GNR Resistance: Global Epidemiology

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Objectives

- Describe emerging patterns of resistance in GNRs
- Review risk factors associated with resistant GNRs
- Discuss the methods to determine outcomes associated with resistance
- Demonstrate outcomes associated with several multidrug resistant GNRs

Mechanisms of Gram (-) Resistance

- ß lactams
  - Production of a ß-lactamase
  - Outer membrane protein changes
  - Multi-drug efflux pumps
- Aminoglycosides
  - Production of AG-modifying enzymes
  - Multi-drug efflux pumps
- Carbapenems
  - Production of a carbapenemase (all carbapenems)
  - Decreased permeability of the outer membrane via porin changes (imipenem)
  - Multi-drug efflux pumps
- Fluoroquinolones
  - Topoisomerase point mutations (*gyrA* and *parC*) (FQ)
  - Multi-drug efflux pumps
  - Modifying enzymes
  - QNR

Arias & Murray N Engl J Med 2009;360:439

Increasing Antimicrobial Resistance Among GNB

- *Klebsiella pneumoniae*
- *Pseudomonas aeruginosa*
- *Acinetobacter baumannii*
- *Escherichia coli*
- *Enterobacter spp.*
- *Berkholderia cepacia*
- *Ralstonia picketii*
- *Stenotrophomonas maltophilia*

Antimicrobial-resistant (R) Pathogens: HAI Infections

TABLE 4. Distribution and Rank Order of Selected Pathogens Associated With Cases of Healthcare-Associated Infection (HAI) Reported to the National Healthcare Safety Network, January 2006–October 2007, by Type of HAI

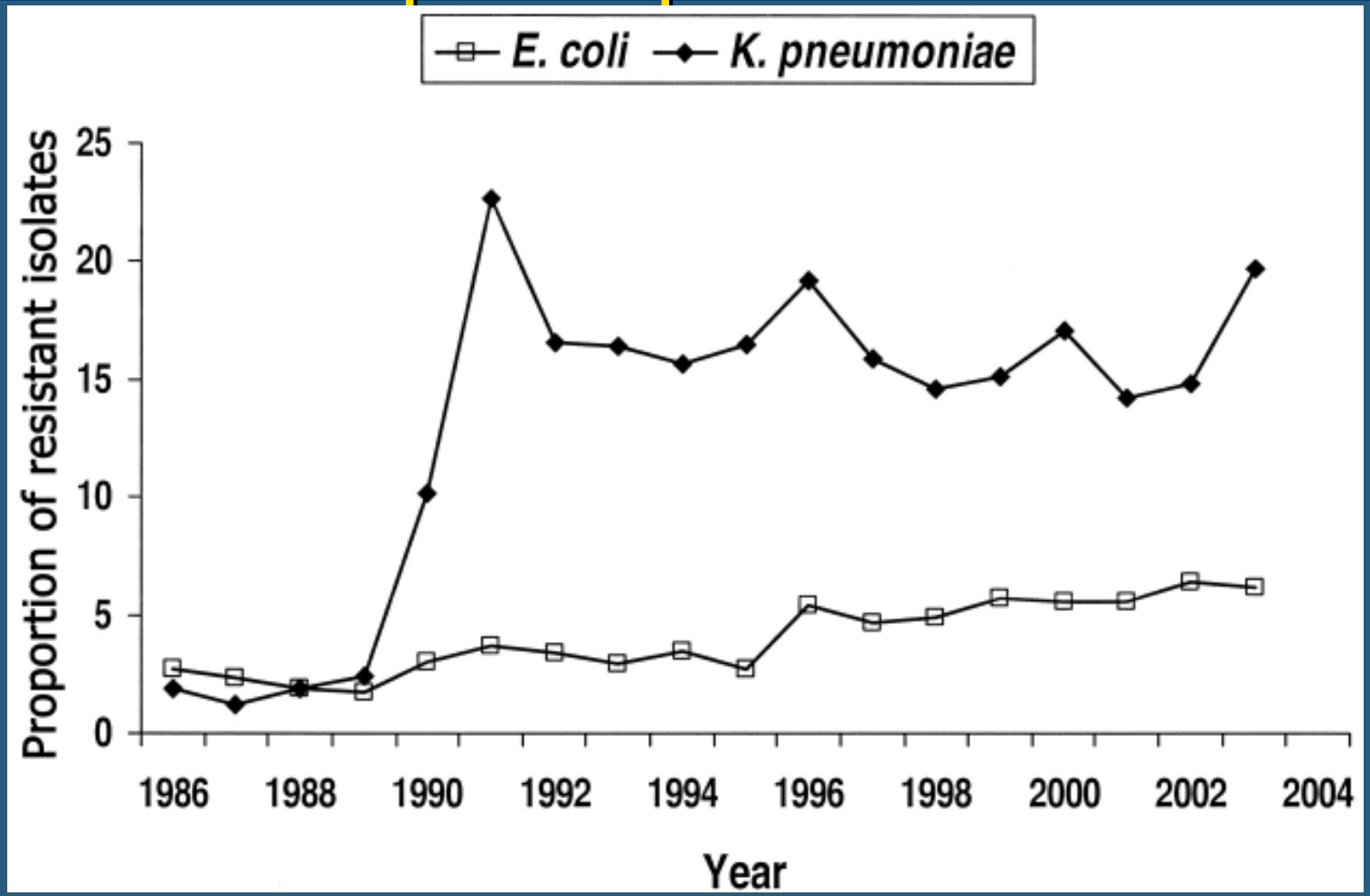
	Overall[a]		CLABSI		CAUTI		VAP		SSI	
Pathogen	No. (%) of pathogenic isolates	Rank	No. (%) of pathogenic isolates	Rank	No. (%) of pathogenic isolates	Rank	No. (%) of pathogenic isolates	Rank	No. (%) of pathogenic isolates	Rank
Escherichia coli	3,264 (9.6)	5	310 (2.7)	8	2,009 (21.4)	1	271 (4.6)	6	671 (9.6)	4
Pseudomonas aeruginosa	2,664 (7.9)	6	357 (3.1)	7	938 (10.0)	4	972 (16.3)	2	390 (5.6)	5
Klebsiella pneumoniae	1,956 (5.8)	7	563 (4.9)	5	722 (7.7)	5	446 (7.5)	5	213 (3.0)	7
Enterobacter species	1,624 (4.8)	8	443 (3.9)	6	384 (4.1)	6	498 (8.4)	3	293 (4.2)	6
Acinetobacter baumannii	902 (2.7)	9	252 (2.2)	9	109 (1.2)	9	498 (8.4)	3	42 (0.6)	9
Klebsiella oxytoca	359 (1.1)	10	99 (0.9)	10	85 (0.9)	10	128 (2.2)	8	47 (0.7)	9

Hidron et al., *Infect Control Hosp Epidemiol* 2008:29:996

Antimicrobial-resistant (R) Pathogens: ICU Infections

Organisms	Isolates (#)	Increase in pathogens resistant (%)
Fluoroquinolone-R *Pseudomonas* spp.	2657	49%
3rd gen cephalosporin-R *E. coli*	1551	48%
MRSA	2546	40%
VRE	4744	40%
Imipenem-R *Pseudomonas* spp.	1839	20%

