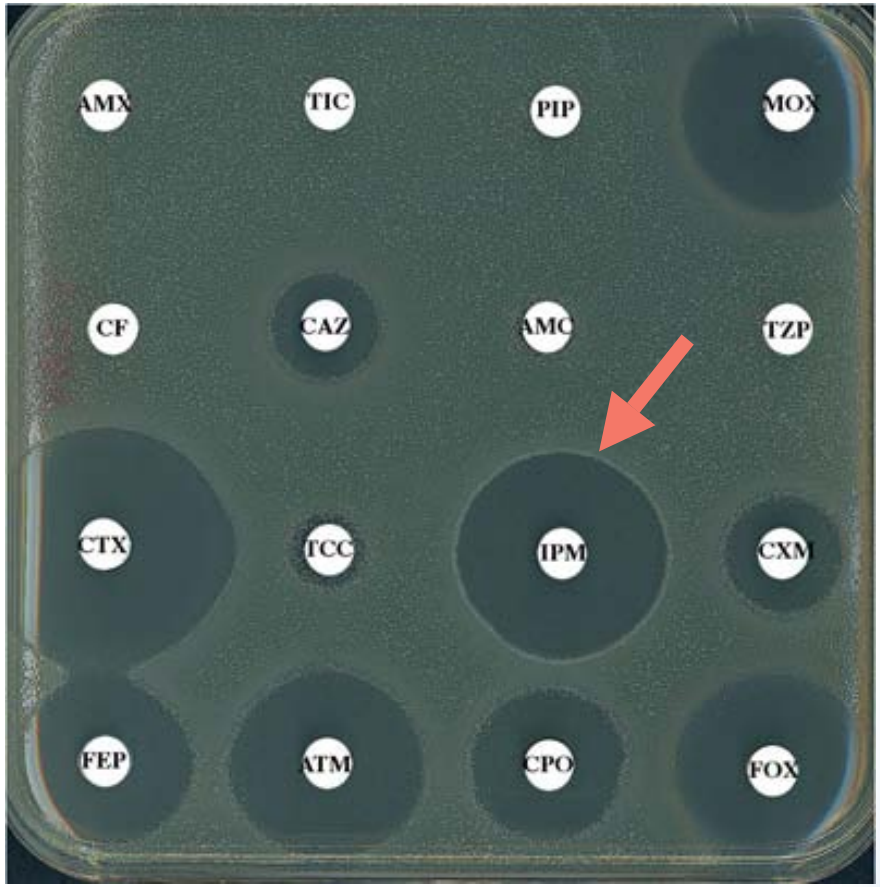
* CLA, clavulanic acid at a fixed concentration of 2 μg/ml; TZB, tazobactam at a fixed concentration of 4 μg/ml.

SHV-1/SHV-38

E. coli (pSHV-1)



E. coli (pSHV-38)



The class A ESBLs with carbapenemase activity

✓ **Chromosome-encoded**

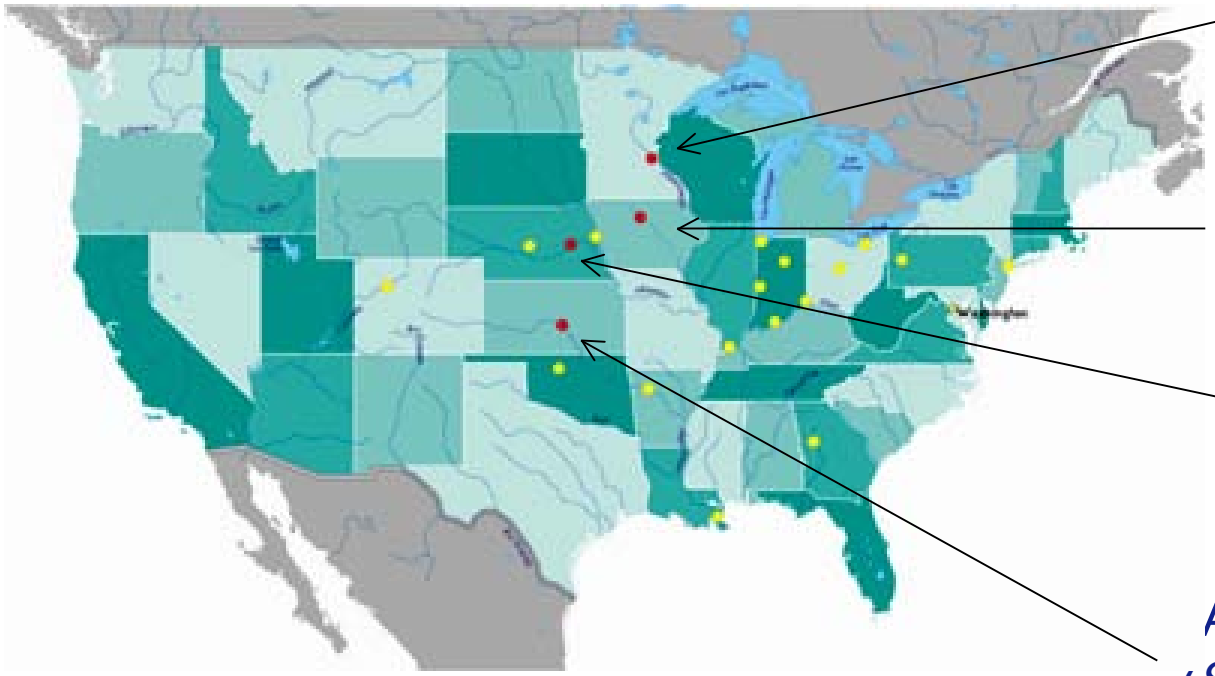
. NMCA	→	*Enterobacter cloacae*
. IMI-1	→	*Enterobacter cloacae*
. Sme-1, -2	→	*Serratia marcescens*
. SFC-1	→	*Serratia fonticola*
. SHV-38	→	*Klebsiella pneumoniae*

✓ **Plasmid-encoded**

. GES-3,-4,-5	→	*K. pneumoniae, E. coli, E. cloacae*
. IMI-2,-3	→	*Enterobacter asburiae, E. cloacae*
. KPC-1, 2, 3, 4	→	*K. pneumoniae, E. cloacae, Salmonella, E. coli*

