

# Therapeutic Options For Multi-drug Resistant Gram-negative Rod Infections

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# **A Consensus Statement**

**“Current options to treat health-care-associated Gram-negative infections are becoming perilously limited as the organisms expand their ability to evade existing antibiotics by development of various resistance mechanisms. Although the epidemiology of drug resistance is difficult to predict, further increases in resistance could lead to a medical and social catastrophe...new antibacterial agents, not subject to existing resistance mechanisms, are urgently required to meet growing clinical problems. However, the source of these new agents is uncertain.”**

**Chopra I, et al. Lancet Infect Dis 2008; 8:133-9.**

# **The Impact of Antimicrobial-Resistant Gram-Negative Infections**

- Resistance to antimicrobial agents is increasing among many gram-negative pathogens<sup>1</sup>
- Infection with resistant pathogens is associated with negative health outcomes<sup>3,4</sup>
  - Mortality/morbidity
  - Length of ICU and hospital stay
  - Healthcare costs
- No new antibiotic classes under development<sup>2</sup>
  - Highlights the need to optimize existing classes of antimicrobials

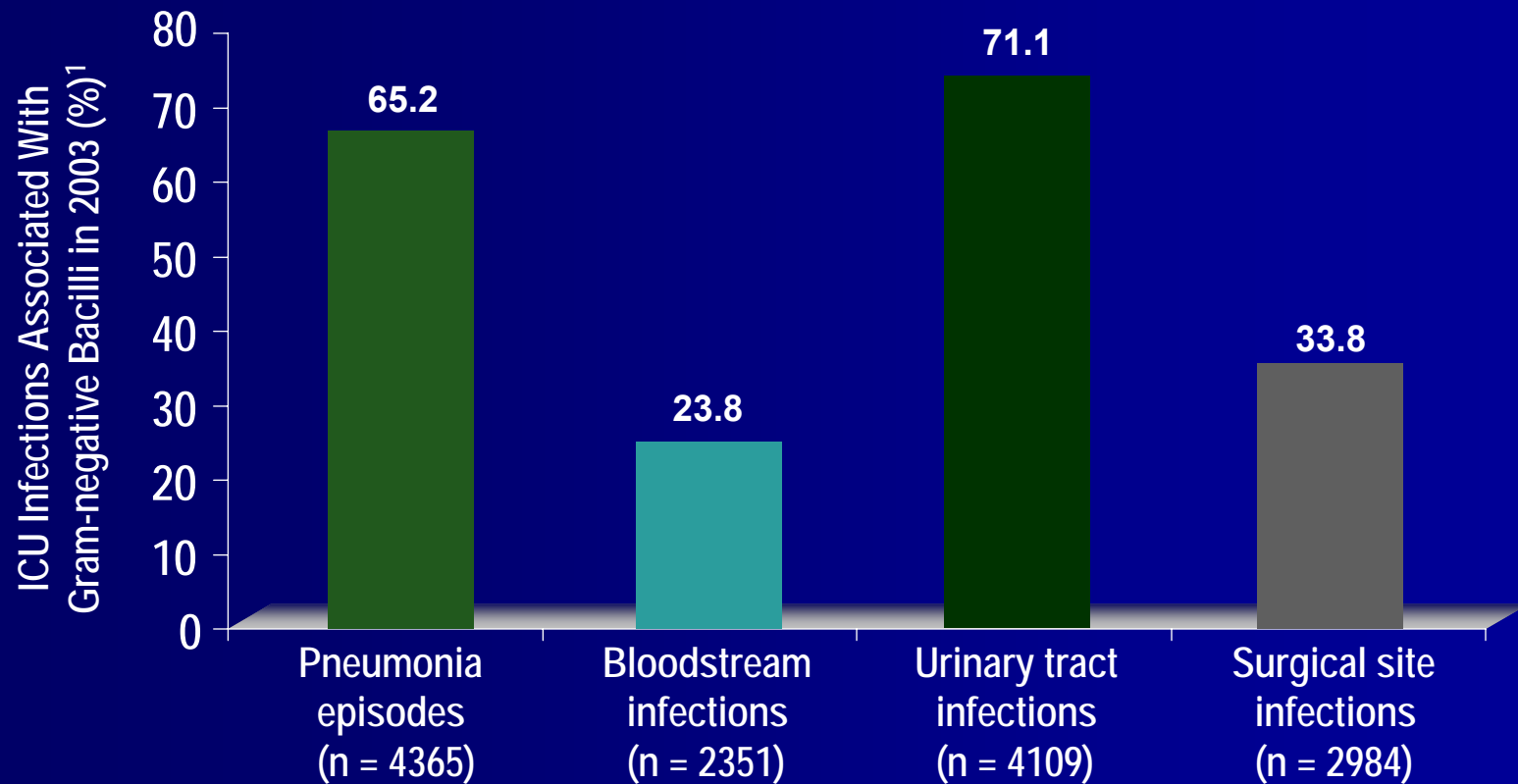
# Death Rates From Resistant Bacteria

	$\approx \text{rate} / 10^5$
MRSA, USA, 2005	6
KPC, Israel, 2007	8
VIM, Greece, 2007	17

**JAMA 1008; 300:2911-3**

# The Role of Gram-Negative Bacilli in Nosocomial Infections

## NNIS epidemiologic data of ICU infections in 2003



**NNIS = National Nosocomial Infections Surveillance System; ICU = Intensive Care Unit**

Gaynes R, et al. *Clin Infect Dis*. 2005;41:848-854.

## Percentage of Nosocomial Infections Associated With Selected Pathogens, 2003

Type of Infection	<i>E coli</i> , %	<i>Enterobacter</i> spp, %	<i>P aeruginosa</i> , %	<i>K pneumoniae</i> , %	<i>Acinetobacter</i> spp, %
Pneumonia (n=4365)	5.0	10.0	18.1	7.2	6.9
Bloodstream infection (n=2351)	3.3	4.4	3.4	4.2	2.4
Urinary tract infection (n=4109)	26.0	6.9	16.3	9.8	1.6
Surgical site infection (n=2984)	6.5	9.0	9.5	3.0	2.1

Boxes indicate most prevalent gram-negative species isolated for type of infection

Data from the National Nosocomial Infections Surveillance (NNIS) System, 2003. Percentages of bacterial ICU isolates are shown.  
 Gaynes R, Edwards JR. *Clin Infect Dis*. 2005;41:848-854.

# Gram-Negative Infections Are Associated With Poor Outcomes in VAP

Pathogen	Prevalence n (%)	Mortality <sup>a</sup> n (%)
<i>P aeruginosa</i>	57 (14.3)	16 (28.6)
<i>K pneumoniae</i>	13 (3.3)	3 (23.1)
<i>Enterobacter</i> spp	13 (3.3)	1 (7.7)
<i>E coli</i>	12 (3.0)	3 (25.0)
<i>Acinetobacter</i> spp	8 (2.0)	4 (50.0)

Adapted from Kollef MH, et al. *Chest*. 2006;129:1210-1218.

**VAP is often associated with gram-negative pathogens and high mortality<sup>1-3</sup>**

<sup>a</sup>Mortality rates reflect patients in each organism category only.

VAP = ventilator-associated pneumonia

Study design and inclusion criteria: 398 patients included from 20 ICUs across the United States. Patients were hospitalized for > 48 h, intubated and receiving mechanical ventilation, and > 18 years of age.

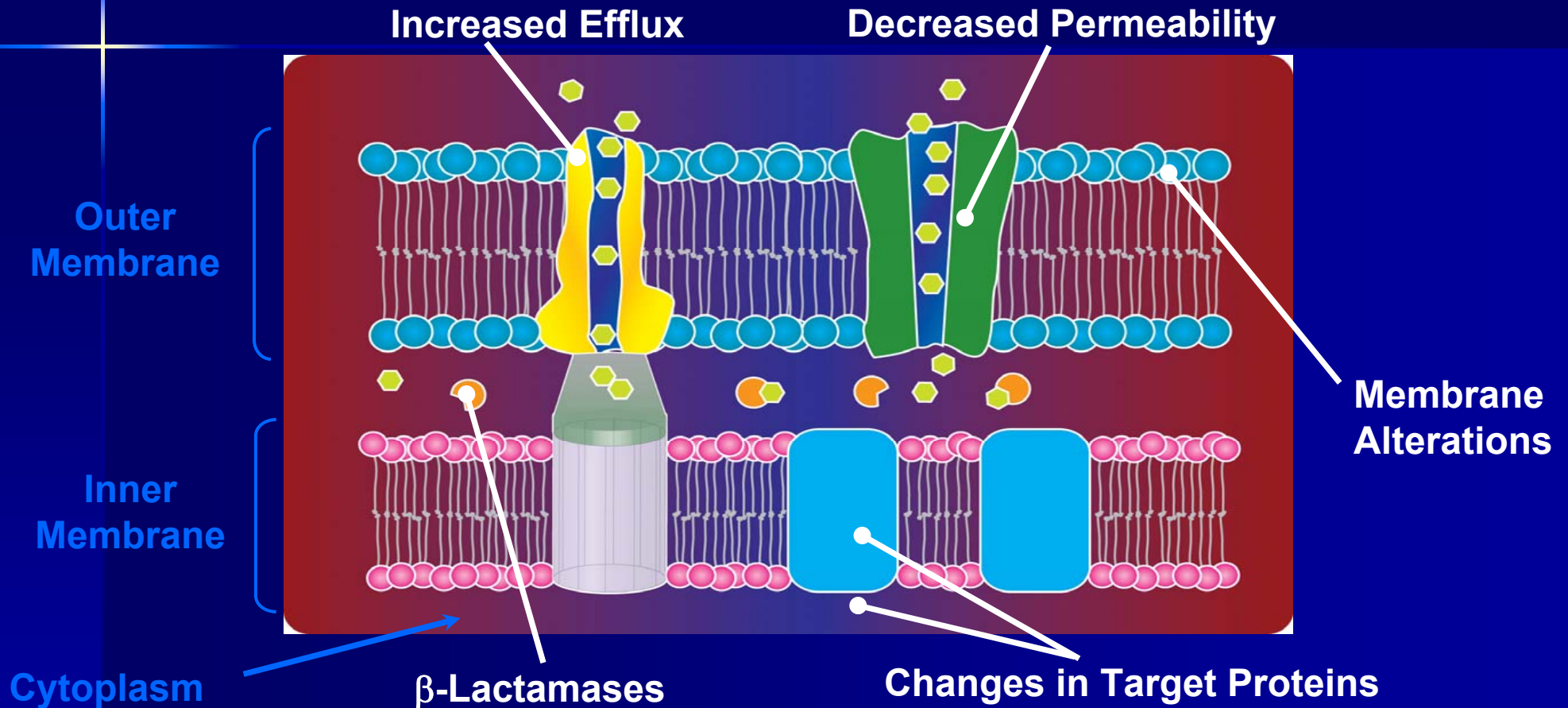
VAP diagnosis based on American College of Chest Physicians criteria. All eligible patients must have had a respiratory tract culture prior to beginning antibiotic therapy. Only first-episode cases of VAP were eligible.