K. pneumoniae & *E. coli* Resistant to 3rd-gen Cephalosporins in ICUs

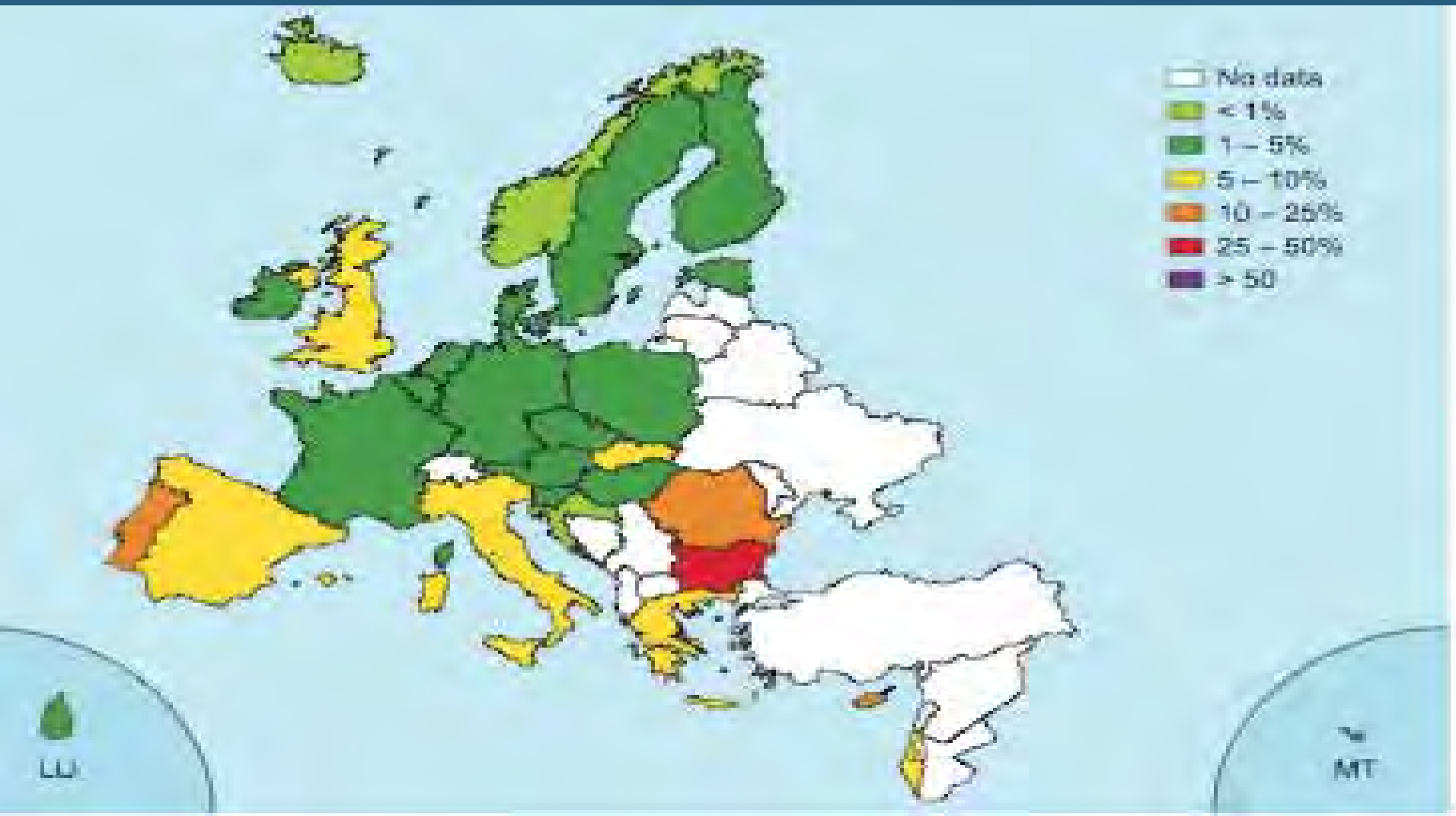


P < .001

P < .001

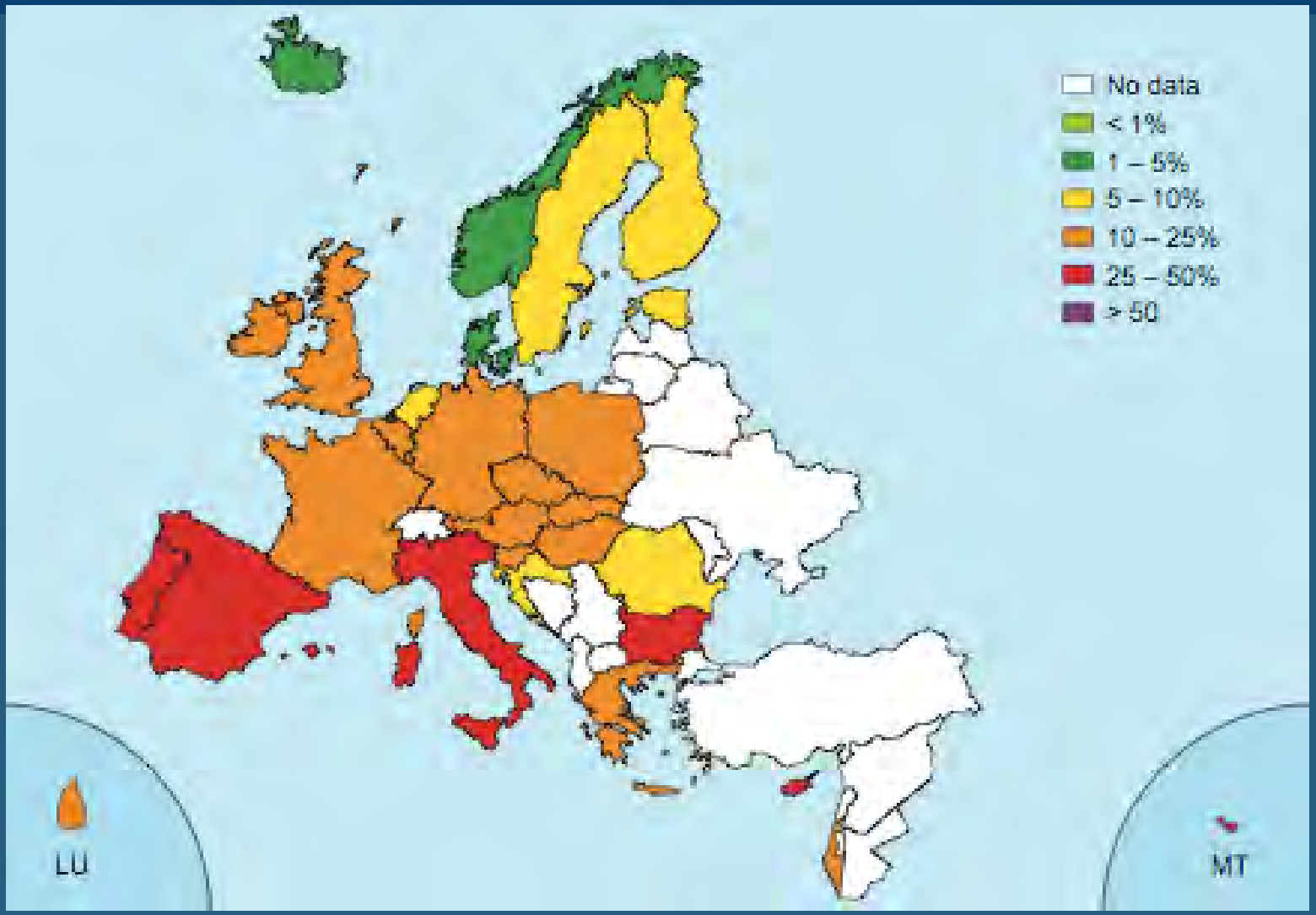
Gaynes R, et al. Clin Infect Dis. 2005;41:848-54.

European prevalence of *E. Coli* resistant to 3rd generation cephalosporins



EARSS report 2006

European prevalence of *E. Coli* resistant to fluoroquinolones



EARSS report 2006

Table 1. Geographic variation in the occurrence of infections caused by *Pseudomonas aeruginosa* in the SENTRY Antimicrobial Surveillance Program (1997–1999).

Country or region	Occurrence by site of infection: total no. of isolates, % *P. aeruginosa* (range[a])			
	Blood	Respiratory	Wound	Urine
Asia-Pacific	3162	1704	791	959
	4.5 (4.4–4.7)	23.4 (22.1–26.0)	13.8 (10.8–14.8)	11.0 (10.0–12.9)
Canada	3840	1659	633	651
	4.3 (3.6–4.9)	17.6 (16.3–18.8)	12.0 (11.8–12.1)	7.5 (7.3–7.6)
Europe	10,815	2572	2305	2135
	5.6 (5.3–6.3)	22.2 (20.4–26.8)	14.0 (13.3–14.7)	7.3 (6.2–8.5)
Latin America	5295	1914	1353	1430
	6.5 (5.6–7.7)	25.0 (21.6–26.9)	11.5 (9.4–12.4)	8.0 (7.4–9.1)
United States	17,399	6711	2191	2569
	4.4 (4.2–4.6)	19.3 (18.2–20.4)	11.9 (10.9–12.9)	6.7 (5.8–7.5)

NOTE. A total of 70,067 strains (6631 *P. aeruginosa* isolates) were analyzed over the 3-year study period.

[a] Range indicates occurrence rates over the 3 study years.

Gales et al Clinical Infectious Diseases 2001;32:S146-S155

ESBL among *E. coli* isolates (1997–1999)

	Isolates Resistant (%)
Latin America	**8.5%**
W. Pacific	**7.9%**
Europe	**5.3%**
US	**3.3%**
Canada	**4.2%**

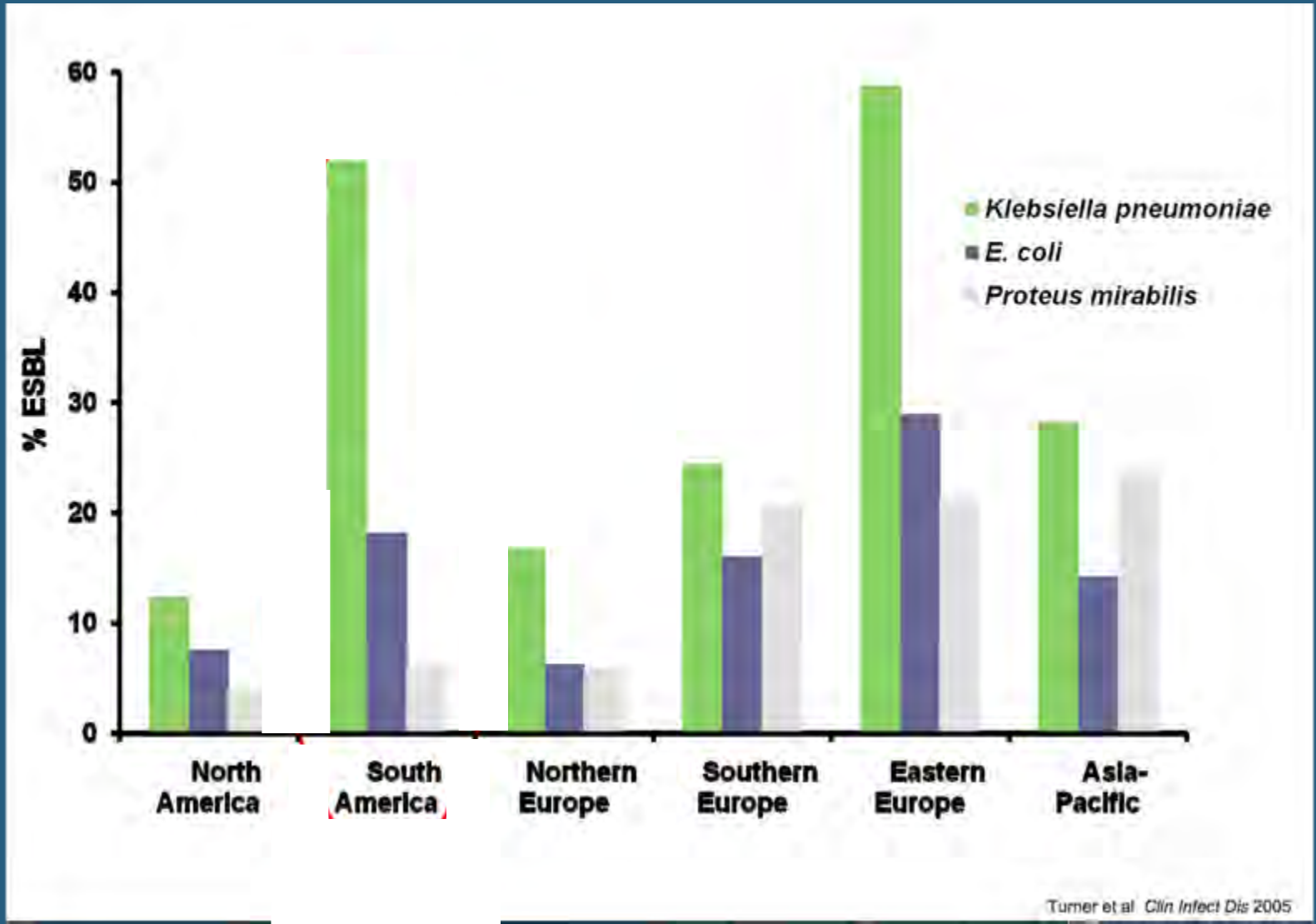
Winokur J, et al. Clin Infect Dis. 2001;32:S94.