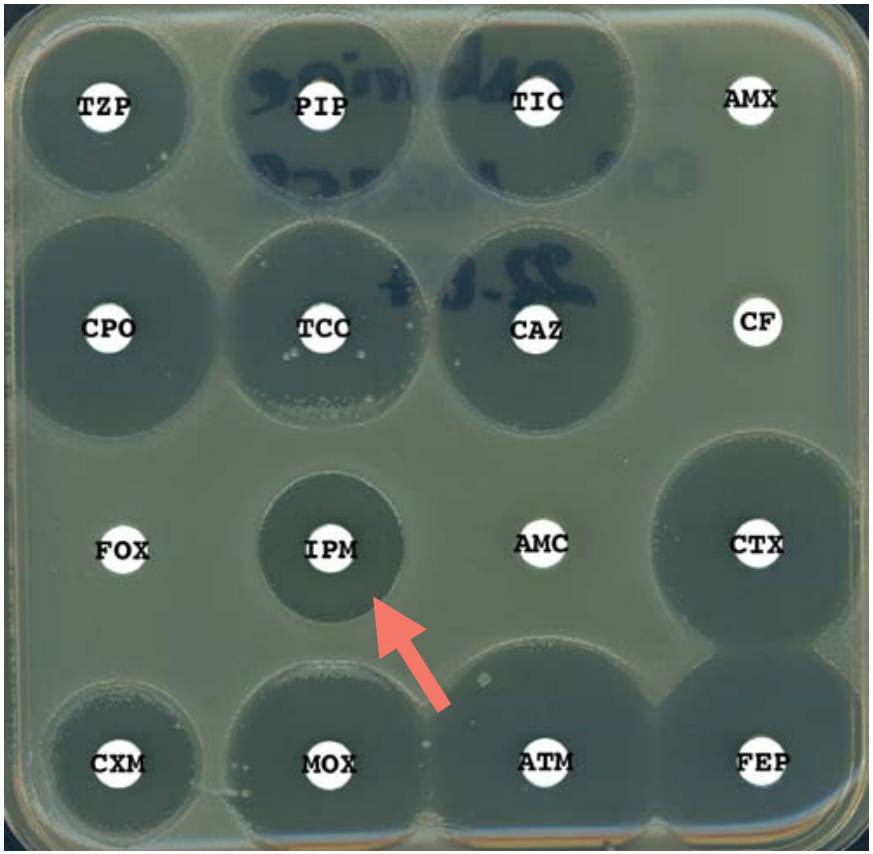
Plasmid-mediated class A carbapenemase; IMI-2

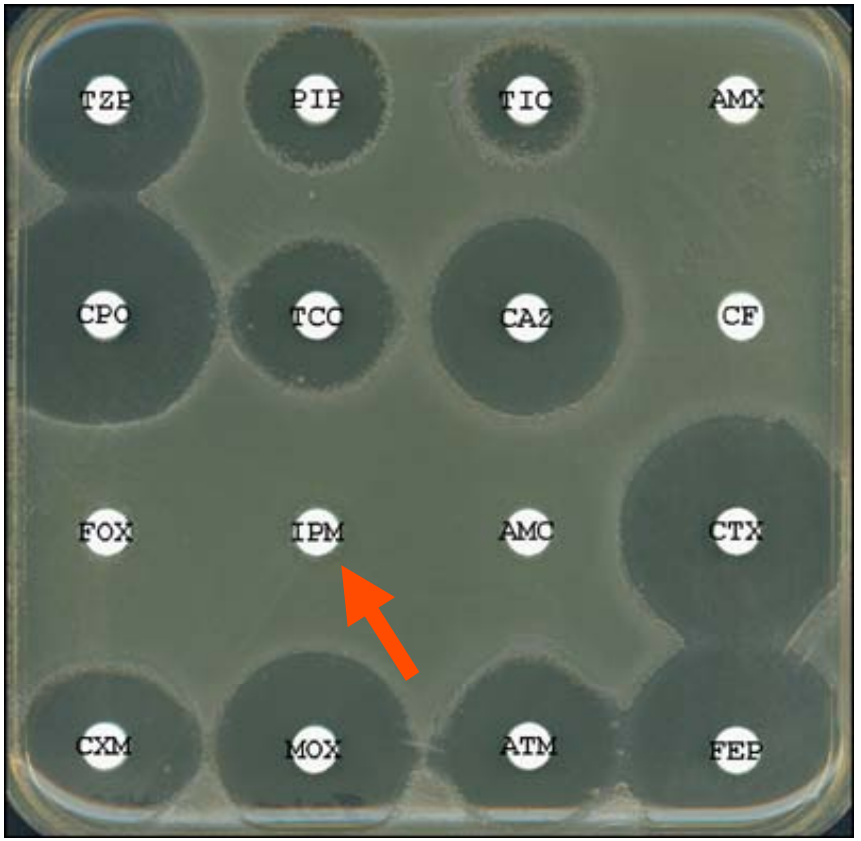
- **1,861 Ampicillin-resistant G$^-$ strains isolated from US rivers (1999-2001)**
- **30 imipenem-resistant G$^-$ strains (Ash et al., Emerg Infect Dis, 2002)**
- **22 *Enterobacter asburiae* resistant to imipenem**
- ***bla*$_{IMI-2}$ gene located on a large-size plasmid**
- **11 nucleotide substitutions, 2 AA changes (N35D, Y105H)**



Aubron , Poirel, Nordmann, Emerg Infect Dis 2005

E. asburiae reference strain/*E. asburiae* IMI-2





Class A carbapenemases; the threat of KPC +++

ORIGINAL INVESTIGATION

Rapid Spread of Carbapenem-Resistant *Klebsiella pneumoniae* in New York City

A New Threat to Our Antibiotic Armamentarium

Simona Bratu, MD; David Landman, MD; Robin Haag, RN; Rose Recco, MD; Antonella Eramo, RN; Maqsood Alam, MD; John Quale, MD

Background: Carbapenem antibiotics are used to treat serious infections caused by extended-spectrum β-lactamase–carrying pathogens. Carbapenem resistance has been unusual in isolates of *Klebsiella pneumoniae*. In this study, the prevalence and molecular epidemiologic characteristics of carbapenem-resistant *K pneumoniae* are analyzed, and the experience involving 2 hospital outbreaks is described.

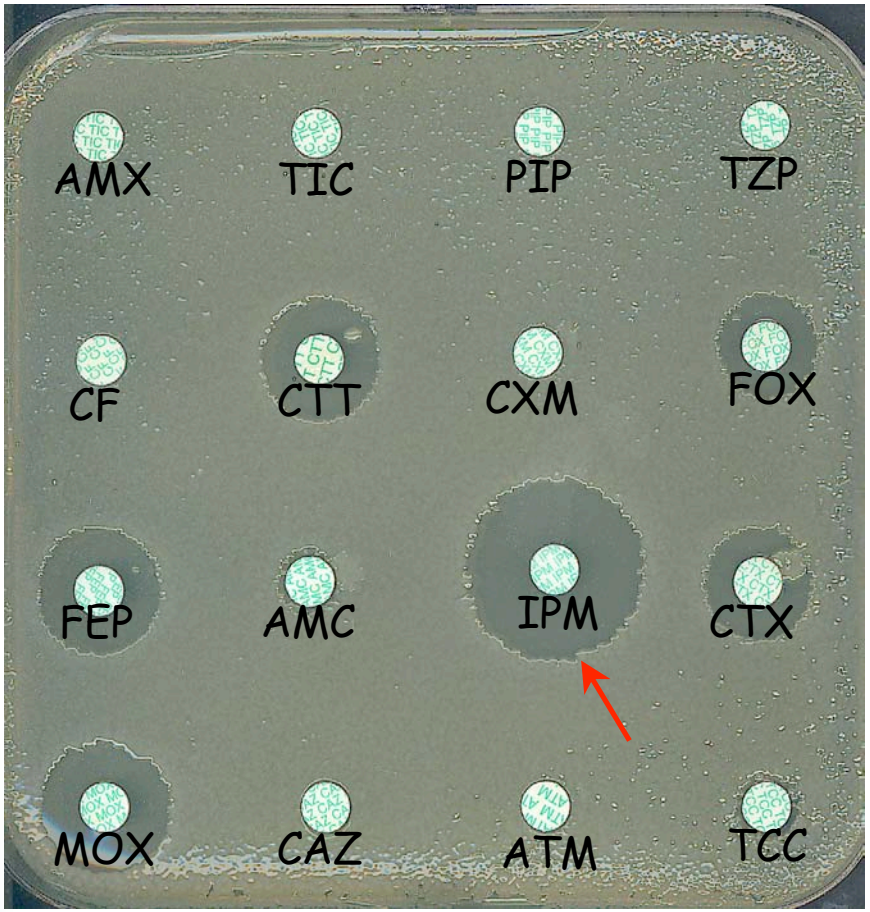
Methods: A citywide surveillance study was conducted in hospitals in Brooklyn. An observational study involving subsequent outbreaks at 2 hospitals was undertaken. Isolates were genetically fingerprinted by ribotyping and were examined for the presence of KPC-type carbapenem-hydrolyzing β-lactamases.