# Antimicrobial Resistance in Gram-Negative Infections

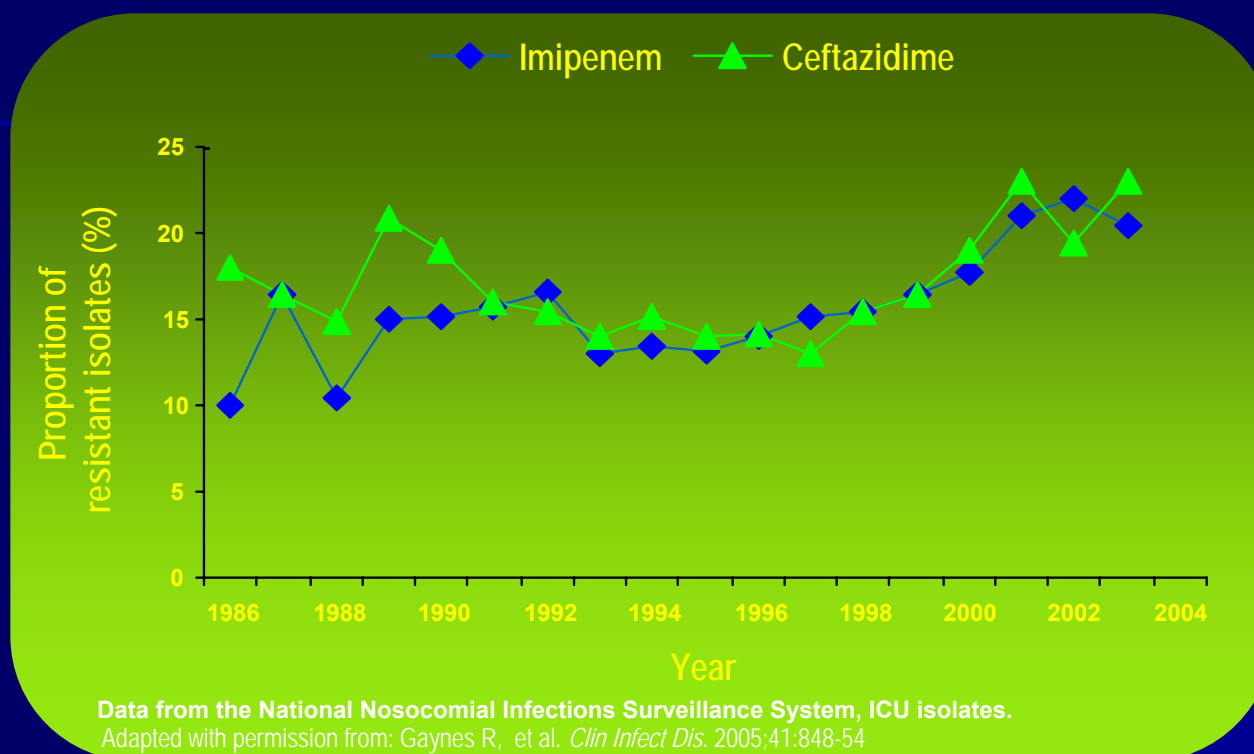
- Resistance is a complex problem<sup>1,2</sup>
  - Multiple/concurrent mechanisms
  - Expanding mechanisms
    - >500 discrete b-lactamases
    - Evolution of carbapenemases
    - Efflux pumps
    - Permeability changes
  - Selective antimicrobial pressure favors amplification of resistant bacteria
- Adverse impact on patient outcomes<sup>3</sup>
  - Mortality, length of stay, healthcare costs



# Selected Resistance Mechanisms in Gram-Negative Pathogens



# Resistance to Imipenem and Ceftazidime Continues to Rise in *Pseudomonas aeruginosa*<sup>1</sup>



- Independent study of 8,244 *P aeruginosa* ICU isolates collected from 1994 to 2000 reported the following average susceptibilities<sup>2</sup>:
  - tobramycin, 87%
  - imipenem, 83%
  - amikacin, 90%
  - piperacillin-tazobactam, 78%
  - cefepime, 71%

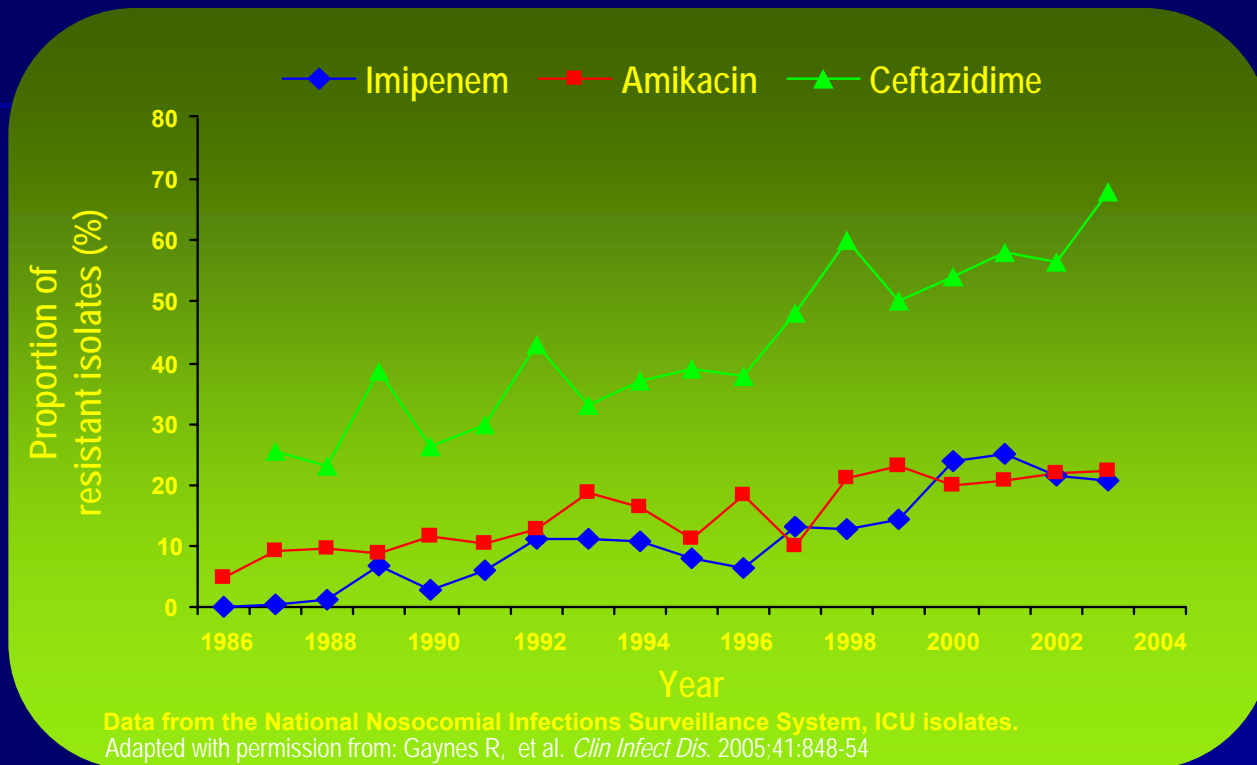
# Prior Therapy Increases the Emergence of Resistance in Infections Caused by *P aeruginosa*

	No. (%) of patients, by previous antibiotic received					
	Imipenem		Third-generation Cephalosporin		Fluoroquinolone	
	No n = 114	Yes n = 21	No n = 73	Yes n = 62	No n = 100	Yes n = 35
Resistance to imipenem	19 (16.7)	11 (52.4) <sup>a</sup>	12 (16.4)	18 (29.0)	18 (18.0)	12 (34.3) <sup>d</sup>
Resistance to ceftazidime	17 (14.9)	7 (33.3)	6 (8.2)	18 (29.0) <sup>b</sup>	14 (14.0)	10 (28.6)
Resistance to ciprofloxacin	35 (30.7)	11 (52.4)	25 (34.2)	21 (33.9)	26 (26.0)	20 (57.1) <sup>c</sup>

<sup>a</sup>P = .0009; <sup>b</sup>P = .003; <sup>c</sup>P = .001; <sup>d</sup>P = .05. All P values are for comparisons between the "No" and "Yes" groups.

Data from a prospective single-ICU study including 135 patients with VAP admitted between January 1994 and August 1999. 125 (93%) of patients had received antibiotics within 15 days prior to receiving the diagnosis of VAP.

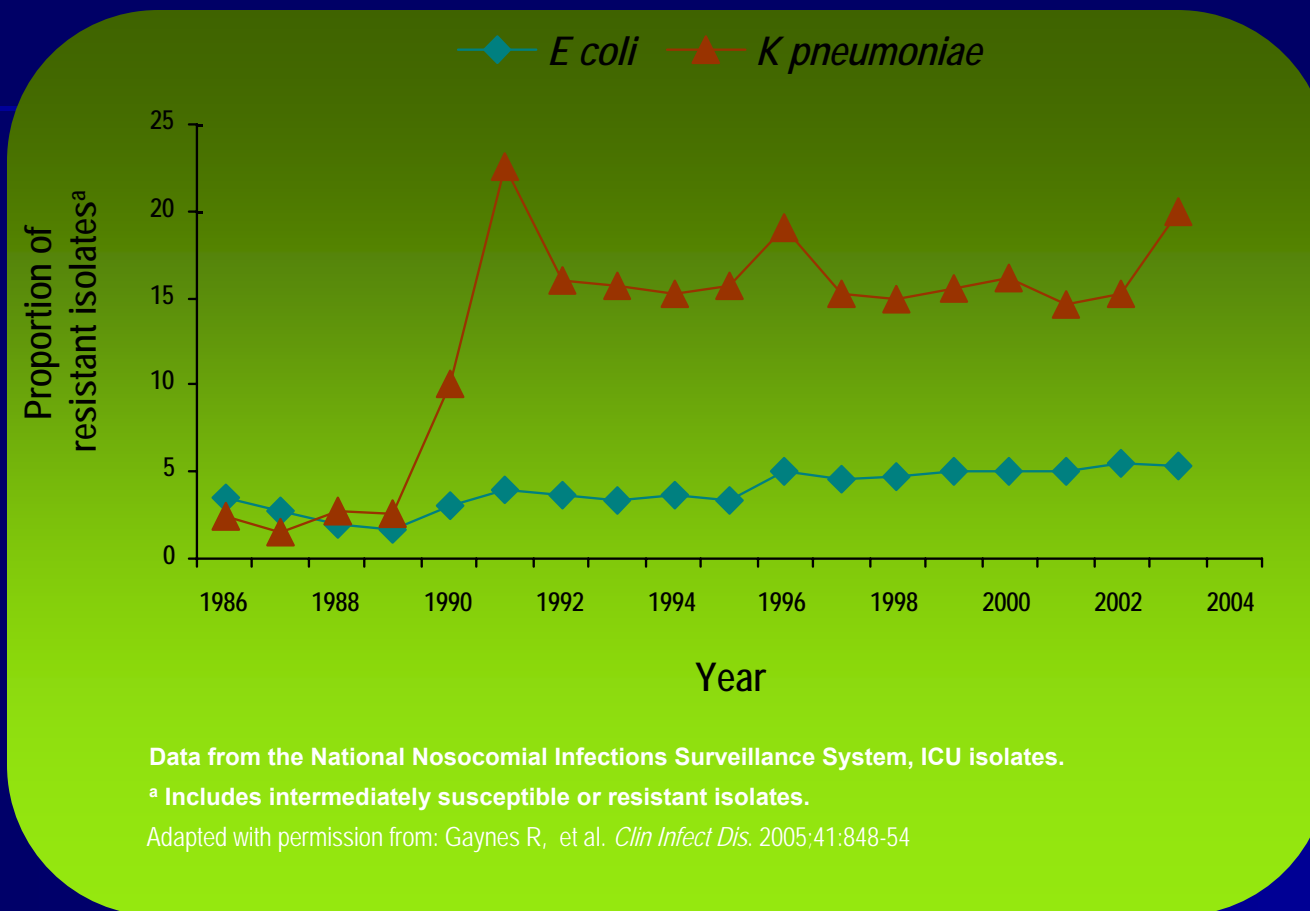
# Resistance Continues to Increase in *Acinetobacter* spp<sup>1</sup>



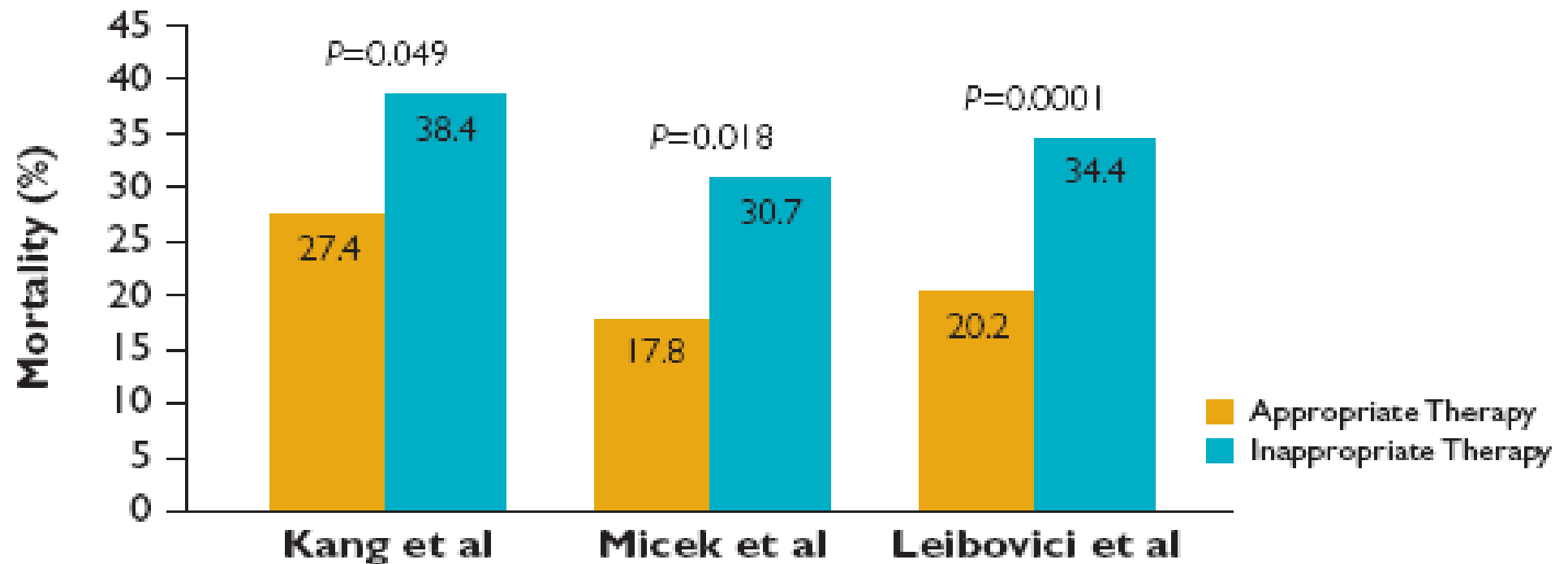
- Recent reports of rapid emergence of resistance to tigecycline among *Acinetobacter* spp worrisome<sup>2-4</sup>
  - Efflux-based mechanism may play a role<sup>4</sup>

1. Gaynes R, et al. *Clin Infect Dis*. 2005;41:848-54. 2. Peleg AY, et al. *J Antimicrob Chemother*. 2007;59:128-131.  
3. Navon-Venezia S, et al. *J Antimicrob Chemother*. 2007;59:772-774. 4. Peleg AY, et al. *Antimicrob Agents Chemother*. 2007. In press.