ESBL: SENTRY > 4000 *K. pneumoniae* Isolates (1997–1999)

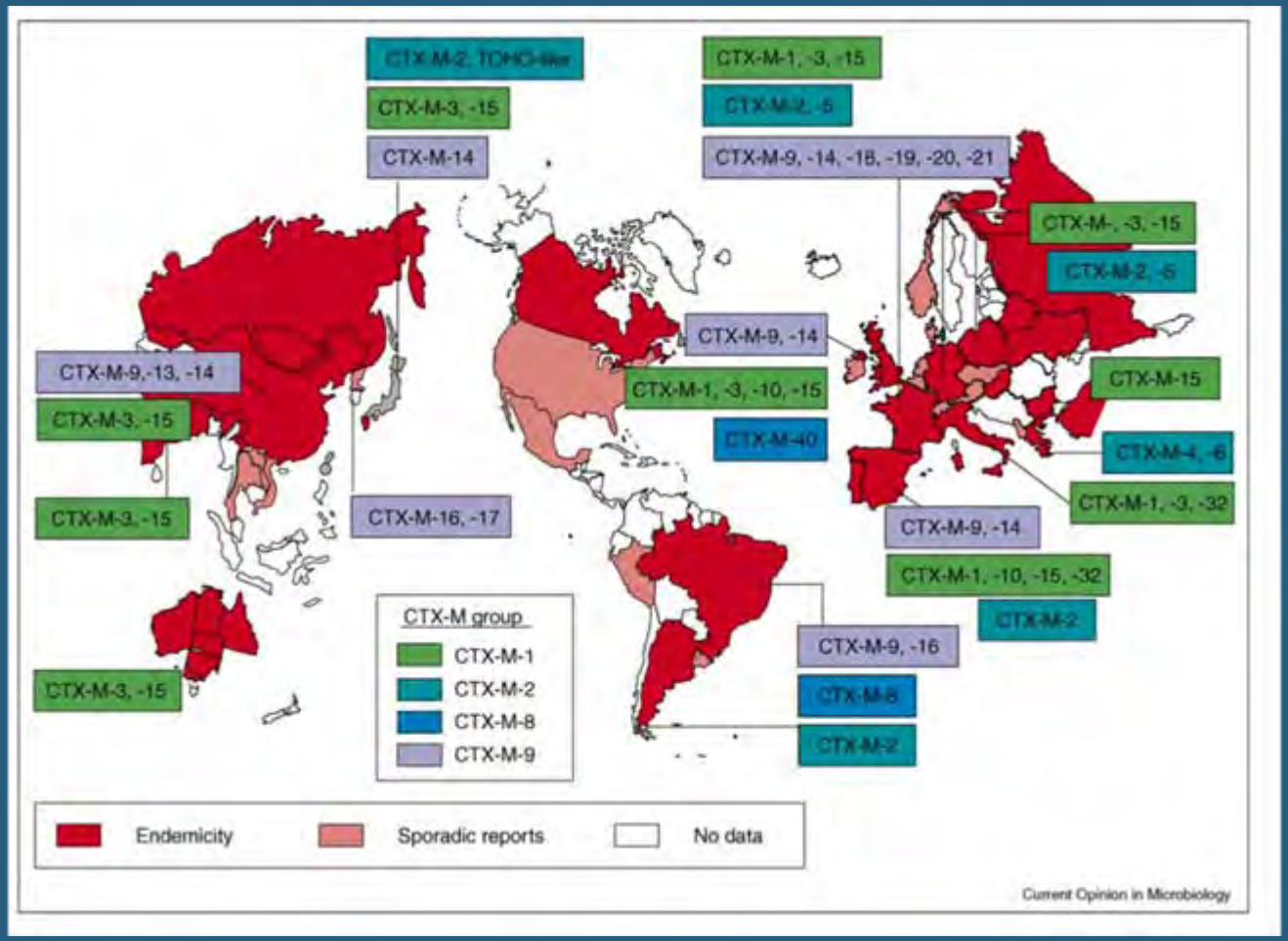
	Isolates Resistant (%)
Latin America	45.5%
W. Pacific	24.6%
Europe	22.6%
US	7.6%
Canada	4.9%

Winokur J, et al. *Clin Infect Dis*. 2001;32:S94.

Global distribution of ESBL's



CTX β-lactamase Pandemic



Canton et al. Current Opinion Micro 2006;9:466-75

CTX β-lactamase Timeline

Table 1

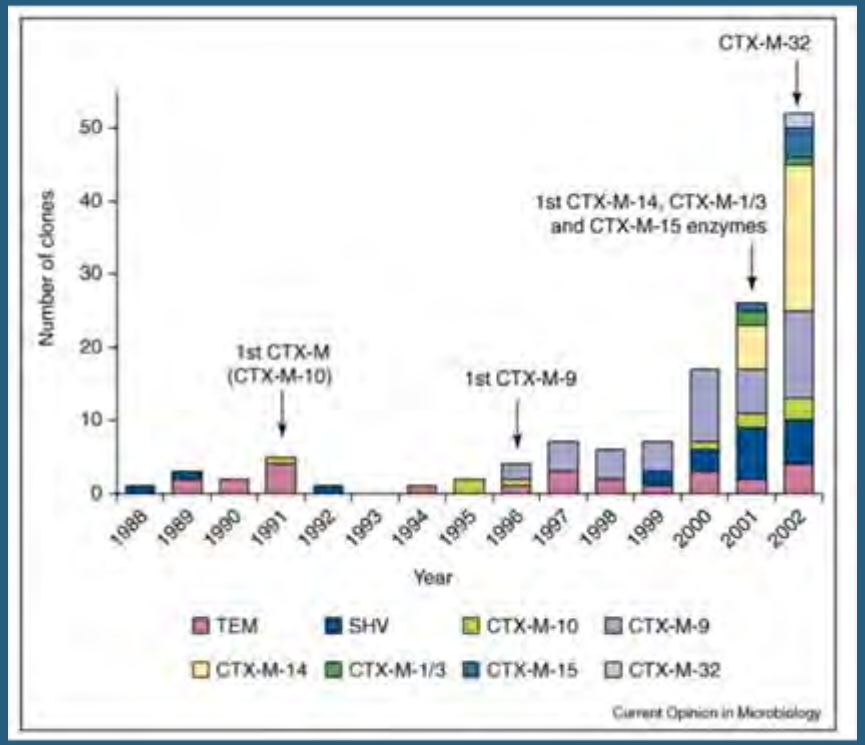
Different CTX-M clusters and origin of *bla*$_{CTX-M}$