Results: Of 602 isolates of *K pneumoniae* collected during the citywide surveillance study, 45% had extended-spectrum β-lactamases. Of the extended-spectrum β-lactamase–producing isolates, 3.3% carried the carbapenem-hydrolyzing β-lactamase KPC-2. Several isolates were reported by the clinical microbiology laboratories as being susceptible to imipenem. Although all the isolates were resistant using agar diffusion methods, minimal inhibitory concentrations of imipenem were substantially lower for several isolates using standard broth microdilution tests and were highly dependent on the inoculum used. Two hospitals experienced the rapid spread of carbapenem-resistant isolates involving 38 patients. Overall 14-day mortality for bacteremic patients was 47%. Most isolates belonged to a single ribotype.

Conclusions: Carbapenem-resistant *K pneumoniae* isolates are rapidly emerging in New York City. The spread of a strain that possesses a carbapenem-hydrolyzing β-lactamase has occurred in regional hospitals. Because these isolates are resistant to virtually all commonly used antibiotics, control of their spread is crucial. However, automated systems used for susceptibility testing may not accurately identify all these isolates, which will severely hamper control efforts.

Arch Intern Med. 2005;165:1430-1435

ESBLs of a novel type; KPC



ANTIMICROBIAL AGENTS AND CHEMOTHERAPY, Apr. 2001, p. 1151–1161 Vol. 45, No. 4
0066-4804/01/$04.00+0 DOI: 10.1128/AAC.45.4.1151–1161.2001

Novel Carbapenem-Hydrolyzing β-Lactamase, KPC-1, from a Carbapenem-Resistant Strain of *Klebsiella pneumoniae*

HESNA YIGIT,[1] ANNE MARIE QUEENAN,[2] GREGORY J. ANDERSON,[1] ANTONIO DOMENECH-SANCHEZ,[3] JAMES W. BIDDLE,[1] CHRISTINE D. STEWARD,[1] SEBASTIAN ALBERTI,[4] KAREN BUSH,[2] AND FRED C. TENOVER[1]*

Hospital Infections Program, National Center for Infectious Diseases, Centers for Disease Control and Prevention, Atlanta, Georgia 30333[1]; The R. W. Johnson Pharmaceutical Research Institute, Raritan, New Jersey 08869[2]; and Unidad de Investigacion, Hospital Son Dureta, Andrea Doria, Palma de Mallorca, 07014,[4] and Área de Microbiologia, Universidad de las Islas Baleares, Crtra. Valldemosa, Palma de Mallorca, 07071,[3] Spain

Received 19 September 2000/Returned for modification 21 November 2000/Accepted 23 January 2001

✓KPC-1:
- 45% Sme-1, 44% NMCA and IMI-1
- plasmid encoded (50-kb)

✓Imipenem resistance inhibited by clavulanic acid

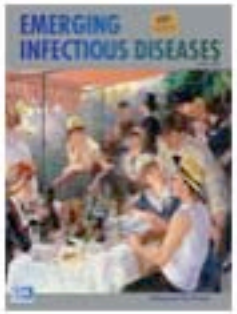
MICs of β-lactams for KPC-1 producers

	MICs (μg/ml)		
	K. pneumoniae 1534	*E. coli* HB101 (KPC-1)	*E.coli* HB101
Ampicillin	>64	>64	4
Cefotaxime	64	8	≤ 1
Ceftazidime	32	8	≤ 0.5
Imipenem	16	8	≤ 0.25
Imipenem+cla	2	0.5	≤ 0.25
Meropenem	16	4	≤ 0.25
Aztreonam	>64	32	≤ 0.5

Spread of KPC producers

The KPCs

Emerging Infectious Diseases • www.cdc.gov/eid • Vol. 12, No. 10, October 2006



KPC Type β-Lactamase, Rural Pennsylvania

Jonathan Pope,* Jennifer Adams,† Yohei Doi,† Dora Szabo,†‡ and David L. Paterson†

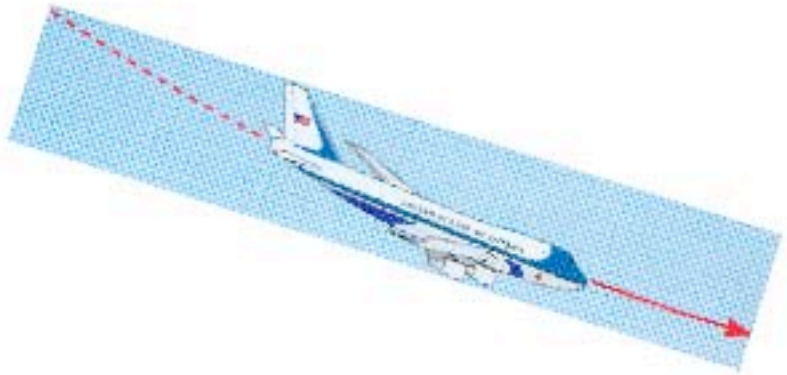
*Dubois Regional Medical Center, Dubois, Pennsylvania, USA; †University of Pittsburgh Medical Center, Pittsburgh, Pennsylvania, USA; and ‡Semmelweis University, Budapest, Hungary