# Resistance to Third-Generation Cephalosporins Among *K pneumoniae* and *E coli*

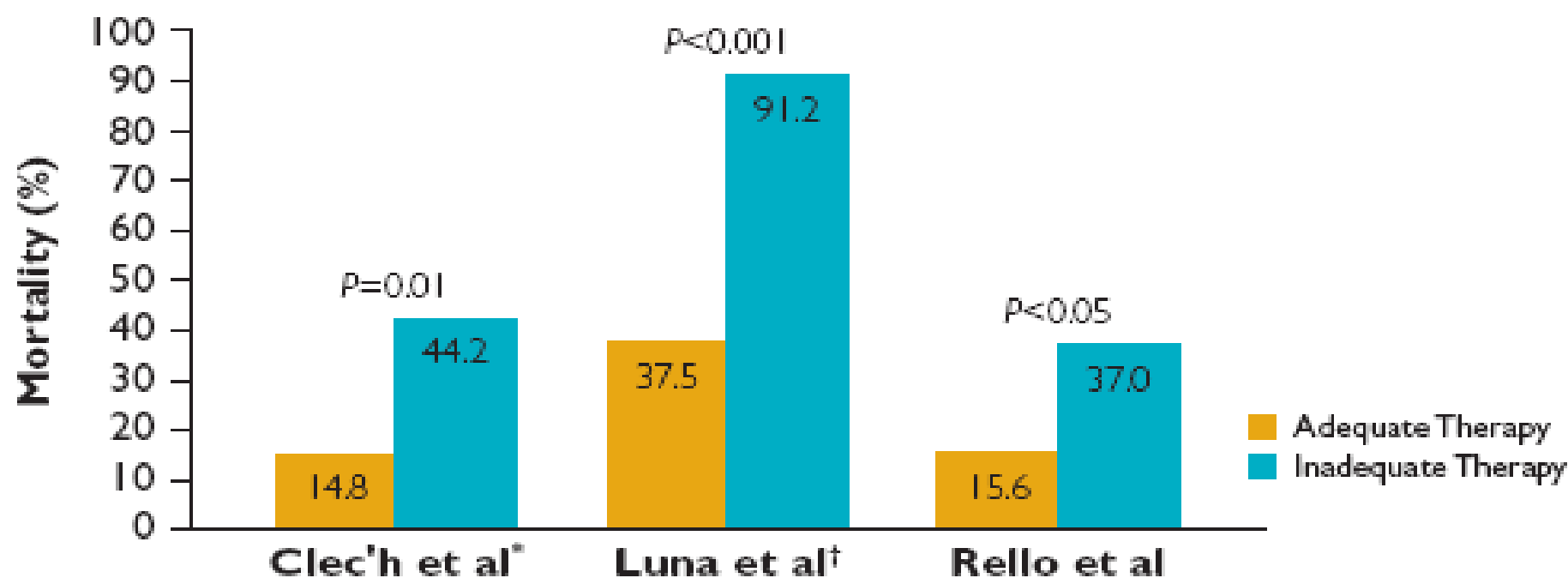


## Bloodstream infection<sup>5-7</sup>



Mortality was compared in patients with bacteremia who received either appropriate or inappropriate initial therapy.

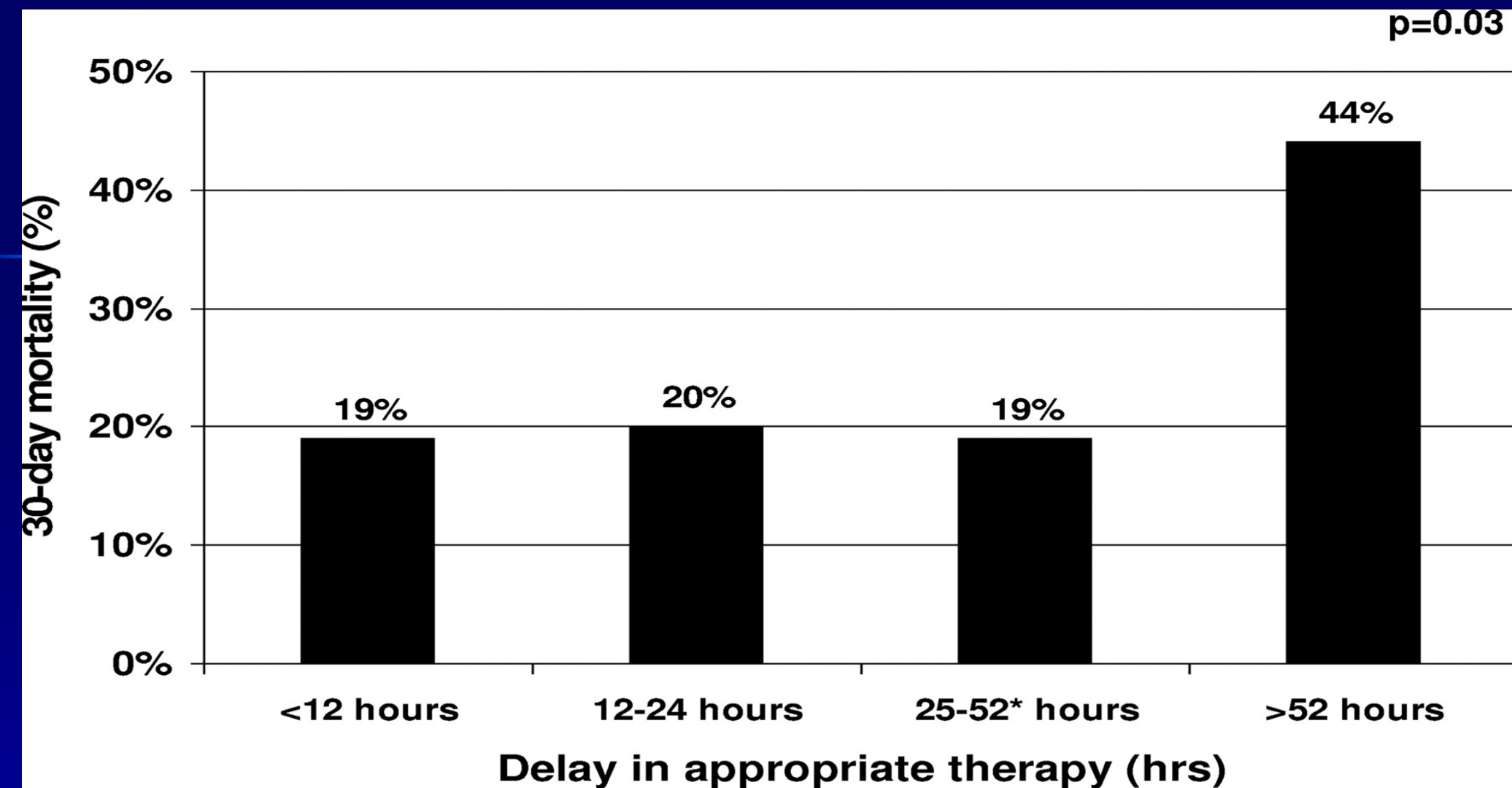
## Ventilator-associated pneumonia<sup>8-10</sup>



\*Patients with a logistic organ dysfunction score  $\leq 4$

† Pre-bronchoalveolar lavage patients

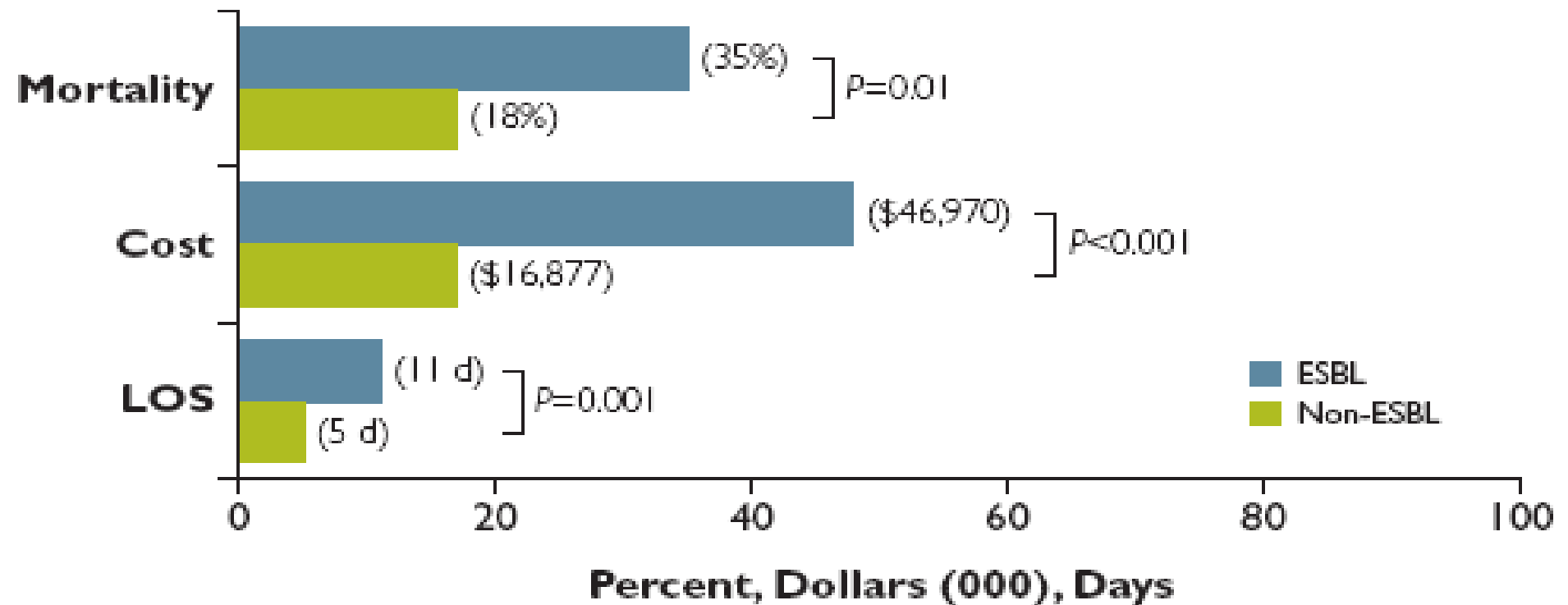
Mortality was compared in patients with ventilator-associated pneumonia (VAP) who received adequate or inadequate antimicrobial therapy.