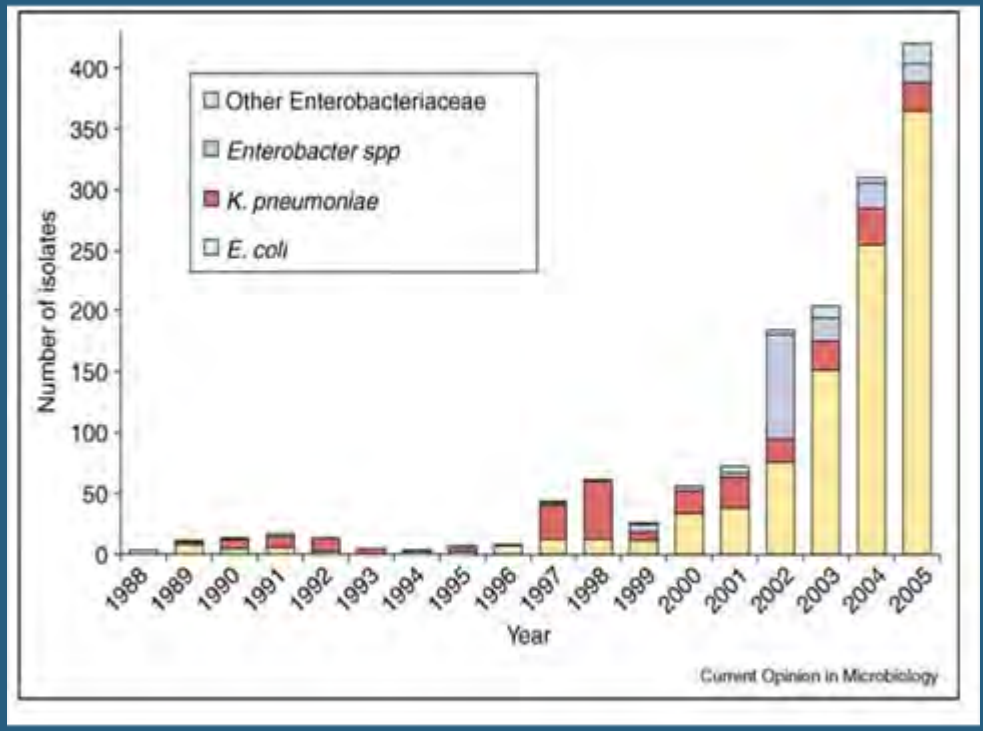
	CTX-M cluster				
	CTX-M-1	CTX-M-2	CTX-M-8	CTX-M-9	CTX-M-25
Year (enzyme, country)[a]	1989 (CTX-M-1, Germany)	1986 (FEC-1, Japan)	1996 (CTX-M-8, Brazil)	1994 (CTX-M-9, Spain)	2000 (CTX-M-25, Canada)
Enzymes	CTX-M-1, -3, -10, -11, -12, -15, -22, -23 -29, -30, -32, -33, -28, -36, -54, UOE-1	CTX-M-2, -4, -6, -7, -20, -31, -44 (previously TOHO-1), FEC-1	CTX-M-40	CTX-M-9, -13, -14, -16, -17, -18, -19, -24, -27, -45 (previously TOHO-2), -46, -47, -48, -49, -50,	CTX-M, -26, -25, -39, -41
Origin	*K. ascorbata*	*K. ascorbata*	*K. georgiana*	*K. georgiana*	ND

[a] Year of first isolation or description (first enzyme described and country of isolation); CTX-M-14 and CTX-M-18 are identical; ND: not defined.

Canton et al. Current Opinion Micro 2006;9:466-75

CTX β-lactamase Madrid



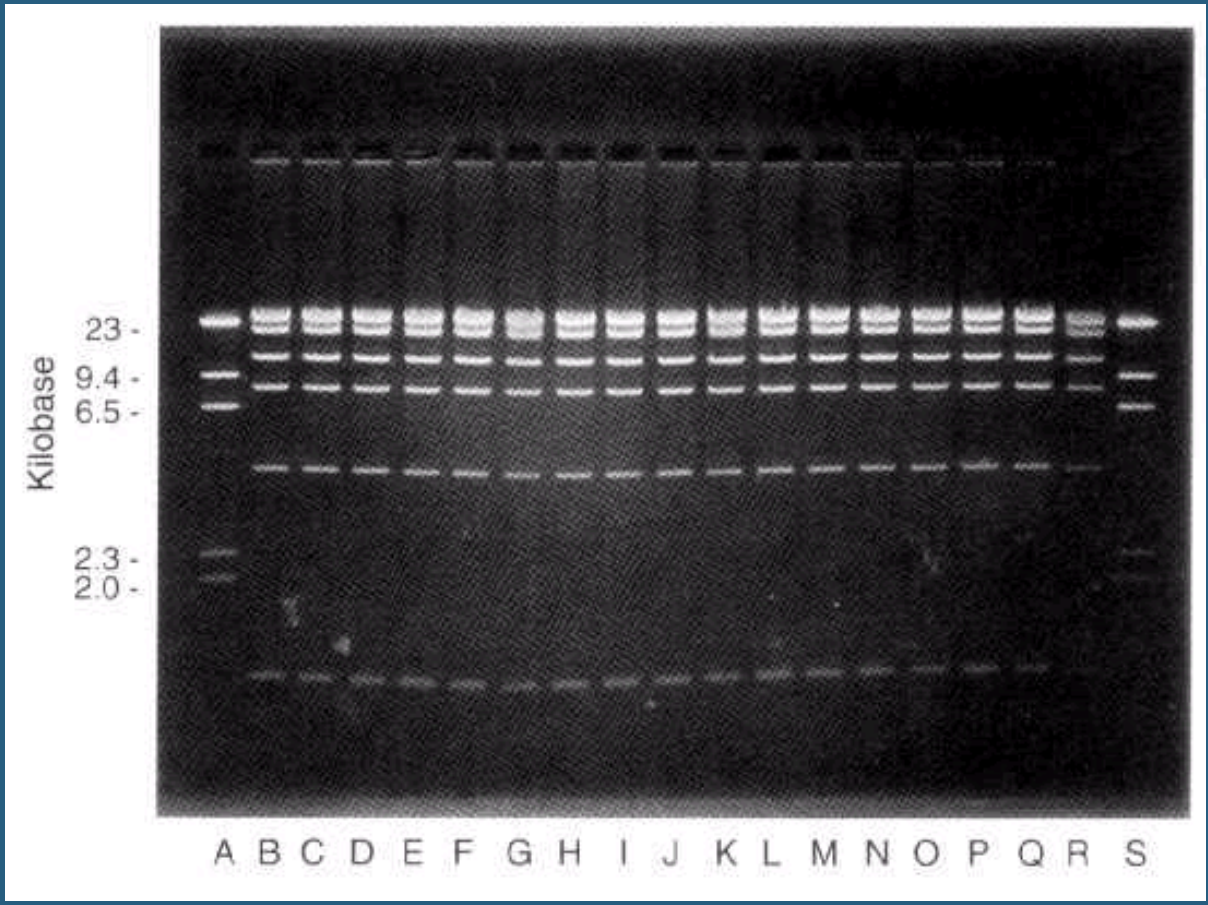


Canton et al. Current Opinion Micro 2006;9:466-75

Are ESBL Outbreaks Clonal?

- *Gardam M, JID 2002;186:1754*
  - 287 screened in a cohort of transplant recipients
  - 66/69 isolates unique by PFGE
  - Majority of isolates *amp C*
  - Many shared common resistance plasmid
- *Paterson D, CID 2001;33:126*
  - ESBL-producing *E. coli* outbreak in liver tx unit
  - Isolates genetically identical
- *Decre D, CID 1998;27:834*
  - 55 acquired cases in medical ICU
  - 85% caused by single epidemic clone

Multiple Antibiotic-Resistant *Klebsiella* and *E.Coli* in Nursing Homes



Weiner et al. JAMA 1999;281:517

Klebsiella Pneumoniae Carbapenemase (KPC)

- KPC confers resistance to all β-lactams including extended-spectrum cephalosporins and carbapenems
- Klebsiella is not the only organism affected and occurs primarily in enteric bacteria and *P. aeruginosa*
- Located on plasmids that encode resistance to other agents such as aminoglycosides

Molecular Class A Carbapenemases

Characteristic

- Bacteria are characterized by **reduced susceptibility to imipenem**,
- MICs can range from mildly elevated (e.g., imipenem MIC of ≤ 4 µg/ml) to fully resistant.
- **These β lactamases, therefore, may go unrecognized following routine susceptibility testing.**

Major families

- NMC/IMI
- SME and
- KPC: KPC1, KPC2, KPC3
- GES

Susceptibility Profile of KPC-Producers

Antimicrobial	Interpretation	Antimicrobial	Interpretation
Amikacin	I	Chloramphenicol	R
Amox/clav	R	Ciprofloxacin	R
Ampicillin	R	Ertapenem	R
Aztreonam	R	Gentamicin	R
Cefazolin	R	Imipenem	R
Cefpodoxime	R	Meropenem	R
Cefotaxime	R	Piperacillin/tazo	R
Cefotetan	R	Tobramycin	R
Cefoxitin	R	Trimeth/Sulfa	R
Ceftazidime	R	Polymyxin B	S
Ceftriaxone	R	Colistin	S
Cefepime	R	Tigecycline	S

Worldwide expansion

- France: 2005. KPC2 in a *K. pneumoniae* from a patient who has been in New York for medical treatment
- Colombia: 2006
- Israel: 2007
- China: 2007
- Greece: 2008
- France: 2009

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

First Detection of the Plasmid-Mediated Class A Carbapenemase KPC-2 in Clinical Isolates of *Klebsiella pneumoniae* from South America

Outbreak of carbapenem-resistant *Klebsiella pneumoniae* producing KPC-3 in a tertiary medical centre in Israel

Plasmid-Mediated KPC-2 in a *Klebsiella pneumoniae* Isolate from China[▽]