ORIGINAL INVESTIGATION

Rapid Spread of Carbapenem-Resistant *Klebsiella pneumoniae* in New York City

A New Threat to Our Antibiotic Armamentarium

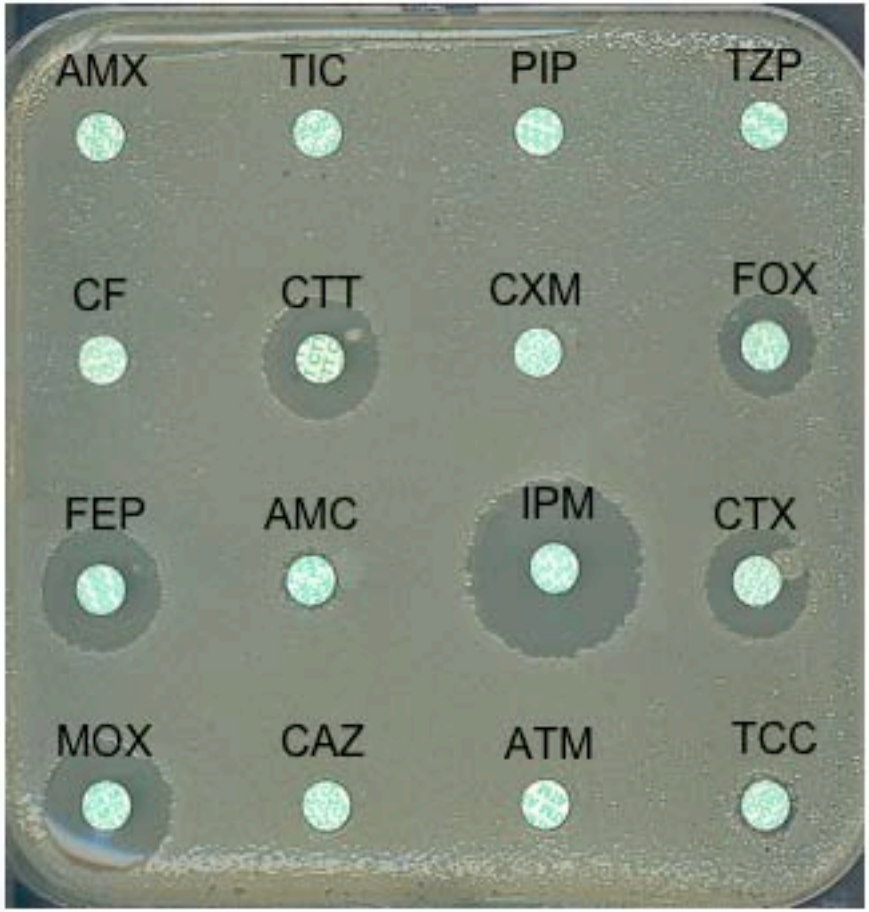
Simona Bratu, MD; David Landman, MD; Robin Haag, RN; Rose Recco, MD; Antonella Eramo, RN; Maqsood Alam, MD; John Quale, MD



… KPC in France

ANTIMICROBIAL AGENTS AND CHEMOTHERAPY, Oct. 2005, p. 4423–4424 Vol. 49, No. 10
0066-4804/05/$08.00+0 doi:10.1128/AAC.49.10.4423–4424.2005

Plasmid-Mediated Carbapenem-Hydrolyzing β-Lactamase KPC in a *Klebsiella pneumoniae* Isolate from France



Thierry Naas
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75014 Paris, France

… KPC in the world, December 2006

Villegas & Quinn AAC 2006; Navon-Venezia & Carmeli AAC 2006

KPC detection; clavulanic acid inhibition ?

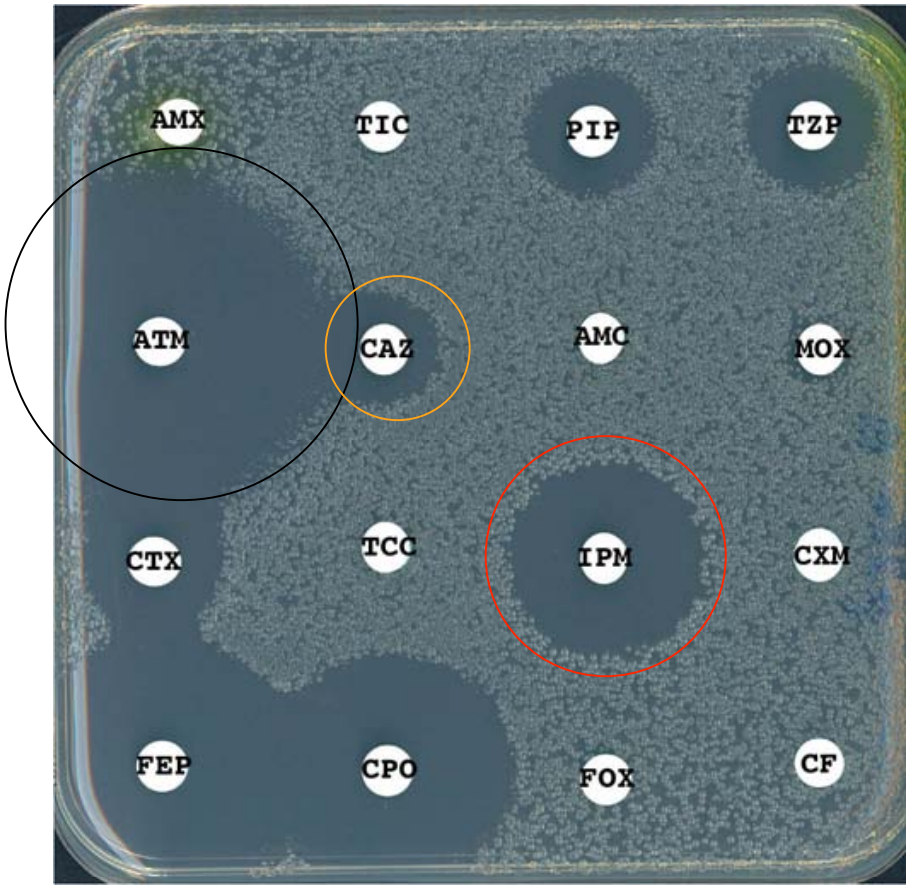
CAZ TCC FEP

AZT TCC IMP

Plasmid-mediated metallo-carbapenemases; class B +++

IMP/VIM

Reference *E. coli* strain (VIM-2)



Metallo-carbapenemases, *Enterobacteriaceae*; 2006

Heterogeneous expression of metallo-carbapenemases in *Enterobacteriaceae*

		MIC (mg/L)	
		imipenem	meropenem
S. marcescens	IMP-type	32 - >128	128 - >128
	VIM-type	64	64
K. pneumoniae	IMP-type	0.25 - >128	0.25 - 64
	VIM-type	2	0.5
Enterobacter *Citrobacter* *E. coli* *S. flexneri*	IMP-type	0.25 - 8	0.25 - 8
	VIM-type	1 - 8	0.5 - 4

Metallo-carbapenemase; detection

Walsh *et al*. JCM, 2002, 2755-9

Association of broad-spectrum ß-lactamases; metalloenzyme + ESBL

ANTIMICROBIAL AGENTS AND CHEMOTHERAPY, Dec. 2004, p. 4929–4930
0066-4804/04/$08.00+0 DOI: 10.1128/AAC.48.12.4929–4930.2004

Vol. 48, No. 12

Letter to the Editor

First Detection of a Carbapenem-Hydrolyzing Metalloenzyme in an *Enterobacteriaceae* Isolate in France