**FIG. 1. Thirty-day mortality stratified by the length of delay in receiving appropriate therapy. \*, CART-derived time to appropriate therapy breakpoint.**

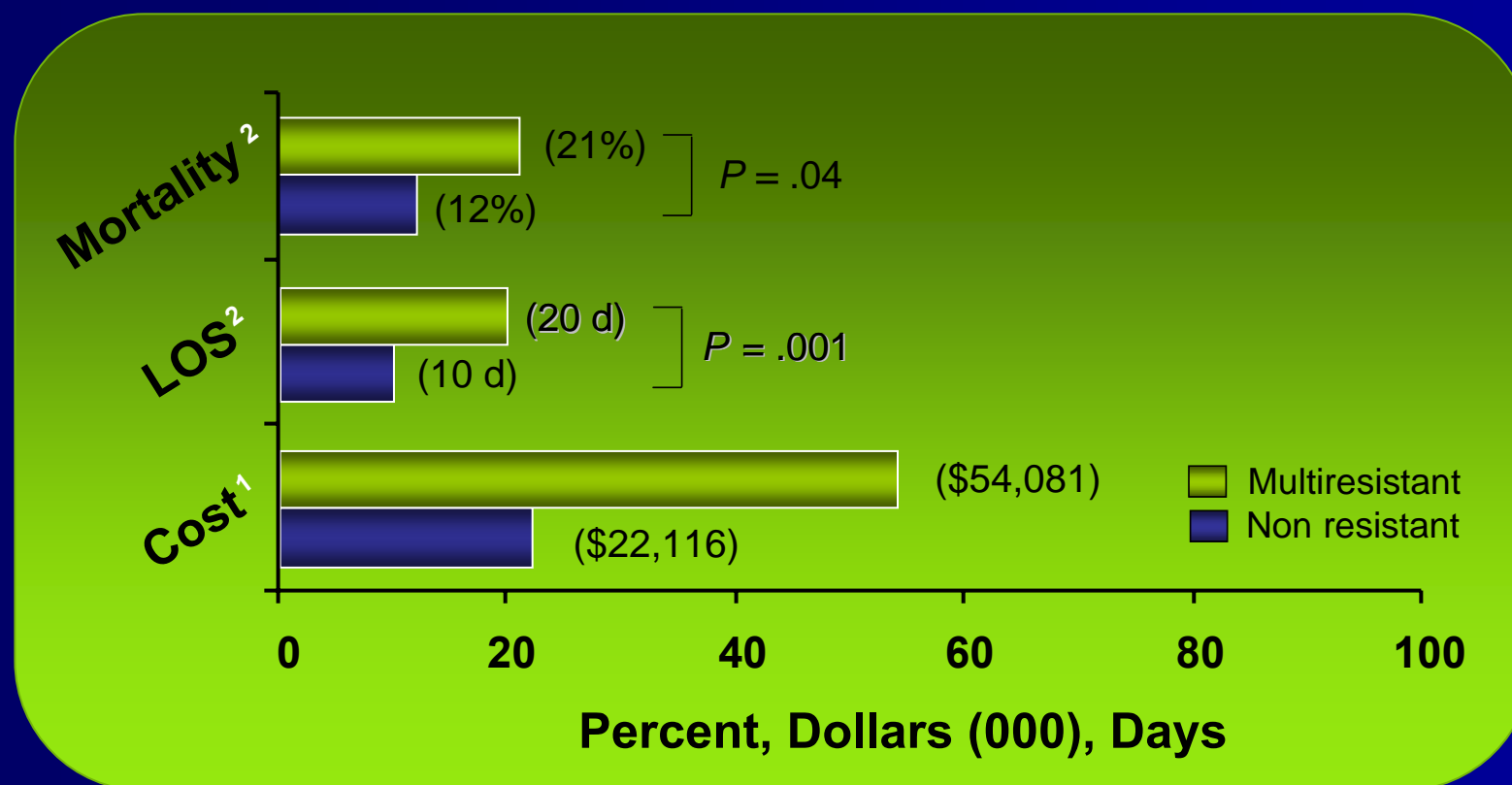


## ESBL-producers in bacteremia<sup>3</sup>



# Negative Outcomes Associated With Resistant Gram-Negative Infections

## Association of MDR *P aeruginosa* With Mortality, LOS, and Cost<sup>1,2</sup>



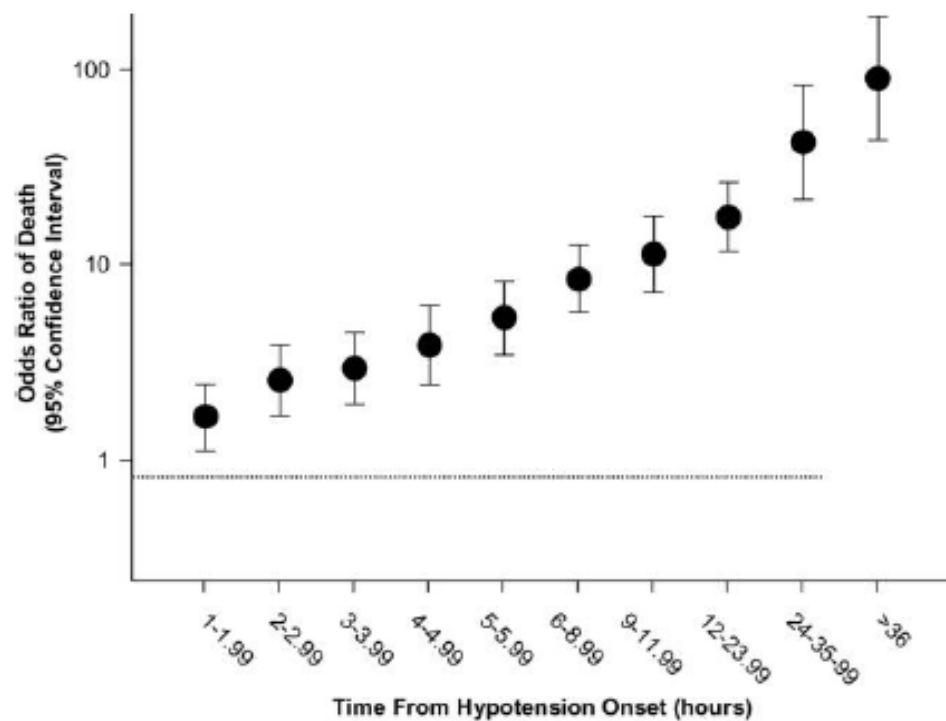
**MDR = multidrug-resistant; LOS = length of stay**

# Negative Outcomes Associated With Resistant Gram-Negative Infections

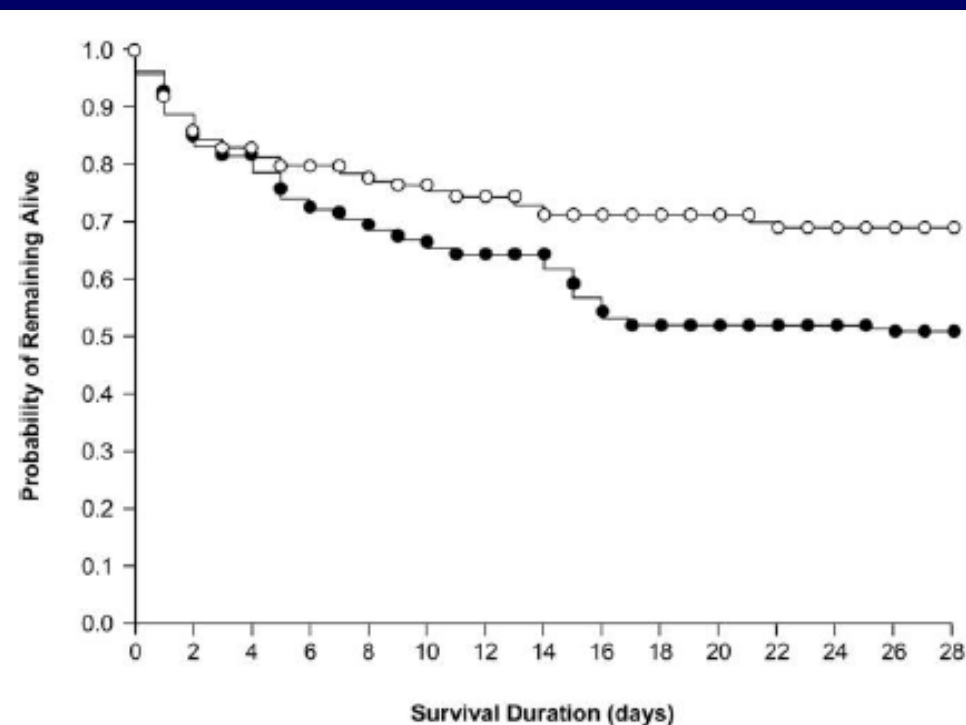
Infection with imipenem-resistant *P aeruginosa* associated with higher mortality, LOS, and hospital costs

Outcome	Imipenem-susceptible	Imipenem-resistant	P value
Mortality	16.7%	31.1%	<.001 <sup>a</sup>
LOS (days)	9	15.5	.02
Hospital costs	\$48 381	\$81 330	<.001

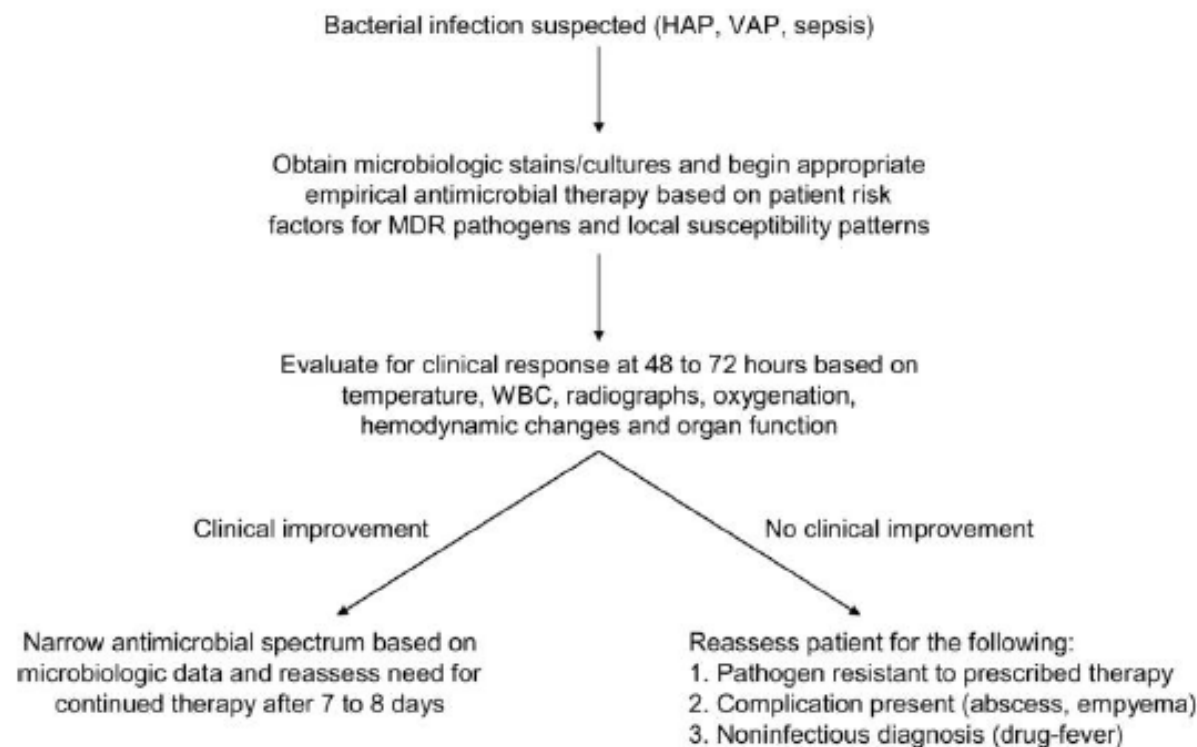
<sup>a</sup> Relative risk, 1.86; 95% CI, 1.38-2.51; LOS = length of stay  
Adapted from: Lautenbach E, et al. *Infect Cont Hosp Epid*. 2006;27:893-900.



**Figure 1.** Mortality risk associated with increasing delays in initiation of effective antimicrobial therapy. Adapted from Kumar A, Roberts D, Wood KE, et al. Duration of hypotension before initiation of effective antimicrobial therapy is the critical determinant of survival in human septic shock. *Crit Care Med* 2006;34:1589–96, with permission from Lippincott Williams & Wilkins [33].