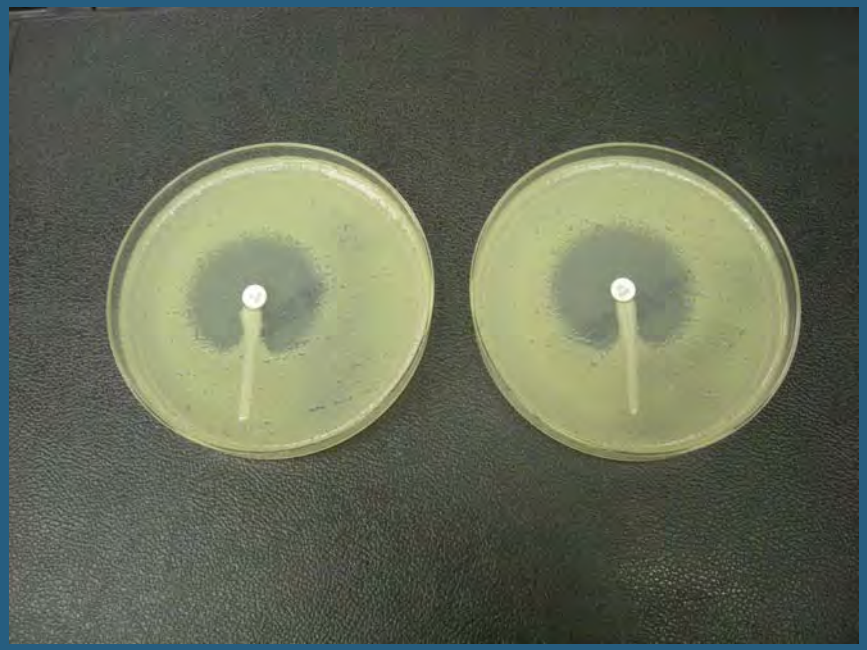
Plasmid-Mediated Carbapenem-Hydrolyzing β-Lactamase KPC-2 in *Klebsiella pneumoniae* Isolate from Greece[▽]

Carbapenemase Production Laboratory Confirmation

Laboratory algorithm

- Screen all ertapenem resistant isolates
- Confirm with modified Hodge test
- Notify patient's physician, infection control
- Test and report tigecycline, colistin

Place patients on contact precautions



Modified Hodge Test

ANTIMICROBIAL AGENTS AND CHEMOTHERAPY, Dec. 2004, p. 4793–4799 Vol. 48, No. 12
0066-4804/04/$08.00+0 DOI: 10.1128/AAC.48.12.4793–4799.2004

Outbreak of *Klebsiella pneumoniae* Producing a New Carbapenem-Hydrolyzing Class A β-Lactamase, KPC-3, in a New York Medical Center

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Identification of Carbapenem-Resistant *Klebsiella pneumoniae* Harboring KPC Enzymes in New Jersey

TOM CHIANG,[1] NORIEL MARIANO,[2] CARL URBAN,[2] RITA COLON-URBAN,[3] LOUISE GRENNER,[2] ROBERT H.K. ENG,[1] DAVID HUANG,[1] HEMA DHOLAKIA,[1] and JAMES J. RAHAL[2]

ABSTRACT

***Klebsiella pneumoniae* isolates harboring KPC enzymes have been identified in many geographical areas since 2001. Numerous problems exist in the detection and treatment of patients with such isolates. The clinical characteristics and molecular epidemiology associated with 12 randomly chosen patients in whom these enzymes were detected by molecular methods are described. This is the first description of the identification of carbapenem-resistant *K. pneumoniae* isolates harboring KPC β-lactamases at the Veterans Administration Hospital in New Jersey (VA NJHCS). Because recognition of carbapenem resistance in *K. pneumoniae* due to KPC enzymes can only be achieved by molecular methods, detection in the Clinical Microbiology Laboratory by routine methods will continue to be difficult, leading to dilemmas in treatment.**

ANTIMICROBIAL AGENTS AND CHEMOTHERAPY, July 2005, p. 3018–3020 Vol. 49, No. 7
0066-4804/05/$08.00+0 doi:10.1128/AAC.49.7.3018–3020.2005

Emergence of KPC-Possessing *Klebsiella pneumoniae* in Brooklyn, New York: Epidemiology and Recommendations for Detection

Simona Bratu,[1] Mohamad Mooty,[1] Satyen Nichani,[1] David Landman,[1] Carl Gullans,[2] Barbara Pettinato,[3] Usha Karumudi,[1] Pooja Tolaney,[1] and John Quale[1]*

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Among 257 isolates of *Klebsiella pneumoniae* collected in Brooklyn, NY, 24% were found to possess bla_{KPC}. Clinical microbiology laboratories that used automated broth microdilution systems reported 15% of the KPC-possessing isolates as susceptible to imipenem. The imipenem MIC was found to be markedly affected by the inoculum. For accurate detection of KPC-possessing *K. pneumoniae*, particular attention should be paid to proper inoculum preparation for broth-based susceptibility methods. In addition, using ertapenem or meropenem for class reporting of carbapenem susceptibility will improve detection.

The Spread of *Klebsiella pneumoniae* Carbapenemase–Producing *K. pneumoniae* to Upstate New York

Ben M. Lomaestro,[1] Ellis H. Tobin,[2] Wenchi Shang,[3] and Thomas Gootz[3]

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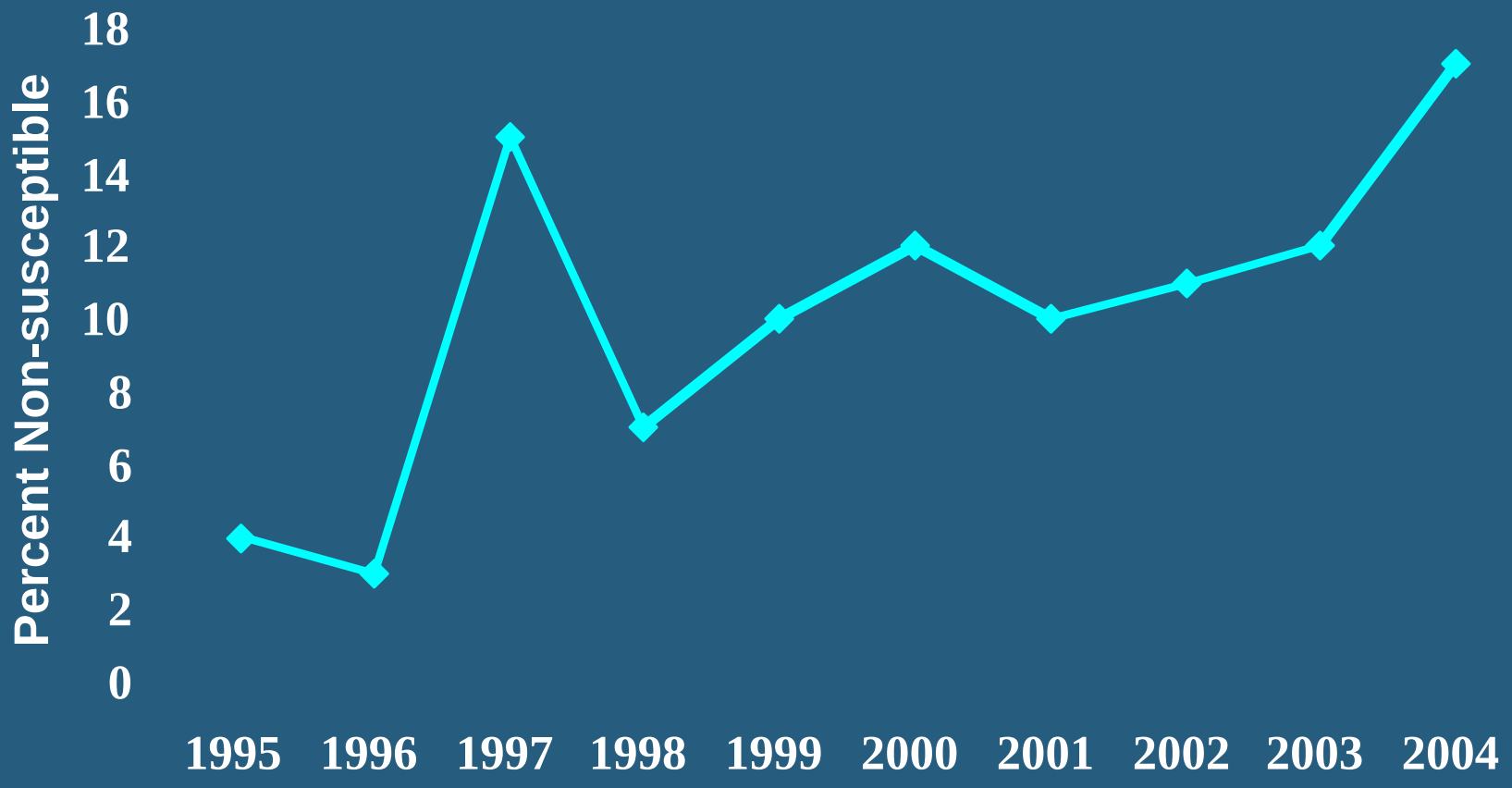
Acinetobacter spp. Non-susceptible to all tested aminoglycosides, beta-lactams, carbapenams and quinolones-NNIS 1995-2004



Acinetobacter spp.

- Emerging gram-negative non-fermenting aerobic coccobacillary rods
- Environmental (soil, water) fruit, vegetables and normal habitants of the skin (40% of healthy volunteers had *A. lwoffii* on skin)
- Robust survival in environment (dry > humid) -20 days at 31% humidity
- Isolated from fomites and environment after patients d/ced
- 27 outbreaks in literature between 1991–2000, mostly MDR, ICU, involves predominately adults and implicated respiratory equipment

Villegas MV and Hartstein AI. Infect Control Hosp Epidemiol. 2003;24:284-95; Bonomo RA, et al. Clin Infect Dis. 2000;31:1414-22. Manikal VM, et al. Clin Infect Dis. 2000;31:101-6; Landman D, et al. Arch Int Med. 2002;162:1515-20; Fourniet PE and Richet H. Clin Infect Dis. 2006;42:692-9.