Marie-Frédérique Lartigue
Laurent Poirel
Patrice Nordmann*
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Faculté de Médecine Paris-Sud
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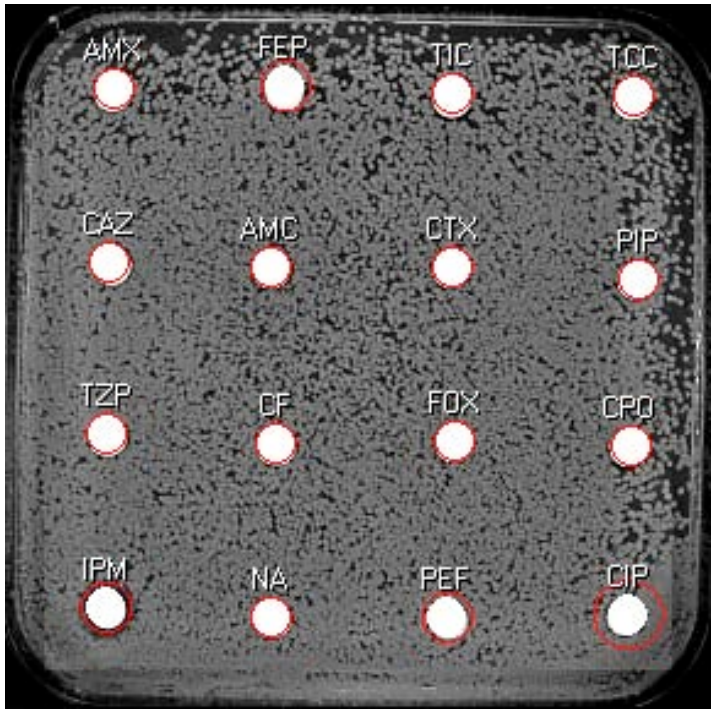
94275 Le Kremlin-Bicêtre, France



Carbapenemase VIM-1
+ ESBL SHV-5

Journal of Antimicrobial Chemotherapy (2006) **57**, 142–145
doi:10.1093/jac/dki389
Advance Access publication 10 November 2005
JAC

First outbreak of multidrug-resistant *Klebsiella pneumoniae* carrying bla_{VIM-1} and bla_{SHV-5} in a French university hospital

Najiby Kassis-Chikhani[1,2], Dominique Decré[3]*, Valérie Gautier[3], Béatrice Burghoffer[3], Faouzi Saliba[4], Daniele Mathieu[1], Didier Samuel[4], Denis Castaing[4], Jean-Claude Petit[3], Elisabeth Dussaix[1] and Guillaume Arlet[3]

Detection

K. pneumoniae
IMP-4 + SHV-12

Poirel, Pham & Nordmann, Pathology, 2004, 36; 266-7.

…. and the worst to come; three broad-spectrum ß-lactamases in a single isolate ?

ANTIMICROBIAL AGENTS AND CHEMOTHERAPY, Dec. 2006, p. 4198–4201 Vol. 50, No. 12
0066-4804/06/$08.00+0 doi:10.1128/AAC.00663-06

Emergence of Multidrug-Resistant *Klebsiella pneumoniae* Isolates Producing VIM-4 Metallo-β-Lactamase, CTX-M-15 Extended-Spectrum β-Lactamase, and CMY-4 AmpC β-Lactamase in a Tunisian University Hospital▽

Sonia Ktari,[1] Guillaume Arlet,[2]* Basma Mnif,[1] Valérie Gautier,[2] Fouzia Mahjoubi,[1] Mounir Ben Jmeaa,[3] Mounir Bouaziz,[4] and Adnane Hammami[1]

TABLE 3. MICs of various β-lactams for the *Klebsiella pneumoniae* isolate recovered from patient 1

Inhibitor(s)*	MIC (μg/ml)					
	Cefotaxime	Ceftazidime	Cefepime	Aztreonam	Imipenem	Meropenem
None	256	256	128	128	32	2
EDTA	64	64	32	128	0.25	0.06
CA	64	128	8	8	32	2
EDTA and CA	4	2	0.06	8	0.25	0.06

* EDTA, 0.4 mM; clavulanic acid (CA), 2 μg/ml.

Plasmid-mediated cephalosporinase; class C

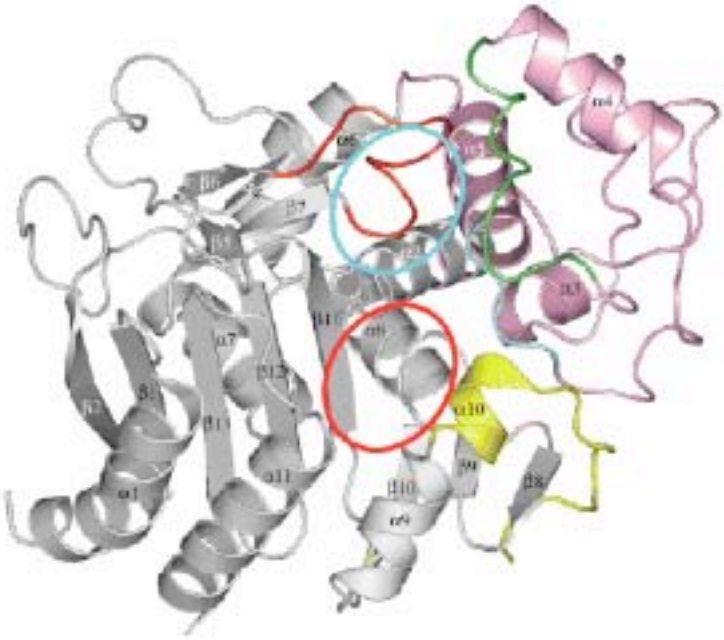
Molecular Microbiology (2006) 60(4), 907–916

doi:10.1111/j.1365-2958.2006.05146.x
First published online 16 March 2006

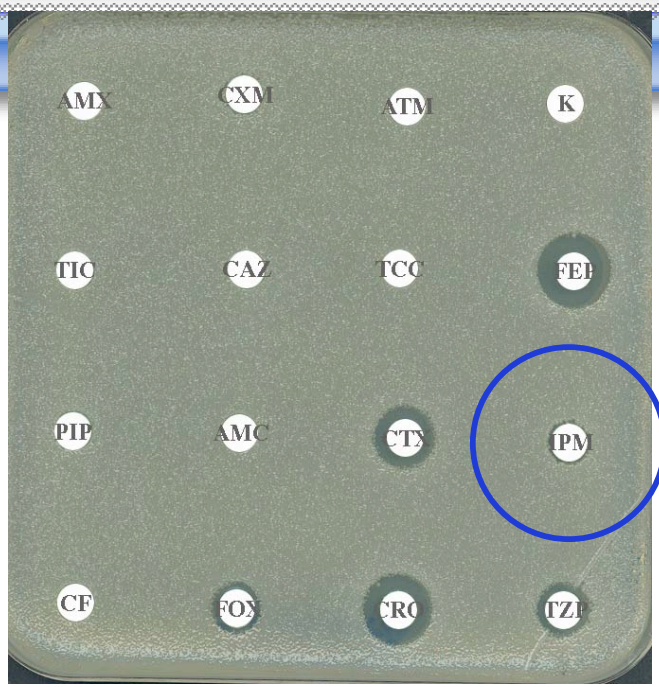
Structural basis for the extended substrate spectrum of CMY-10, a plasmid-encoded class C β-lactamase