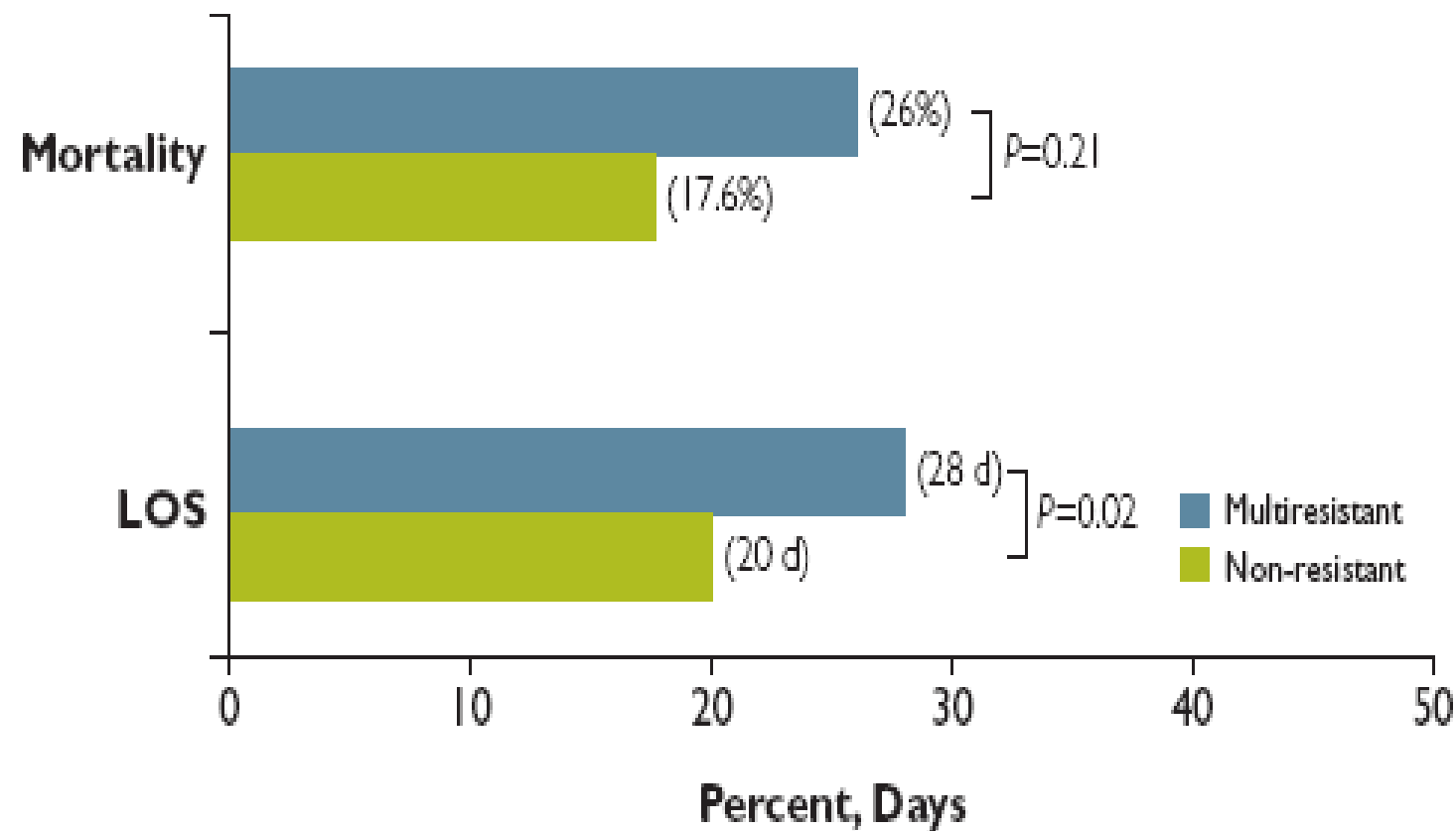


**Figure 2.** Improved survival probability after implementation of a standardized hospital order set for the emergency department. Filled circles denote patients with septic shock managed in the "before" period, and open circles denote patients with septic shock managed in the "after" period ( $P < .001$ , log-rank test). Reprinted from Micek ST, Roubinian N, Heuring T, et al. Before-after study of a standardized hospital order set for the management of septic shock. Crit Care Med 2006;34:2707-13 [6], with permission from Lippincott Williams & Wilkins.

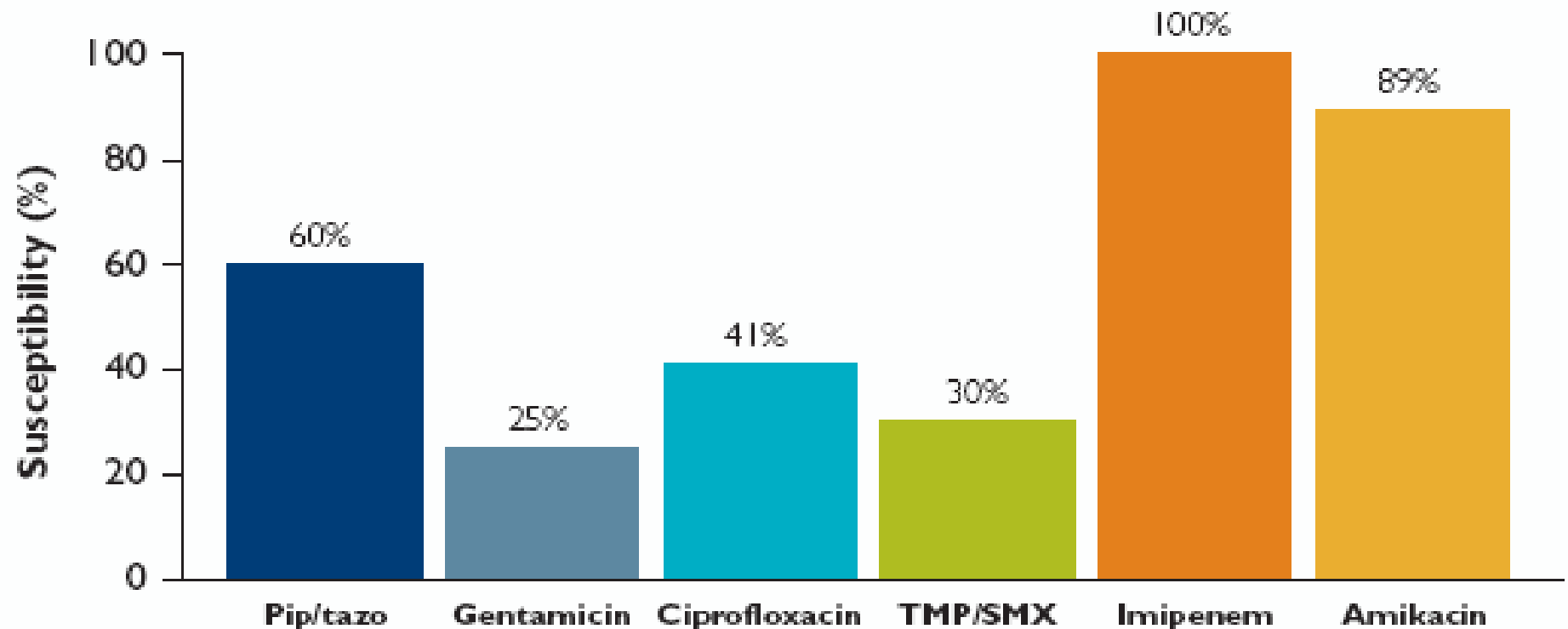


**Figure 3.** Practice algorithm for providing appropriate initial antimicrobial treatment. HAP, hospital-acquired pneumonia; MDR, multidrug resistant; VAP, ventilator-associated pneumonia. Adapted from Kollef MH, Micek ST. Strategies to prevent antimicrobial resistance in the ICU. Crit Care Med 2005;33:1845–53 [77], with permission from Lippincott Williams & Wilkins.

## MDR *Acinetobacter* spp<sup>4</sup>



## Susceptibility of ESBL-producers<sup>8</sup>

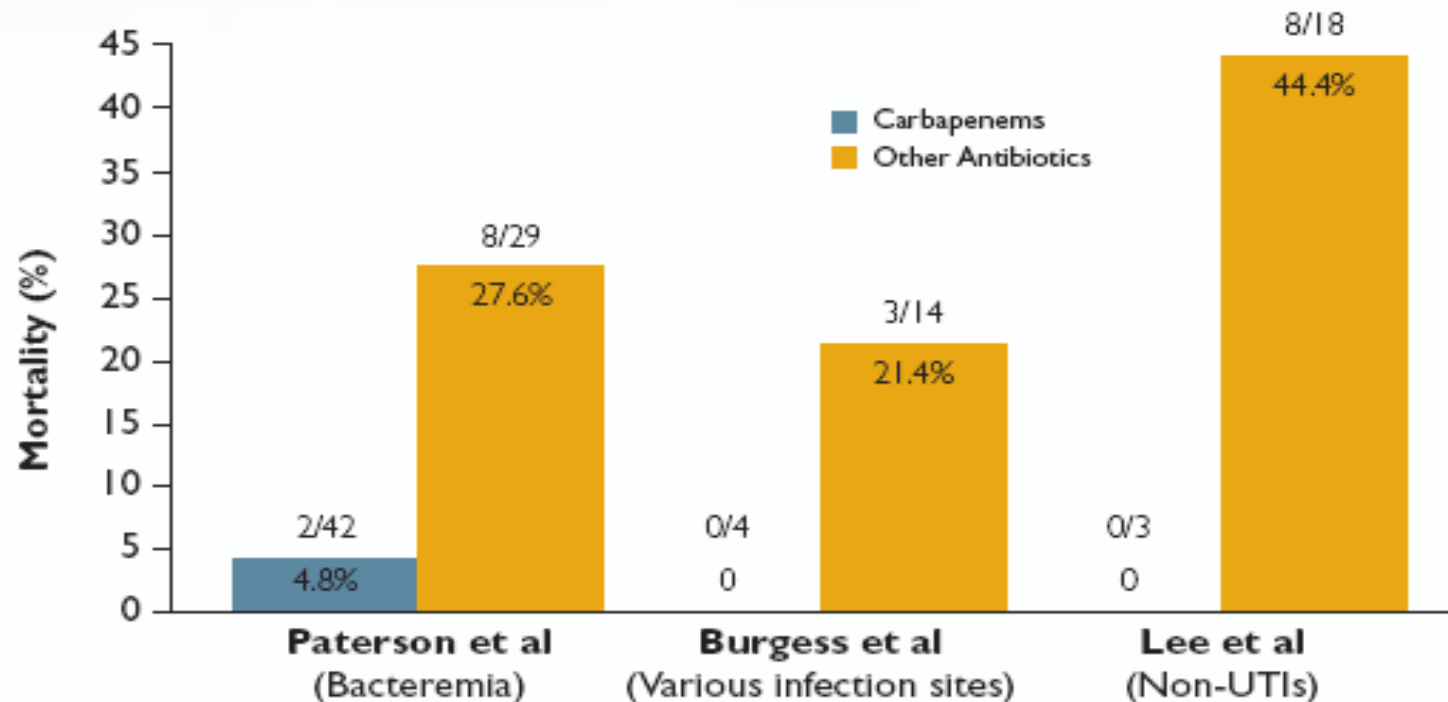


Susceptibility rates of 312 confirmed ESBL isolates from an urban hospital

Pip/tazo = piperacillin-tazobactam; TMP/SMX = trimethoprim-sulfamethoxazole

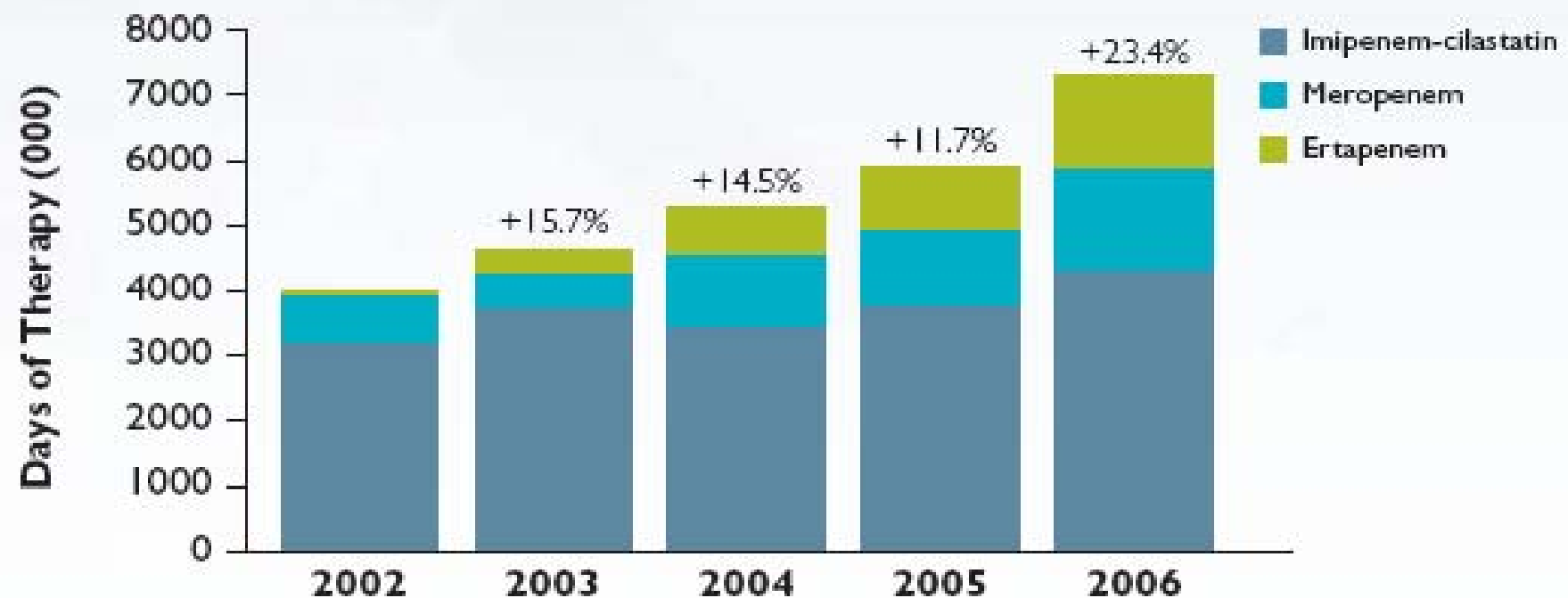


## Carbapenems are an appropriate choice for infections by ESBL-producers<sup>4-6</sup>



- Patients receiving a carbapenem (either as monotherapy or combination therapy) for an ESBL infection have been shown to have lower mortality than patients treated with other antibiotics.<sup>4-6</sup>