A Singapore Acinetobacter outbreak

- Outbreak of multi-resistant AB in TTSH: Feb-Sep 1996
- 103 patients affected; 16 infected, 74 colonized
- Male:female; 2:1, Age 1-99 (mean 56)
- 67% neurosurgery patients, 14% neuro, 9% GS, 6% ortho, 1% Gen Med
- LOS mean 85 days, range 3-366
- Time to acquisition: mean 27 days, range 1-192

Ling ML et al. Infect Control Hosp Epidemiol 2001;22:48-9

Locations of Healthcare Outbreaks Caused by *A. baumannii*

Location	Outbreaks (#)
Multiple healthcare facilities	2
Multiple services and/or departments within the same healthcare facility	2
Adult ICU	26
Neonatal ICU	3
Burn unit	4
Neurosurgery unit	3
Surgery unit	2
Internal medicine unit	1
Oncology unit	1

Fournier PE and Richet H. Clin Infect Dis. 2006;42:692-9.

MDR *Acinetobacter outbreaks- common respiratory sources*

COMMON SOURCE OUTBREAKS AND CLUSTERS WITH RESPIRATORY SITE PREDOMINANCE

Reference	Hospital Setting	No. of Patients	Duration	Common Source	Control Measures Predominantly Directed Against the Common Source
16	Adult ICUs	45	6 mo	Ventilator spirometers	Removal of all spirometers, sterile gloves for patient contact, strict hand washing
19	Multiple ICUs	19	1 mo	Wright respirometers	Restrict use of each respirometer to a single unit, volume measurements done at most distal portion of tubing, enforced and observed strict hand washing
24	Neonatal ICU	10	6 mo	Mouthpiece of resuscitator bag	Sterilization of resuscitator bags after use
27	Surgical ICU	30	9 mo	Demand valve reservoir of ventilator	Filters placed at end of inspiratory and expiratory tubing with technical modification of ventilator
28	Adult, pediatric, and neonatal ICUs	93	10 mo	Reusable ventilator circuits and resuscitation bags	Ethylene oxide terminal sterilization of circuits and resuscitation bags, disposable gloves used for final packaging of sterilized circuits and bags
35	General ICU	6	1 mo	Reusable ventilator tubing and humidifier	Use of disposable ventilator tubing
36	Adult mixed ICU	48	6 mo	In-line temperature and oxygen monitor probes	Ethylene oxide sterilization of probes or discard after use
39	Adult mixed ICU	7	1 mo	Peak flow meter	High-level glutaraldehyde disinfection of flow meter, use of disposable mouthpiece, hand washing
48	Adult ICU	5	1 wk	Temperature probe of ventilator humidifier	Sterilization of probes with H_2O_2 free radicals
50	Surgical and medical ICUs	Not stated	48 mo	Ventilator temperature probes	Ethylene oxide terminal sterilization of temperature probes, hand washing, cohorting culture-positive patients, separation of clean and dirty areas in respiratory therapy department
53	Multiple adult ICUs	13	1 mo	Multidose acetylcysteine nebulization to multiple patients (presumed)	New acetylcysteine nebulizer for each patient, enforcement of proper handling of multidose vials
59	Neonatal ICU	9	2 wk	Suction catheter and bottle	New suction catheter for each neonate, short-term unit closure, cohorting staff, hand hygiene
60	Adult ICU	23	7 mo	"Y" piece of ventilator	Replacement of ventilators

ICU = intensive care unit.

Villegas et al. ICHE 2003:24:(4);284-95

MDR *Acinetobacter outbreaks: common non-respiratory sources*

COMMON SOURCE OUTBREAKS AND CLUSTERS WITHOUT RESPIRATORY SITE PREDOMINANCE

Reference	Hospital Setting	No. of Patients	Duration	Predominant Site	Common Source	Control Measures Predominantly Directed Against the Common Source
13	Medical wards	24	4 mo	Blood	Bedside humidifiers	Removal of humidifiers
14	Medical ICU	14	4 mo	Dialysis drainage fluid	Warming bath water	Autoclaving the baths, disinfection of heating elements after each use, drying of dialysis fluid bottles after removal from bath
17	Cardiac catheterization laboratory	37	10 mo	See text	Hospital-prepared distilled water	Ethylene oxide sterilization of catheters, no distilled water to rinse catheters
18	Urology ward	8	2 wk	Urine	Bedpan and urine jugs	Discontinuing use of malfunctioning bedpan washer, 1% hypochlorite disinfection of washed jugs followed by drainage
22	Dialysis center	16	1 wk	See text	Heparinized saline solution	Discard diluted heparin after each shift
23	Burn unit	63	21 mo	Wound	Patient mattresses	Discard mattresses
25	Hospital wide	8	5 mo	Blood	Bedside humidifiers	Removal of humidifiers
32	Neonatal ICU	7	1 d	Blood	IV nutrition fluids (presumed)	
33	Pediatric ward	5	1 d	CSF	Multidose methotrexate and attached aspirating needle (presumed)	Sterile disposable needles for methotrexate reconstitution
34	Multiple ICUs	75	17 mo	Blood	Reusable pressure transducers in arterial lines	Ethylene oxide terminal sterilization of pressure transducers between patients
45	Hospital wide	128	26 mo	Mixed	Feather pillows washed at low temperature	Elimination of feather pillows, switch to synthetic pillows, washing pillows at 85°C
61	Pediatric oncology ward	3	4 mo	Blood	Water taps in staff room with mesh aerators	Water taps and aerators removed and replaced, reinforcement of hand antisepsis and judicious use of gloving

Villegas et al. ICHE 2003:24:(4);284-95

MDR *Acinetobacter* Risk Factors For Acquisition

Table 2. Characteristics of the Multidrug-Resistant *Acinetobacter* Surveillance Culture Study Cohort

	Without MDR *Acinetobacter*	With MDR *Acinetobacter*	All
Patients	n = 1098	n = 13	N = 1111
Age, mean (95% CI) [range], y	56.4 (55.4-57.4) [17-102]	49.1 (39.4-58.8) [19-74]	56.3 (55.3-57.3) [17-102]
Women, No. (%), [95% CI]	527 (48.0) [45.0-51.0]	10 (76.9) [46.2-95.0]	537 (48.3) [45.4-51.3]
Paraplegia, No. (%) [95% CI]	12 (1.1) [0.6-1.9]	3 (23.1) [5.0-53.8]	15 (1.4) [0.8-2.2]
Admissions	n = 1210	n = 13	N = 1223
Admitted directly from a long-term care or rehabilitation facility, No. (%) [95% CI][a]	47 (3.9) [2.9-5.1]	6 (46.2) [19.2-74.9]	52 (4.3) [3.2-5.5]

Abbreviations: CI, confidence interval; MDR, multidrug-resistant.
[a]Of 13 patients with MDR *Acinetobacter*, 9 (69%) had been in a long-term care or rehabilitation facility within the preceding 6 months.

Maragakis et al. JAMA 2008;299:2536

Risk Factors: An Exhaustive (ing) List

- Age
- Duration of hospitalization
- ICU admission
- Renal insufficiency
- Immunosuppression
- Neutropenia
- Hematologic malignancy
- Solid organ transplant
- Bone marrow transplant
- AIDS
- Prior surgery
- Antibiotics - General
  - Number / Duration
- Antibiotics - Specific
  - Almost all implicated
- Diarrhea / *C. difficile*
- Central venous catheter
- Urinary catheter
- Prior colonization
- Exposure to another source
  - Infected/colonized patient
  - Inanimate Object
  - Health Care Worker

Outcomes Related to ESBL-Producing *Escherichia coli* and *Klebsiella pneumoniae*

- Retrospective matched cohort study of pts admitted 1997-8
  - Cases: hospitalized patients with culture positive for extended-spectrum β -lactamase- (ESBL) producing *E coli* or *K pneumoniae* (n=33)
  - Controls: hospitalized patients with culture positive for non-ESBL-producing *E coli* or *K pneumoniae* (n=66)
  - Sites: urinary 51.5%, wound 15%, catheter 12%, blood 9%, respiratory 9%, abdominal 3%
  - Total antibiotic exposure was the only independent predictor of ESBL-producing *E coli* or *K pneumoniae*