Jae Young Kim,[1] Ha Il Jung,[2,3] Young Jun An,[1,2] Jung Hun Lee,[3] So Jung Kim,[2,4] Seok Hoon Jeong,[5] Kye Joon Lee,[1] Pann-Ghill Suh,[4] Heung-Soo Lee,[1] Sang Hee Lee[2*] and Sun-Shin Cha[2†]

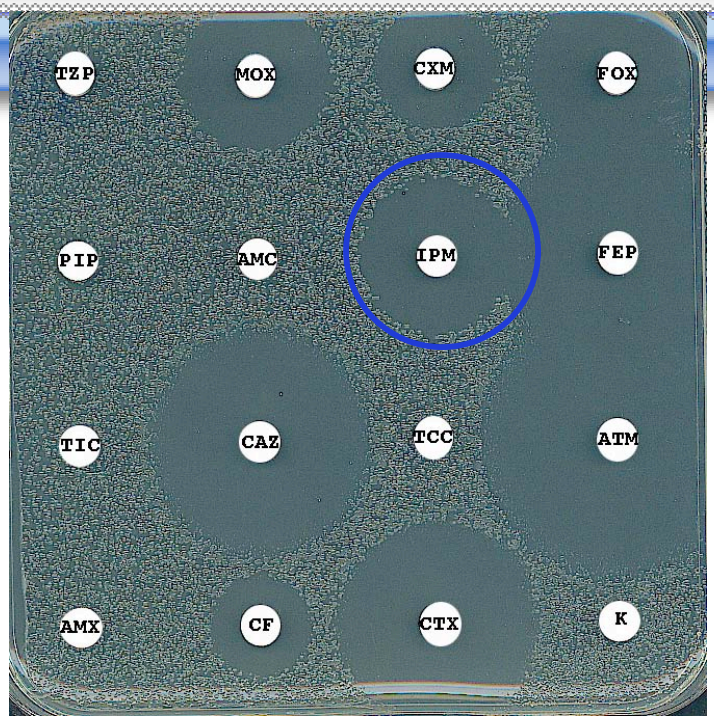
[1]*School of Biological Sciences, Seoul National University, Seoul 151-742, Republic of Korea.*
[2]*Beamline Division, Pohang Accelerator Laboratory, Pohang, Kyungbuk 790-784, Republic of Korea.*
[3]*Department of Biological Sciences, Myongji University, Yongin, Kyunggido 449-728, Republic of Korea.*
[4]*Department of Life Science, Pohang University of Science and Technology, Pohang, Kyungbuk 790-784, Republic of Korea.*
[5]*Department of Laboratory Medicine, Kosin University College of Medicine, Busan 602-702, Republic of Korea.*



Multidrug resistance in *K.pneumoniae*; plasmid-mediated OXA-48; class D



K. pneumoniae



E. coli reference (OXA-48)

….from *Shewanella* oneidensis…

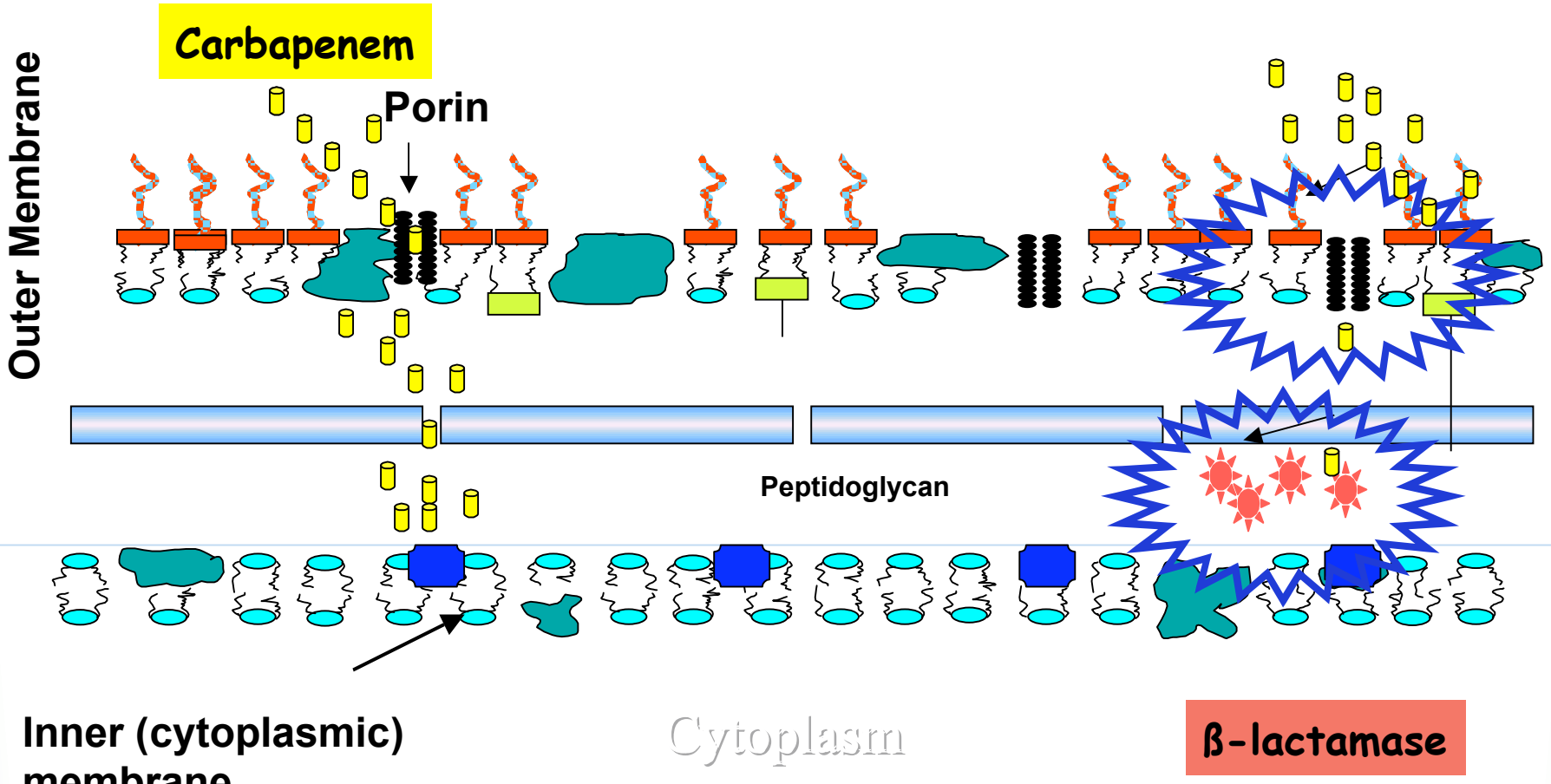
Poirel, Héritier, Tolun, Nordmann AAC 2004; Poirel, Heritier, Nordmann, Tolun AAC 2004