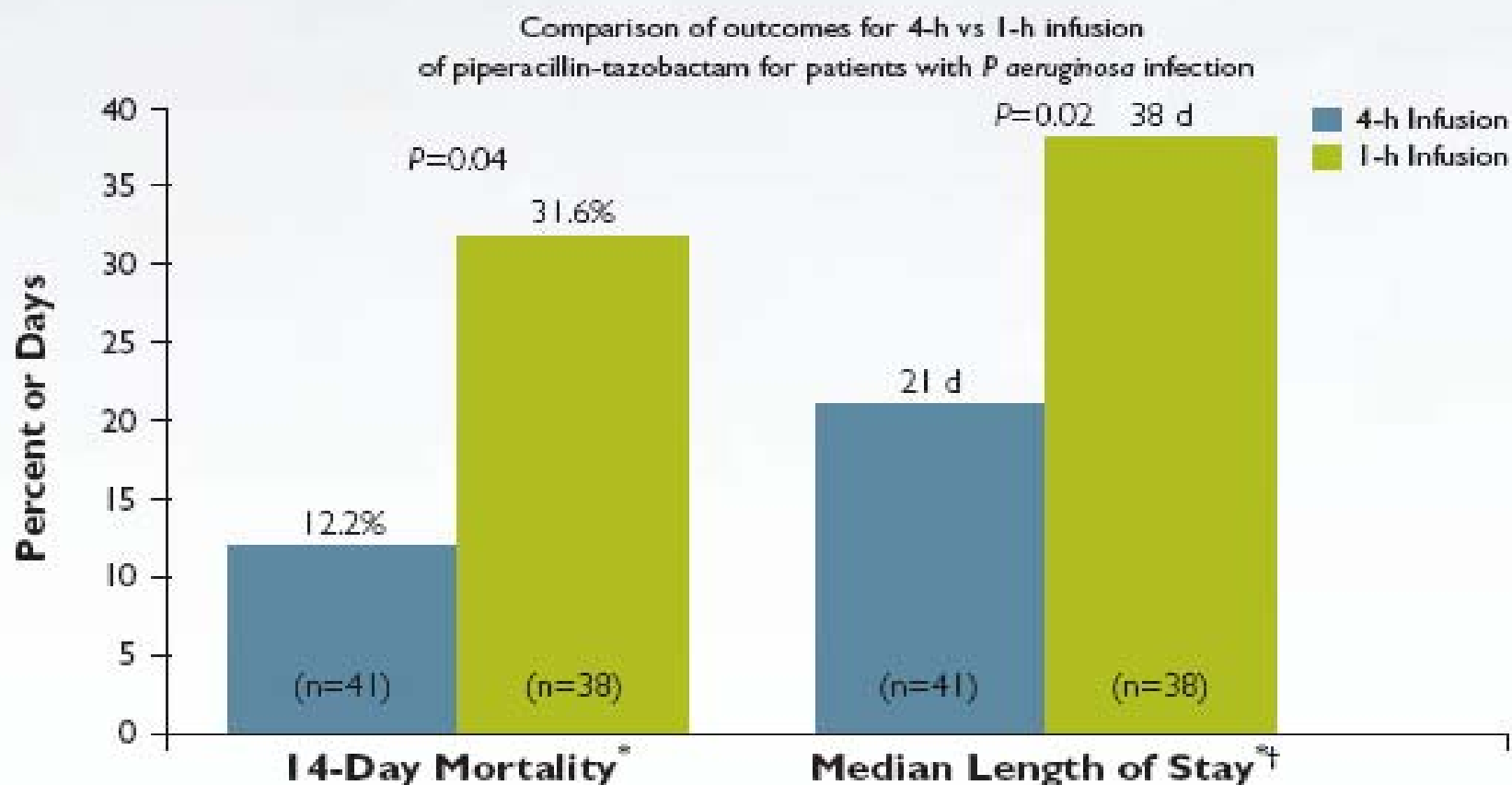
## Carbapenem use is increasing<sup>7</sup>



Source: AMR; data reflect annual totals through June 2006; % represent total carbapenem days of therapy growth vs prior year (eg, 2005 vs 2004).

Carbapenems: imipenem-cilastatin, meropenem, ertapenem.

## Extended $\beta$ -lactam infusions may improve outcomes for patients with severe infections<sup>6</sup>

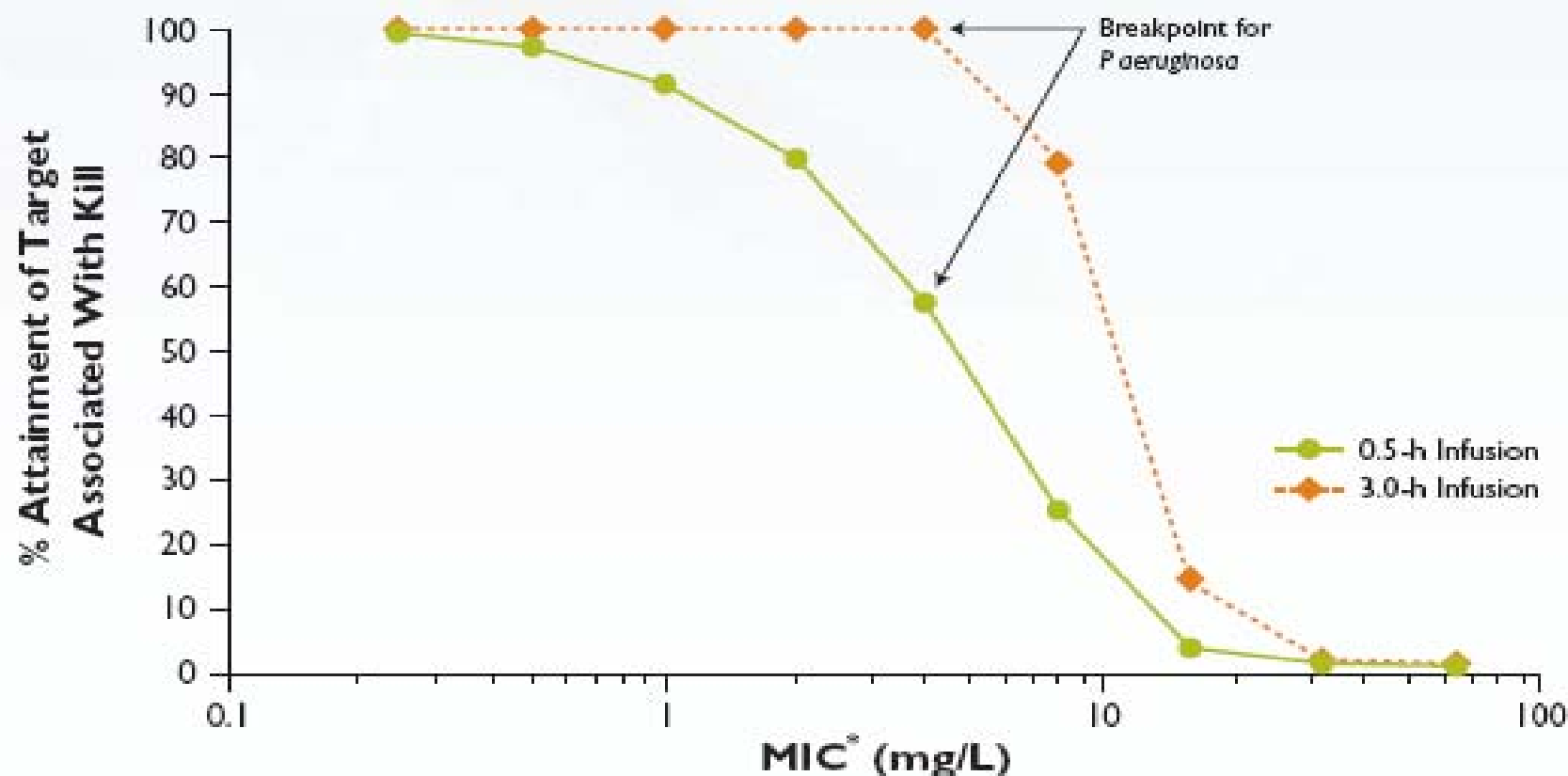


\*Excludes patients with Acute Physiological and Chronic Health Evaluation (APACHE II) score <17.

†Excludes patients who died within 14 days of collecting *P. aeruginosa* culture.

## Extended carbapenem infusions may improve chance of killing resistant pathogens<sup>7</sup>

Probability of achieving adequate *in vitro* bacterial killing (target %T > MIC) for a carbapenem



\*Near maximal killing effect for carbapenem assumed to be drug-free concentration >40% of dosing interval.

Adapted with permission.<sup>7</sup>

## **Resistance among *P. aeruginosa* bloodstream isolates (n=100)**

	<b>% resistant</b>
<b>amikacin</b>	<b>8</b>
<b>aztreonam</b>	<b>37</b>
<b>cefepime</b>	<b>20</b>
<b>ciprofloxacin</b>	<b>50</b>
<b>meropenem</b>	<b>34</b>
<b>pip-tazo</b>	<b>39</b>
<b>tobramycin</b>	<b>33</b>
<b>≥ 4 agents</b>	<b>12</b>

# **Emerging Carbapenem Resistance in Gram-Negative Bacilli**

- **No new drugs for gram-negative bacilli**
- **Significantly limits treatment options for life-threatening infections**
- **Emerging resistance mechanisms, carbapenemases are mobile**
- **Detection of carbapenemases and implementation of infection control practices are necessary to limit spread**

# Carbapenemases

Classification	Enzyme	Most Common Bacteria
Class A	KPC, SME, IMI, NMC, GES	Enterobacteriaceae (reports in <i>P. aeruginosa</i> )
Class B (metallo- $\beta$ - lactamase)	IMP, VIM, GIM, SPM	<i>P. aeruginosa</i> Enterobacteriaceae <i>Acinetobacter</i> spp.
Class D	OXA	<i>Acinetobacter</i> spp.

# Carbapenemases in the U.S.

Enzyme	Bacteria
KPC	Enterobacteriaceae
SME	<i>Serratia marcesens</i>
Metallo- $\beta$ -Lactamase	<i>P. aeruginosa</i> & <i>Acinetobacter</i> spp.
OXA	<i>Acinetobacter</i> spp.



# Metallo- $\beta$ -Lactamases

- Requires zinc for  $\beta$ -lactamase activity
- VIM and IMP are the most common enzymes
- Very mobile resistance mechanism
- Reported in *P. aeruginosa*, *Acinetobacter* spp., Enterobacteriaceae
- One report of VIM-producing *P. aeruginosa* in the United States

# **Metallo-b-Lactamases Phenotype**

- **Confer resistance to all b-lactam agents except aztreonam**
- **Can be detected by the Modified Hodge Test**
- **Can be differentiated from other carbapenemases by assays using EDTA to inhibit the b-lactamase**

# SME Carbapenemase

- Found exclusively in *Serratia marcescens*
- Isolated sporadically in the United States
- Confers resistance to carbapenems, but not extended spectrum cephalosporins

# Susceptibility Profile of an SME-Producer

Antimicrobial	Interpretation	Antimicrobial	Interpretation
Amox/clav	R	Ceftazidime	S
Ampicillin	R	Ceftriaxone	S
Aztreonam	S	Cefepime	S
Cefazolin	R	Ertapenem	R
Cefpodoxime	S	Imipenem	R
Cefotaxime	S	Meropenem	R
Cetotetan	S	Pipercillin/Tazo	S
Cefoxitin	R		

# **Klebsiella Pneumoniae Carbapenemase**

- KPC is a class A b-lactamase
  - Confers resistance to all b-lactams including extended-spectrum cephalosporins and carbapenems
- Occurs in Enterobacteriaceae
  - Most commonly in *Klebsiella pneumoniae*
  - Also reported in: *K. oxytoca*, *Citrobacter freundii*, *Enterobacter* spp., *Escherichia coli*, *Salmonella* spp., *Serratia* spp.,
- Also reported in *Pseudomonas aeruginosa* (Columbia & Puerto Rico)