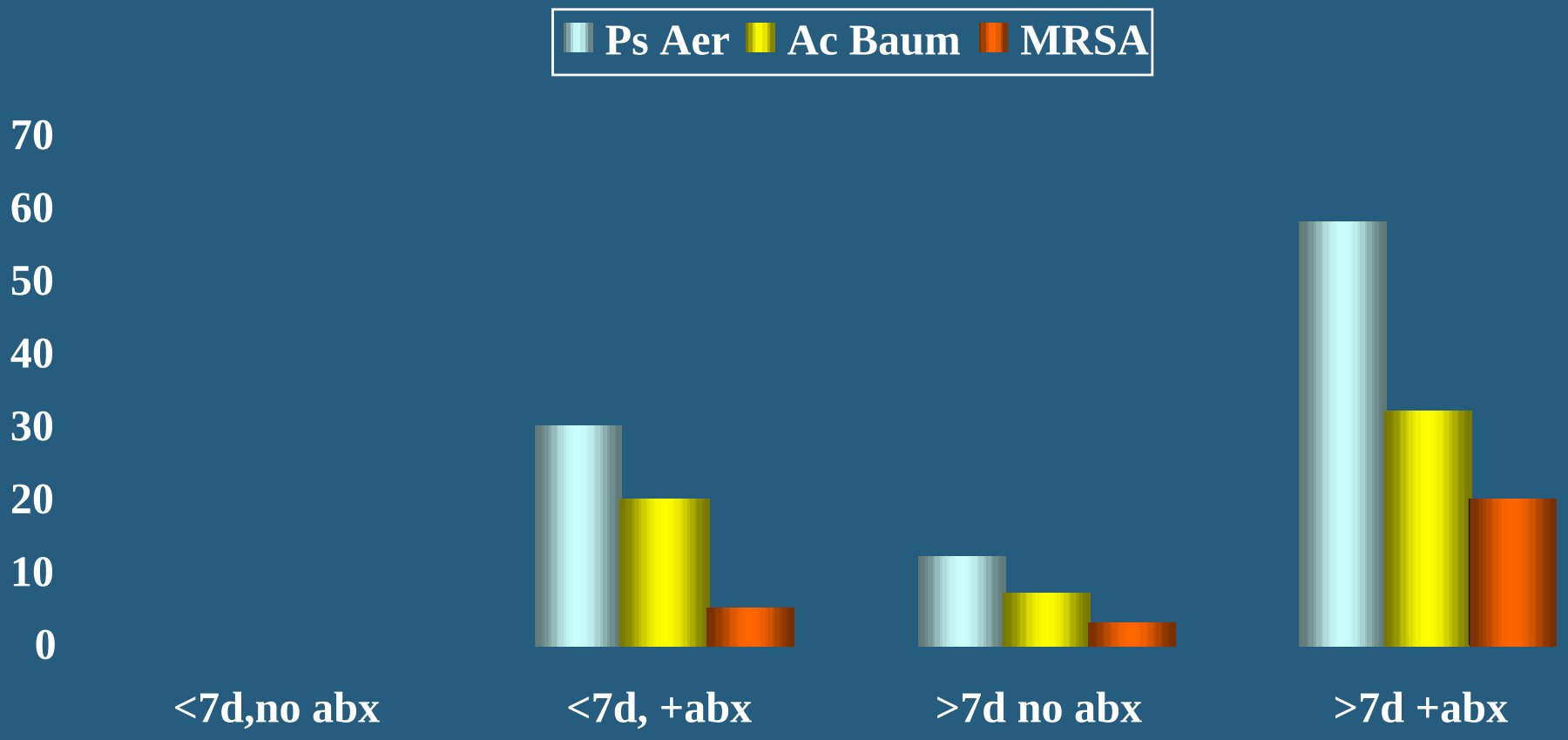
Lautenbach E, et al. Clin Infect Dis. 2001; 32:1162-1171.

Risk Factors: Modifiable Variables

- Age
- Duration of hospitalization
- ICU admission
- Renal insufficiency
- Immunosuppression
- Neutropenia
- Hematologic malignancy
- Solid organ transplant
- Bone marrow transplant
- AIDS
- Prior surgery

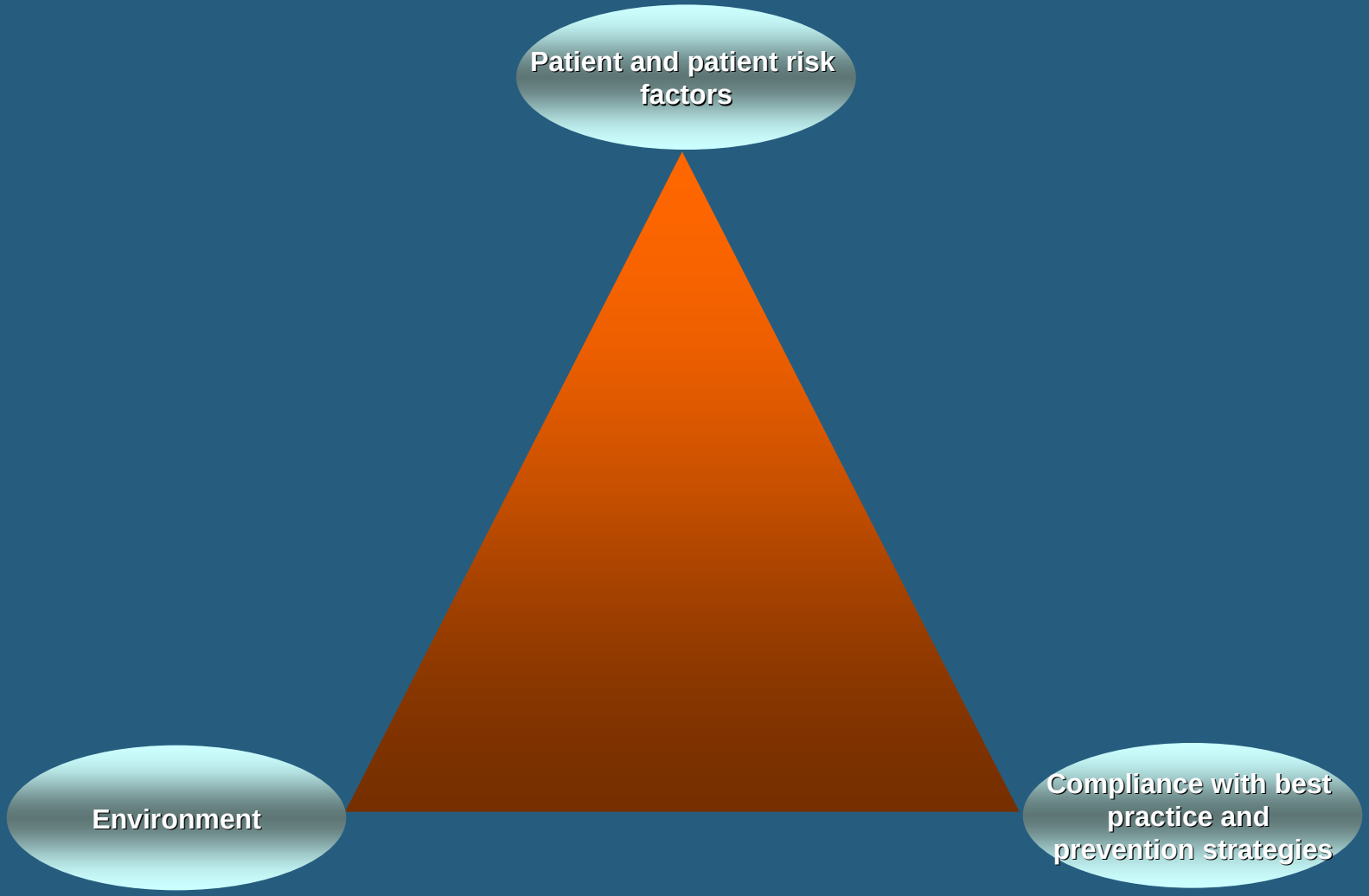
- Antibiotics - General
  - Number / Duration
- Antibiotics - Specific
  - Almost all implicated
- Diarrhea / *C. difficile*
- Central venous catheter
- Urinary catheter
- Prior colonization
- Exposure to another source
  - Infected/colonized patient
  - Inanimate Object
  - Health Care Worker

Antibiotic resistance in the ICU



Trouillet JL et al. Am J Resp Crit Care Med 1998;157:531-9

Framework for transmission



Why Does Measuring Outcomes Associated with Antimicrobial Resistance Matter?

- To justify interventions to prevent the acquisition of resistant pathogens in the healthcare setting
  - Infection control programs
  - Antibiotic management programs
- To influence healthcare workers to follow guidelines about isolation and make rational antibiotic choices
- To provide data for policymakers who make decisions about the funding of programs to track and prevent the spread of resistant pathogens
- To provide data about outcomes associated with certain infections to define prognosis for individual patients

Methodologic Issues in Antibiotic Resistance Outcome Studies:

- Morbidity*
  - LOS
  - ICU admission
  - Need for surgery/other procedures
  - Activity level at discharge
  - Loss of functional time (e.g., missed work)
- Mortality
  - In-hospital only
  - In-hospital and discharge
  - All-cause
  - Attributable to infection
- Economic*
  - Hospital cost
  - Hospital charges
  - Resource utilization
  - Health care costs

* More sensitive outcome measures for MDROs

Cosgrove SE & Carmeli Y. Clin Infect Dis. 2003; 36:1433-1437.

Methodologic Issues in Antibiotic Resistance Outcome Studies: Choice of Comparison Group

Comparison Group	Interpretation
Not infected	Impact of added infection
Infected with susceptible strain	Impact of resistance
Colonized with resistant strain	Impact of progressing from colonization to infection

Cosgrove SE etal. *Clin Infect Dis*. 2003; 36:1433-1437.
Kaye KS et al. *Emerg Infect Dis*. 2004; 10: 1125-1128.

Methodologic Issues in Resistance Outcome Studies: Factors That Improve Reliability of Measure

- Controlling for length of stay (LOS)
  - Correlation between LOS before the infection and the mortality, LOS, and costs afterwards
- Adjustment for underlying severity of illness
  - No well-validated method for infectious disease outcomes
  - Options include APACHE, McCabe and Jackson, etc
  - Also adjust for underlying comorbidities
  - Measurement of both should occur before infection occurs

Outcomes Related to Resistance in *Pseudomonas aeruginosa*

- Patient admissions with *P aeruginosa* infection 1994-6 (n=489)
  - 1/3 nosocomial
  - 1/3 with resistance to ceftazidime, ciprofloxacin, imipenem, and/or piperacillin at baseline
  - Emergence of resistance in 6%
  - Sites: wound 41%, urine 22%, respiratory 21%, effusion 5%, blood 4%, tissue 4%

Carmeli Y, et al. Arch Intern Med. 1999; 159:1127.