ANTIMICROBIAL AGENTS AND CHEMOTHERAPY, June 2002, p. 2004–2006 Vol. 46, No. 6
0066-4804/02/$04.00+0 DOI: 10.1128/AAC.46.6.2004–2006.2002

Chromosome-Encoded Class D β-Lactamase OXA-23 in *Proteus mirabilis*

R. Bonnet,[1]* H. Marchandin,[2] C. Chanal,[1] D. Sirot,[1] R. Labia,[3] C. De Champs,[1] E. Jumas-Bilak,[4] and J. Sirot[1]

Most frequent mechanisms of resistance +++; combined mechanisms



Combined mechanisms of resistance

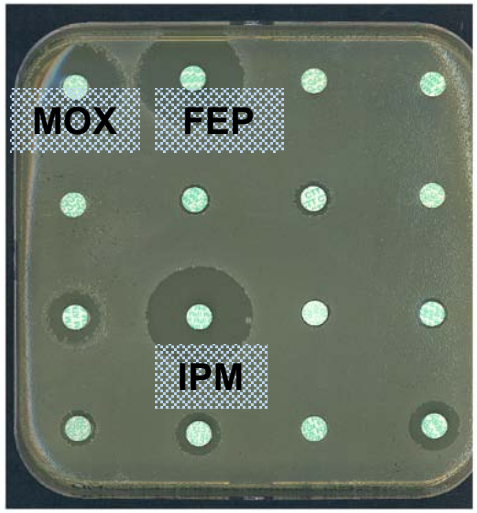
***Enterobacteriaceae* (++*Enterobacter* spp.)**

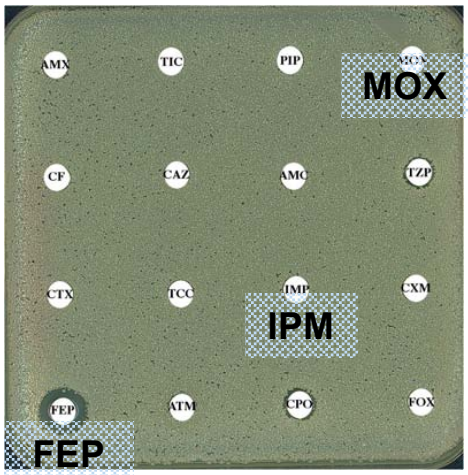
- Overproduced cephalosporinase
- Plasmid-mediated cephalosporinase
- Plasmid-mediated ESBL