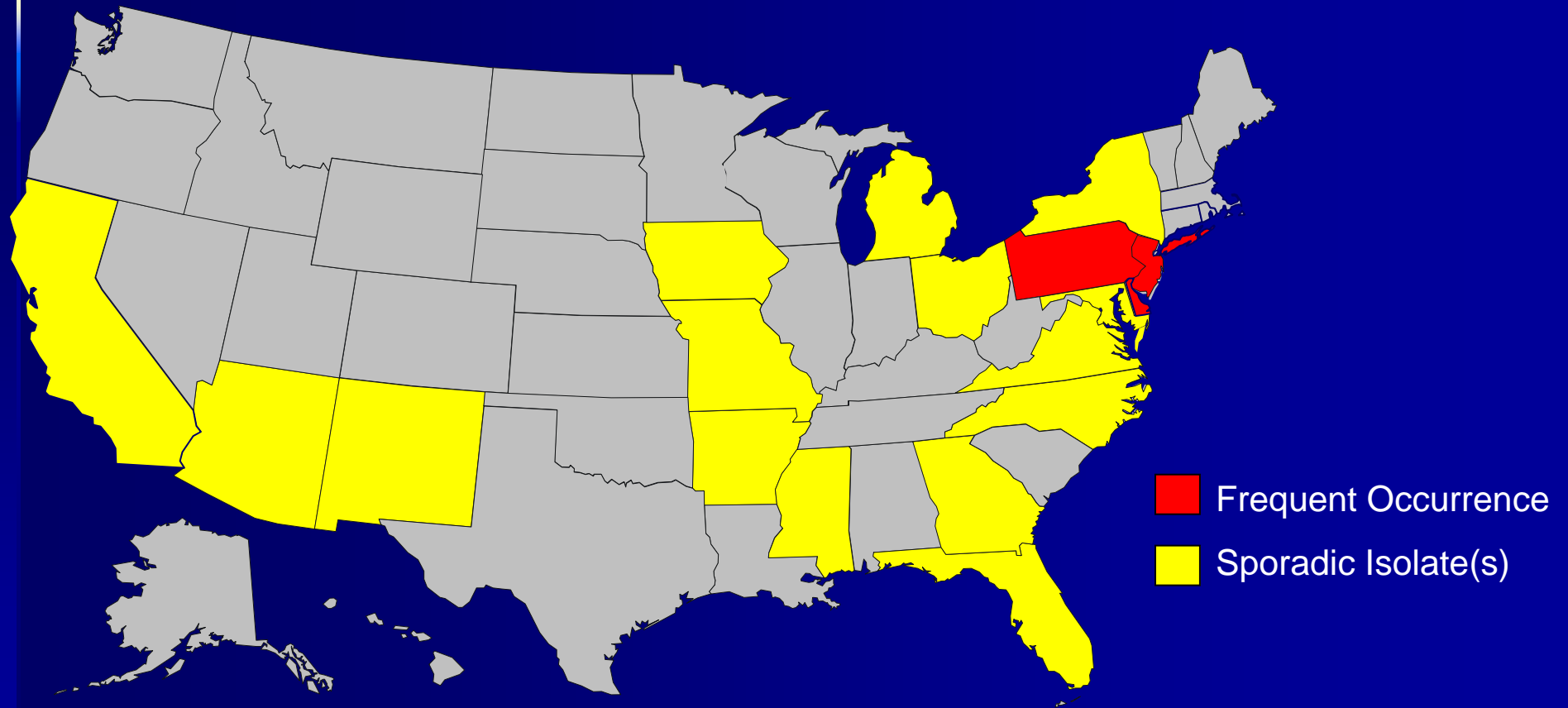
# Susceptibility Profile of KPC-Producing *K. pneumoniae*

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	Pipercillin/Tazo	R
Cetotetan	R	Tobramycin	R
Cefoxitin	R	Trimeth/Sulfa	R
Ceftazidime	R	Polymyxin B	MIC >4mg/ml
Ceftriaxone	R	Colistin	MIC >4mg/ml
Cefepime	R	Tigecycline	S

# KPC Enzymes

- Located on plasmids; conjugative and nonconjugative
- *bla*<sub>KPC</sub> is usually flanked by transposon sequences
- *bla*<sub>KPC</sub> reported on plasmids with:
  - Normal spectrum b-lactamases
  - Extended spectrum b-lactamases
  - Aminoglycoside resistance

# Geographical Distribution of KPC-Producers





# **Impact of Carbapenem-Resistant *K. pneumoniae* – Mt Sinai, NYC, 2004-6**

- 99 cases (+99 carbapenem-suseptible *K.p.*)
- Risks: transplant, MV, longer LOS, exposure to cephalosporins and carbapenems (15x)
- Mortality: cases 48% controls 20% (from infection 38% vs 12%)

**Infect Control Hosp Epidemiol 2008; 29:1099-1106**

# **Impact of KPC-Producing Organisms**

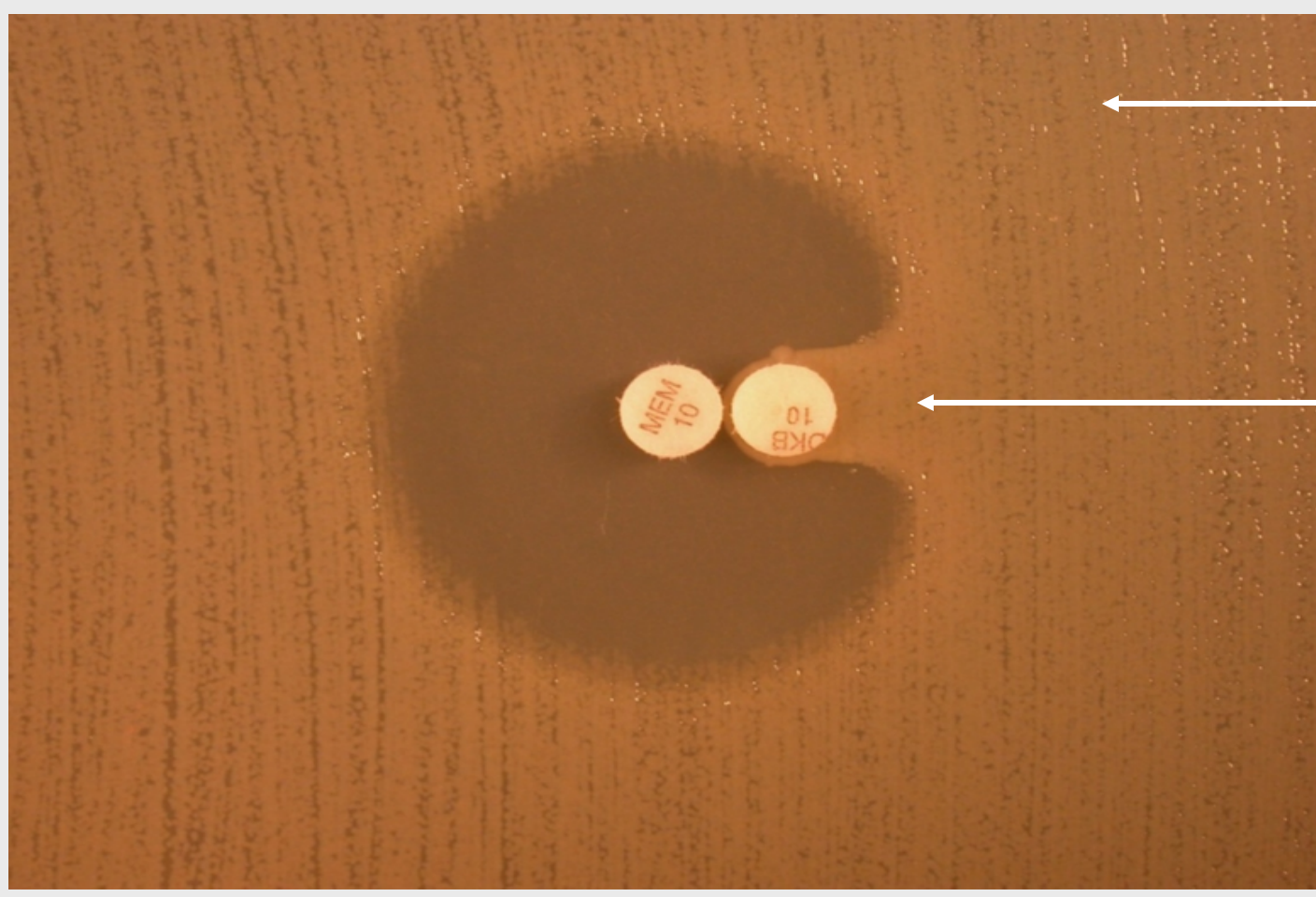
## **University of Virginia; 8/07 – 2/09**

- **36 patients, 42 isolates**
- **4 genera, 8 species**
- **Mortality: overall 34%, bacteremia 66% (8/12)**

# When to Suspect a KPC-Producer

- Enterobacteriaceae – especially *Klebsiella pneumoniae* that are resistant to extended-spectrum cephalosporins:
  - MIC range for 151 KPC-producing isolates
    - Ceftazidime 32 to >64 microg/ml
    - Ceftriaxone  $\geq 64$  microg/ml
    - Cefotaxime  $\geq 64$  microg/ml
  - Variable susceptibility to cefoxitin and cefepime

# Indirect Carbapenemase Test

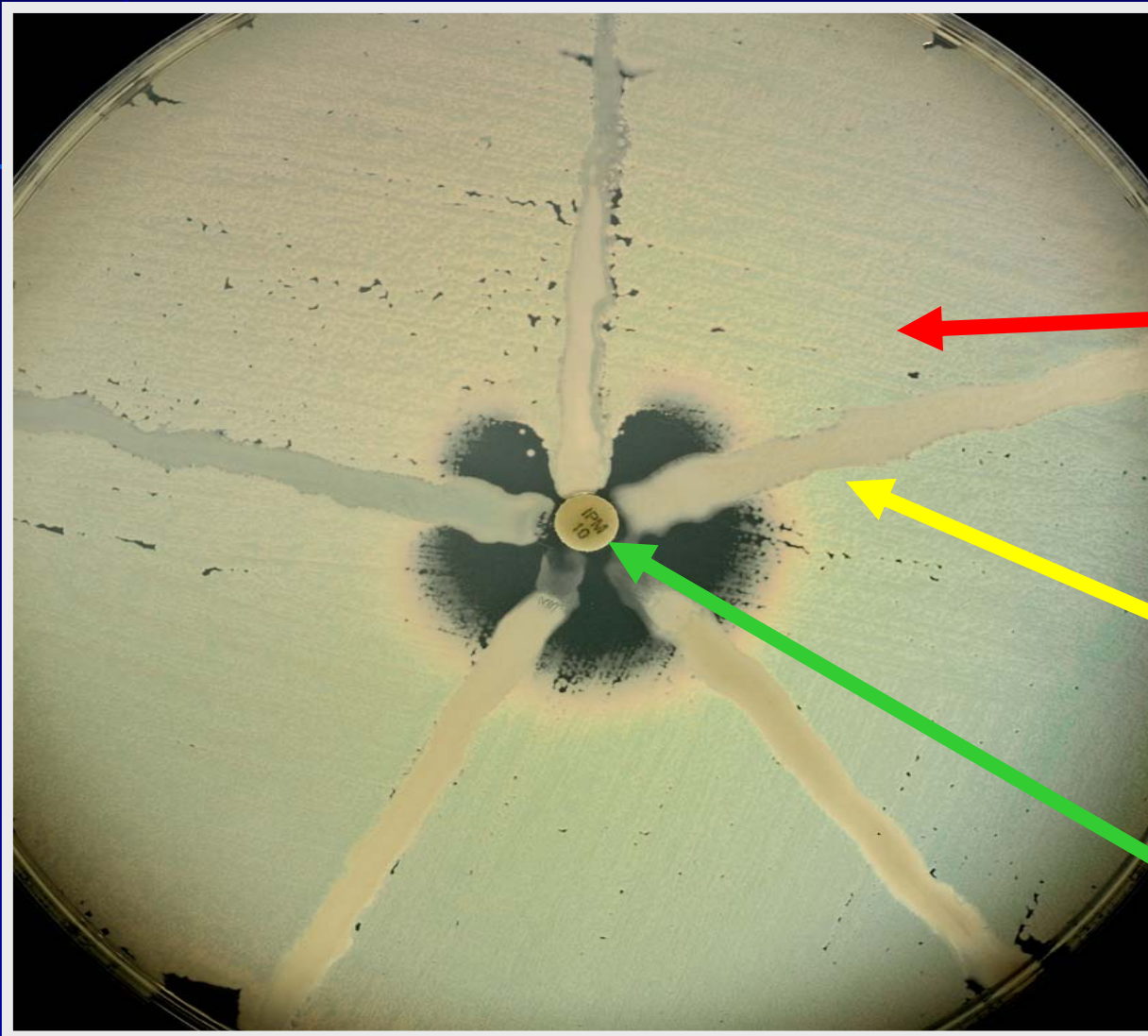


Lawn =  
*E. coli*  
ATCC 25922

Test isolate  
only  
on TE disk

Used with permission from Ken Thomson

# Modified Hodge Test



Lawn of *E. coli* ATCC 25922  
1:10 dilution of a  
0.5 McFarland suspension

Test isolates

Imipenem disk

Described by Lee et al. CMI, 7, 88-102. 2001.