Independent Outcomes Related to Resistance in *Pseudomonas aeruginosa*

	Resistance at Baseline			Emergence of Resistance		
Outcome	RR	(95% CI)	*P*	RR	(95% CI)	*P*
Mortality†	1.3	(0.6-2.8)	.52	3.0	(1.2-1.78)	.02
LOS	1.0	(0.9-1.2)	.71	1.7	(1.3-2.3)	<.001
Daily Hospital charges	1.0	(1.0-1.4)	.41	1.1	(0.9-1.3)	.43

† Variables included in model: ICU stay, female, Charlson comorbidity score

Carmeli Y, et al. Arch Intern Med. 1999; 159:1127.

Outcomes Related to Emergence of 3rd-Generation Cephalosporin Resistant *Enterobacter* species

- Nested matched cohort study of pts admitted 1994-7
  - Cases: with initial *Enterobacter* sp. strain susceptible to 3rd-generation cephalosporin and resistant strain was subsequently isolated (n=46)
  - Controls: susceptible *Enterobacter* strains were isolated (n=113)
- Controls matched based on
  - Site from which *Enterobacter* was isolated
  - LOS prior to isolation of susceptible strain
  - LOS of controls exposure time

Cosgrove SE, et al. *Arch Intern Med*. 2002; 162:185.

Independent Outcomes for Patients With Emergence of Third-Generation Cephalosporin Resistance *Enterobacter* species

Outcome	Emergence of Resistance	No EOR	OR	Attributable to EOR	*P*
Mortality†	26%	13%	5.02	--	.01
Median LOS	30	19	1.47	9	<.001
Hospital Charges	$79,323	$40,406	1.51	$29,379	<.001

† Variables included in model: McCabe score, number of comorbidities, ICU stay

Cosgrove SE, et al. Arch Intern Med. 2002; 162:185.

Outcomes Related to ESBL-Producing *Escherichia coli* and *Klebsiella pneumoniae*

- Retrospective matched cohort study of pts admitted 1997-8
  - Cases: hospitalized patients with culture positive for extended-spectrum β -lactamase- (ESBL) producing *E coli* or *K pneumoniae* (n=33)
  - Controls: hospitalized patients with culture positive for non-ESBL-producing *E coli* or *K pneumoniae* (n=66)
  - Sites: urinary 51.5%, wound 15%, catheter 12%, blood 9%, respiratory 9%, abdominal 3%
  - Total antibiotic exposure was the only independent predictor of ESBL-producing *E coli* or *K pneumoniae*

Lautenbach E, et al. Clin Infect Dis. 2001; 32:1162-1171.

Outcomes for Patients With Infection Due to ESBL-Producing *E. coli* and *K. pneumoniae*

Outcome	Case Patients	Control Patients	RR	*P*
Mortality	15%	9%	1.91	.35
Median LOS‡	11	7	1.23	.34
Median Charge‡	$66,590	$22,231	1.71	.04

Controlling for APACHE II score and LOS before infection

Lautenbach E, et al. Clin Infect Dis. 2001; 32:1162-1171.

Outcomes for Patients With Infection Due to Acinetobacter

Table 2. Matched univariate analysis comparing outcomes of patients with multidrug-resistant (MDR) *Acinetobacter* infection with those with susceptible *Acinetobacter* infection and those without *Acinetobacter* infection, Baltimore hospitals, 2003–2004

Outcome evaluated	MDR *Acinetobacter*, n = 96	Susceptible *Acinetobacter*, n = 91	p values for *MDR Acinetobacter* vs. susceptible, n = 182	Uninfected, n = 89	p values for *MDR Acinetobacter* vs. uninfected, n = 178
Mean length of stay after index day, d	27.5	19.8	0.02	18.6	<0.01
Mean intensive care unit length of stay after index day, d	13.3	6.7	0.04	7.3	<0.01
Mortality rate (%)	26.0	17.6	0.21	11.2	<0.01

Sunenshine, et al. EID. 2007; 13:97.

Outcomes for Patients With Infection Due to Acinetobacter

Table 3. Multivariable analysis of outcomes of patients with and without multidrug-resistant (MDR) *Acinetobacter* infections, Baltimore hospitals, 2003–2004*

Outcome evaluated	MDR *Acinetobacter* vs. susceptible† OR (95% CI)	MDR *Acinetobacter* vs. uninfected† OR (95% CI)
Length of stay, d	2.5 (1.2–5.2)	2.5 (1.2–5.4)
Intensive care unit length of stay, d	2.1 (1.0–4.3)	4.2 (1.5–11.6)
Mortality rate (%)	2.6 (0.3–26.1)	6.6 (0.4–108.3)

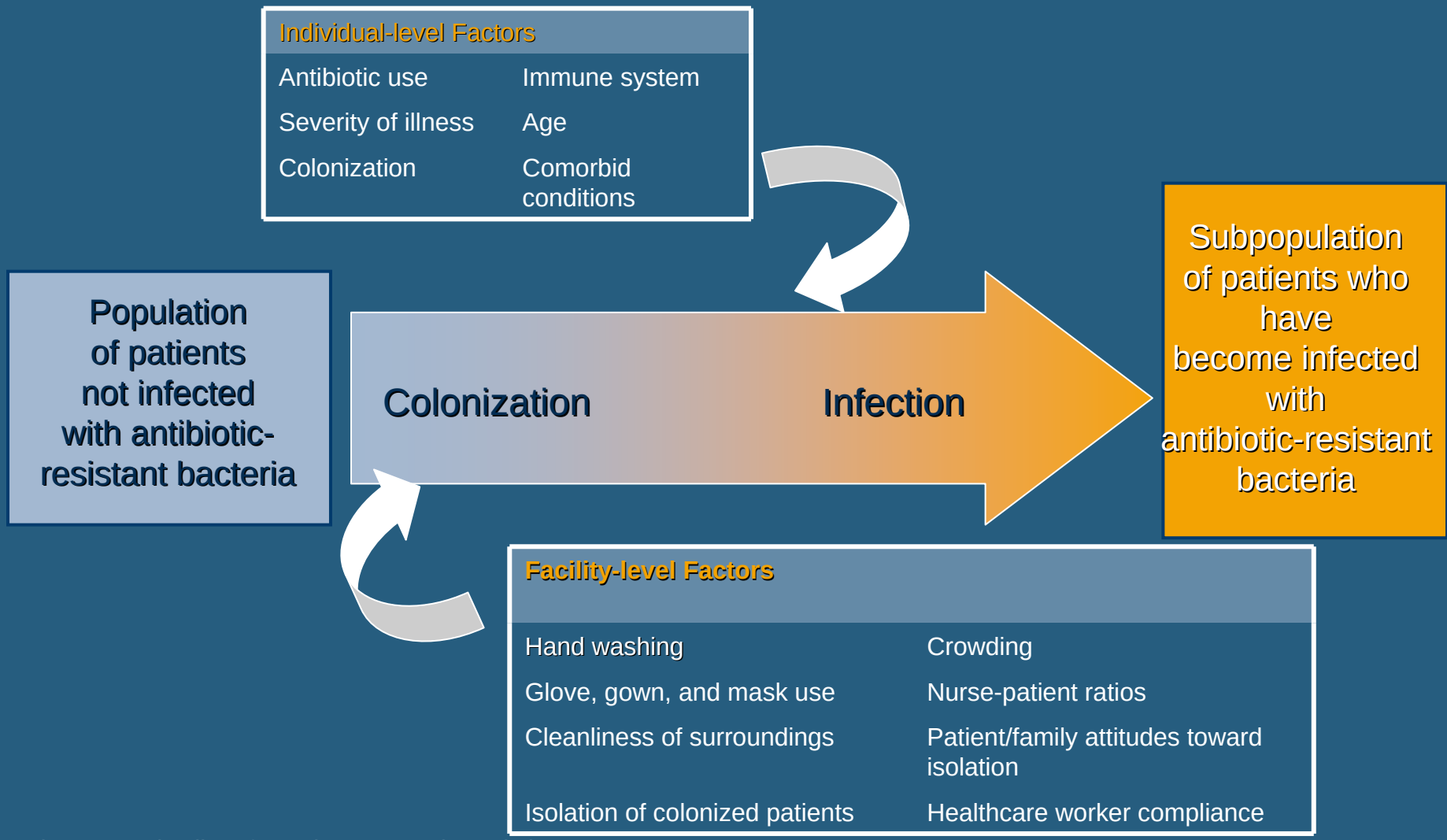
*OR, odds ratio; CI, confidence interval.
†Models include modified Acute Physiology and Chronic Health Evaluation III score to control for severity of illness and Charlson index to control for underlying disease.

Sunenshine, et al. EID. 2007; 13:97.

Possible Explanations for Increased Mortality, LOS, and Cost Related to Infection with Resistant Organisms

- Factors related to the host
  - Severity of underlying disease is synergistic with infection with resistant organisms
- Factors related to the organism
  - Increased virulence
- Factors related to the treatment
  - Decreased effectiveness and/or increased toxicity of antibiotics available for treatment
  - Delay in or absence of microbiologically appropriate antibiotic selection
  - Increased need for surgical intervention

Factors That Influence the Acquisition of a Nosocomial MDRO/Infection



Harris AD, et al. Clin Infect Dis. 2006;43(Suppl 2):S57-S61.

Potential prevention and control measures

- Surveillance
- Education
- Immunization and chemoprophylaxis
- Infection Prevention/Control
  - Hand hygiene
  - Isolation and barrier precautions
  - Cohorting or separation of colonized/infected and non-colonized patients
  - Control of environmental or other potential sources
  - Decolonization of the patient
- Antibiotic stewardship/management

In Sum

- GNRs are important pathogens emerging in healthcare. Their increasing importance, associated morbidity, mortality and costs should drive our prevention and control efforts.
- Measuring outcomes associated with resistance is “tricky” and requires an understanding of the methods used in the study.