Resistance to CIIIG

Decreased OM permeability

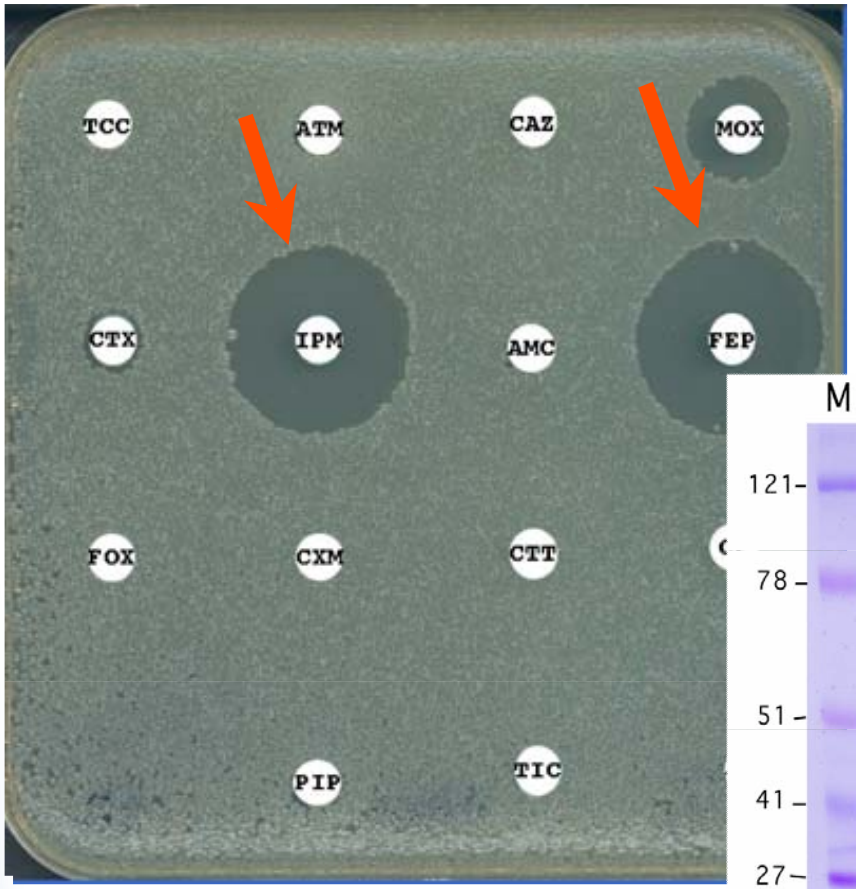
Additional Resistance to carbapenems



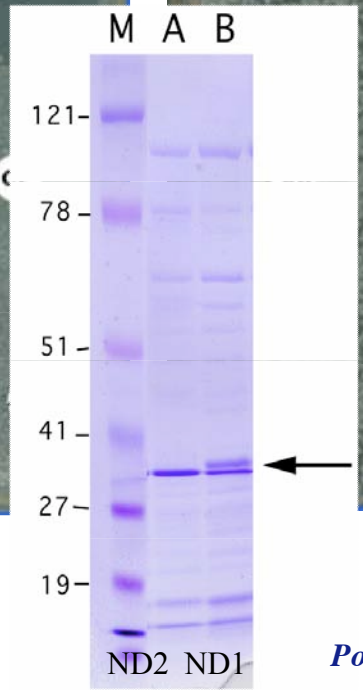


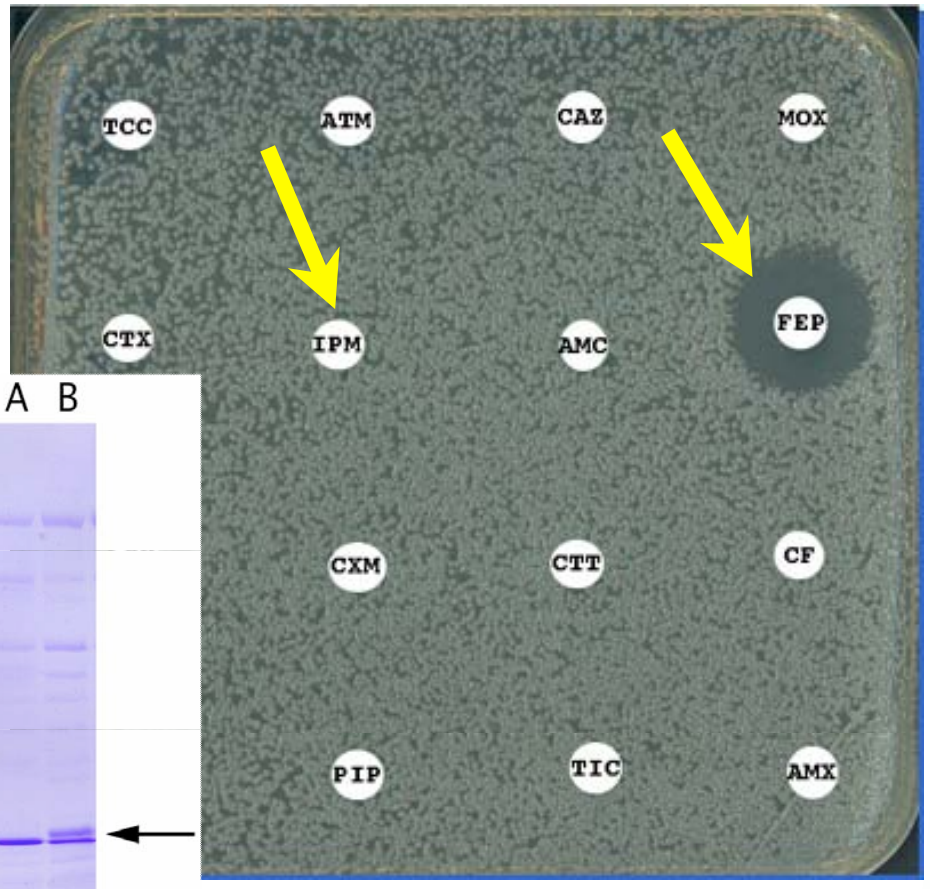
Lee EH, Nicolas MH, Kitzis MD, Pialoux G, Collatz E, Gutmann L. Association of two resistance mechanisms in a clinical isolate of Enterobacter cloacae with high-level resistance to imipenem. Antimicrob Agents Chemother. 1991, 35:1093-8.

Plasmid-mediated cephalosporinase CMY-2 + permeability defect



E. coli ND1





E. coli ND 2

Poirel, Heritier, Spicq & Nordmann JCM 2004, 36; 266-7.

Overall trend of resistance (i)

The Global View: Imipenem % Susceptibility

	Enterobacteriacae	*Pseudomonas*	*Acinetobacter*
USA	≥99	85	92
Europe	≥97	79	83
Japan	≥98	52	95
South America	≥98	60	73

MYSTIC (Meropenem Yearly Susceptibility Test Information Collection)

Diag. Microb. Infect. Dis. 2004. Turner. 50:291, Rhomberg et al. 49:273, Jones et al. 49:211.

Int. J. Antimicrob. Agents. 2002. Pfaller et al 19:383

Overall trend of resistance (ii)

Worldwide nosocomial prevalence and resistance. ICU. 2000-2004

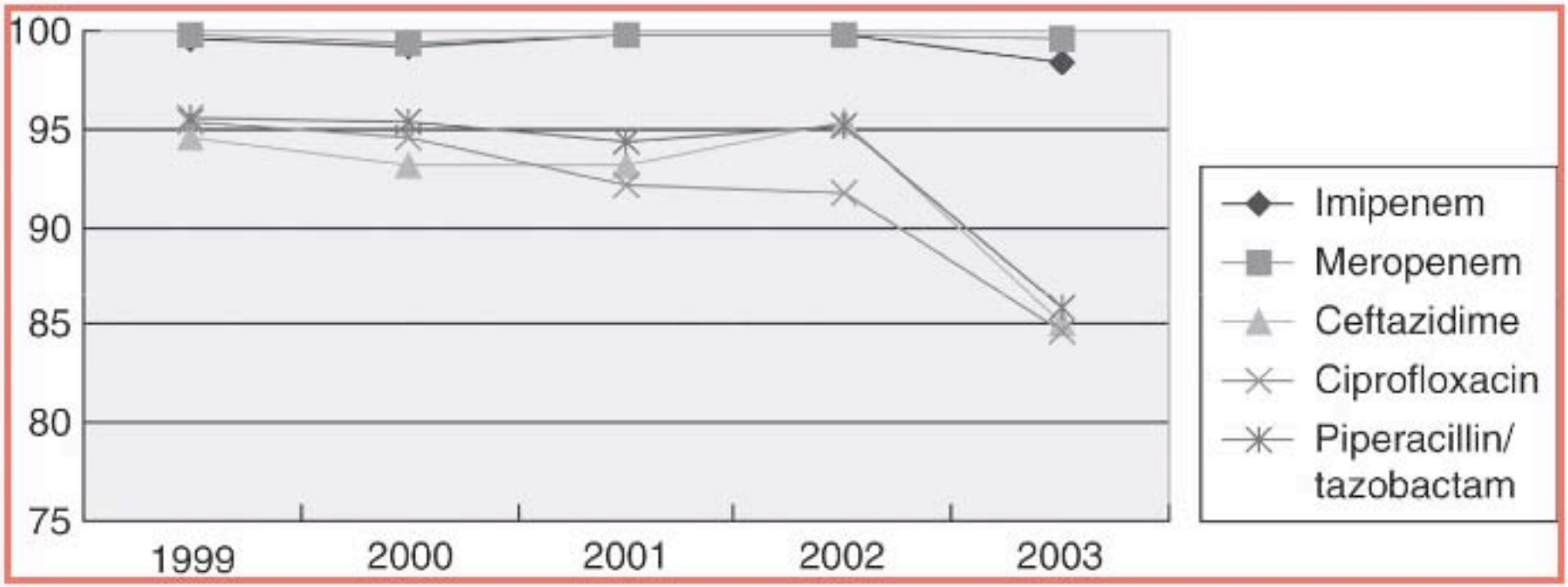
Percentage susceptibility to imipenem

	E. coli	*Klebsiella spp.*	*Enterobacter spp.*
Argentina	100	99	99
Mexico	96	97	73
Peru	92	82	85
Cyprus	98	97	100
Germany	100	100	99
Sweden	100	100	99
Turkey	99	100	95
China	100	99	96
Russia	100	100	100
Korea	100	98	93
Philippines	92	100	80
Malaysia	100	100	100
Saudi Arabia	98	93	100
South Africa	100	100	99

Adapted from Rodloff et al. JAC 2006

Reseau REUSSIR; France. 2002; 97-100% susceptibility to imipenem- *Enterobacteriaceae*

Overall trend of resistance in *Enterobacteriaceae* (iii)



North America- Mystic program

Rodloff, Goldstein & Torres; JAC, 2006

Take home message

1. Overall good and stable levels of susceptibility to carbapenems of *Enterobacteriaceae,* worldwide; carbapenems remain the most active ß-lactams
2. Emergence of resistance mechanisms of clinical significance; ß-lactamases KPC and metallo-enzymes
3. Requirement for early detection of carbapenem-resistant isolates for avoiding outbreaks
4. Need for an improvement of techniques for rapid detection and surveillance of carbapenem-resistant carriers

Ackowledgments; T. Naas, L. Poirel, and many other colleagues inside and outside Bicêtre