# KPC-Detection

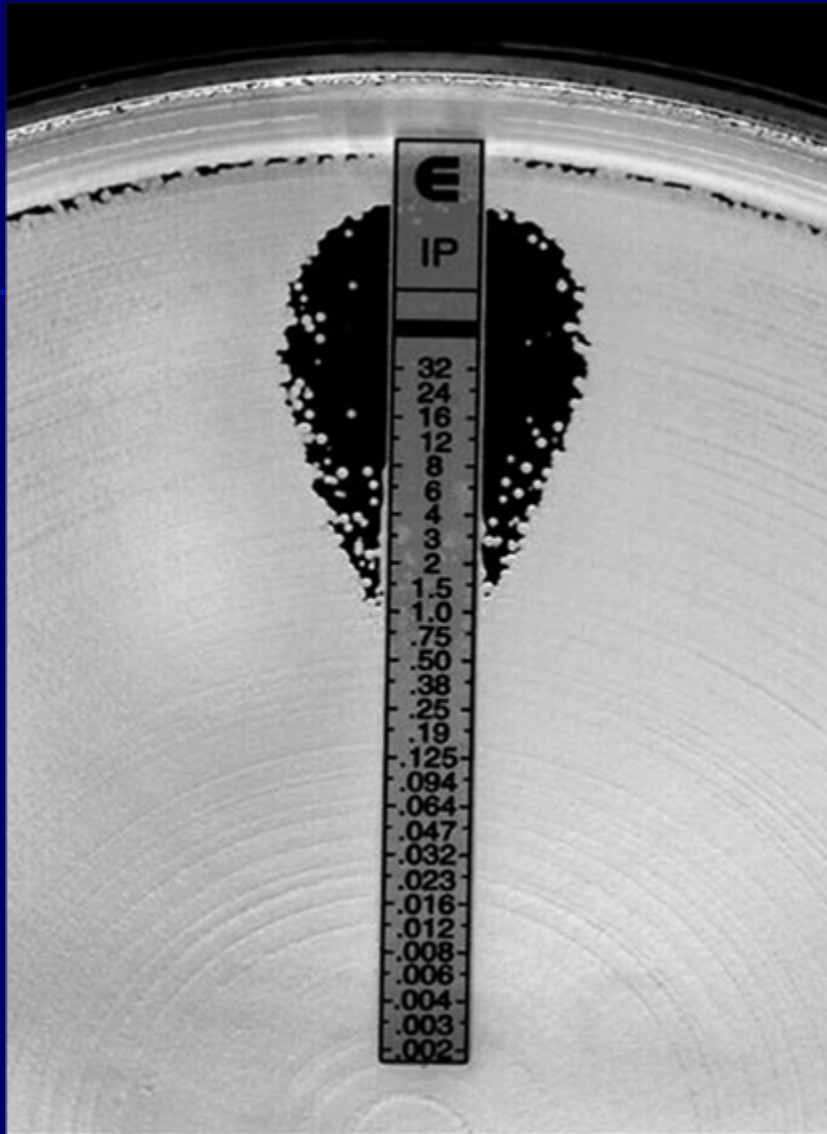
- Possible screening criteria for KPC-Producers
  - Ertapenem non-susceptibility by any method
  - Imipenem or Meropenem MIC  $\geq 2$  microg/ml
- Possible confirmation tests
  - Modified Hodge Test (carbapenemase or no carbapenemase)
  - PCR for *bla*<sub>KPC</sub>

## Susceptibility rates of KPC-producing *K.pneumoniae* against carbapenem antibiotics when tested by automated systems.

Test	Emerg. Infect. Dis.12:1209, 2006	J Clin Microbiol 45:2723, 2007
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	<i>n</i> = 15	<i>n</i> = 31
<b>Microscan</b>		
Imipenem	7%	26%
Meropenem	7%	16%
Ertapenem	NT	0%
<b>Vitek</b>		
Imipenem	67%	45%
Meropenem	67%	48%
Ertapenem	NT	NT
<b>Vitek2</b>		
Imipenem	33%	29%
Meropenem	33%	52%
Ertapenem	NT	6%
<b>Phoenix</b>		
Imipenem	13%	19%
Meropenem	13%	39%
Ertapenem	NT	NT
<b>Sensititre</b>		
Imipenem	87%	71%
Meropenem	80%	58%
Ertapenem	NT	NT





**Figure 1**

**Susceptibility test of a KPC-producing *K. pneumoniae* using the Etest methodology. Note the presence of scattered colonies, making it difficult to read the defined endpoint. (Reprinted from Emerg. Infect. Dis. 12:1209–1213, 2006.)**



# Infections due to *A. baumannii*

risks: immunocompromise, serious comorbidities, procedures, broad spectrum Abx

spectrum: VAP, bacteremia, UTI, cSSSIs, abdominal, CNS, CAP (Australia, 32% bacteremia, ARDS) wounds

Antimicrob Agents Chemother 2007; 51:3471-84

# Antimicrobial resistance in *Acinetobacter* sp.

$\beta$  lactams: beta-lactamases (class A-D), altered PBPs, altered porins, efflux pumps

AGs: AMEs, efflux pumps

FQs: DNA gyrase modification (gyrA, par C),  
efflux pumps

Tetracyclines: efflux pumps, ribosomal protection protein

polymyxins: heteroresistance, change LPS

**AAC 2007; 51: 3471-84**

# Susceptibility of *A. baumannii* to selected antibiotics, 2001-2004 (SENTRY)

	% susceptible			
	FEP	CIP	IMI	SAM
North America	57	54	89(84)	71
Europe	44	39	74(70)	48
Asia/Pacific	58	55	74(73)	59
Latin America	36	35	86(84)	52

# Meropenem resistance in *A. baumannii*

%

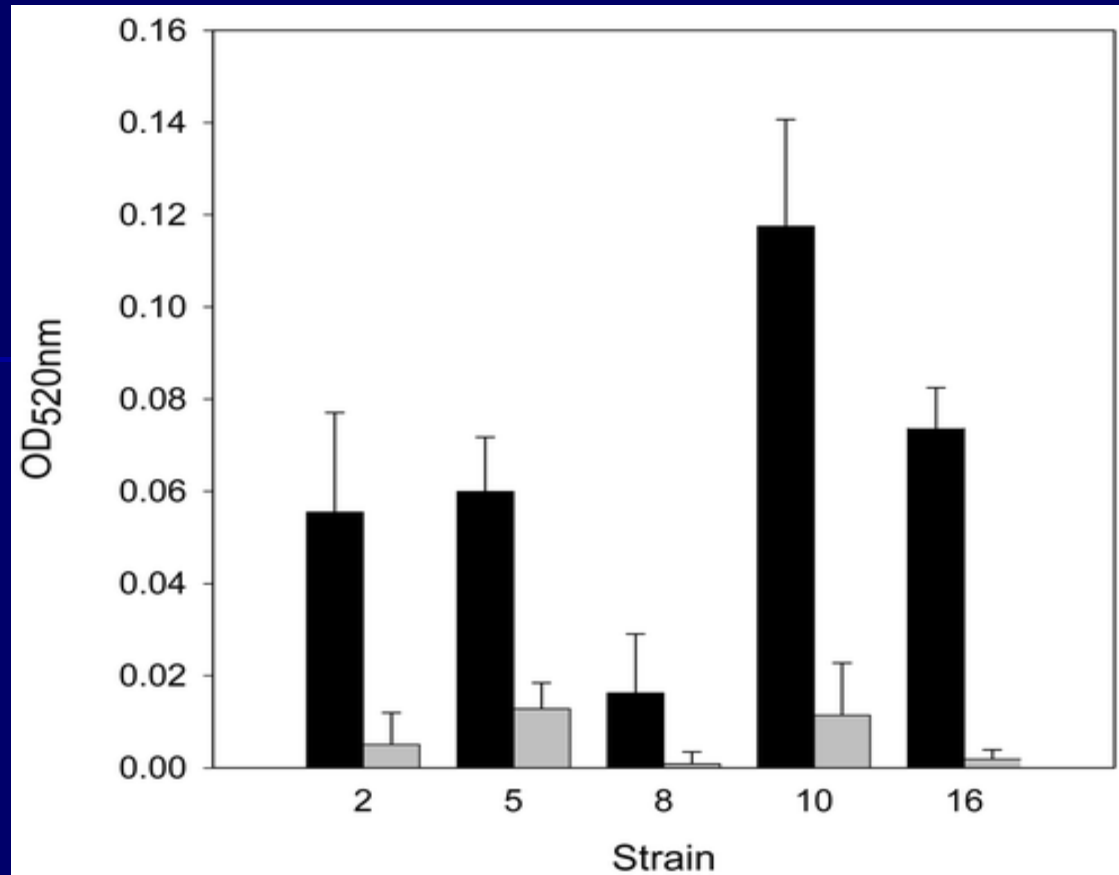
	susc	int	resistant
1998	84.8	9.4	5.9
2002	72.5	4.4	23.1
2005	64.4	7.0	28.6

[www.mystic-data.org](http://www.mystic-data.org)

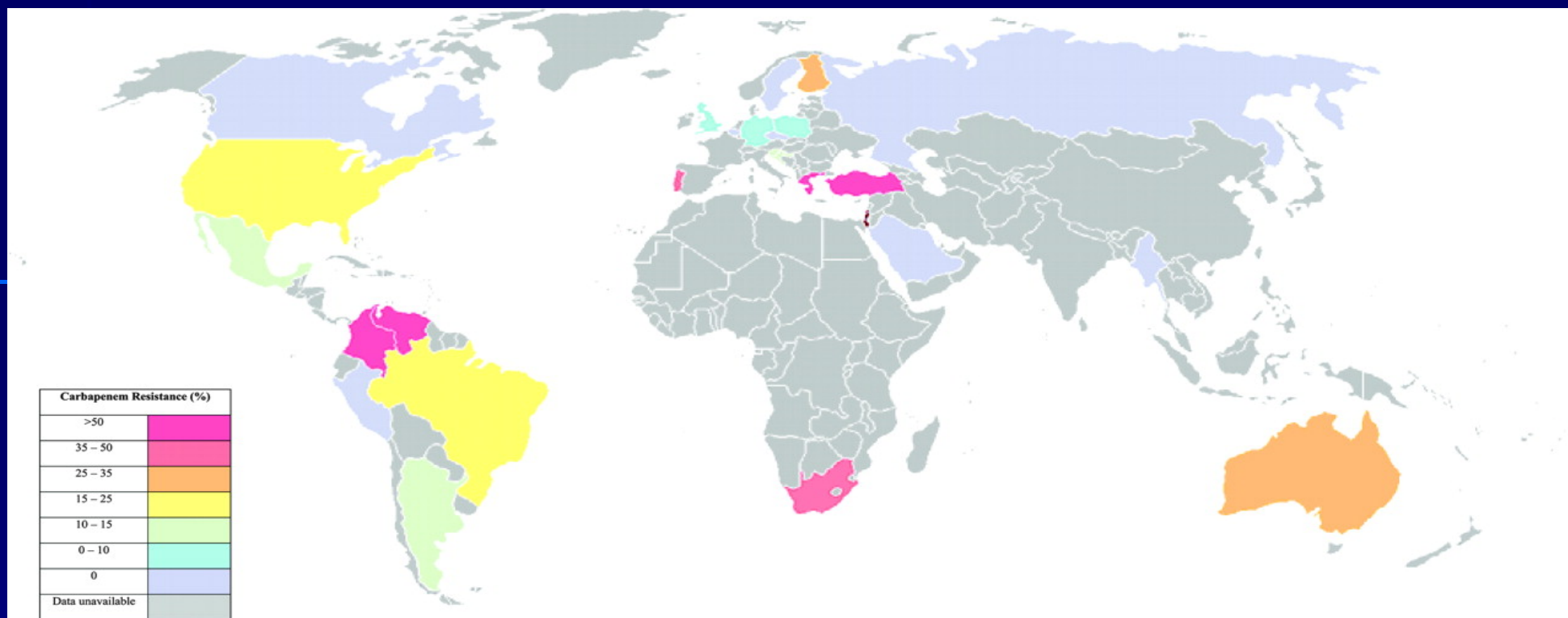
**Table 2. Fractional inhibition concentration (FICs) of the combination of colistin and rifampicin against colistin-susceptible strains of *Acinetobacter baumannii*.**

Strain	FIC of colistin-susceptible strain
3	0.31
5	0.53
6	0.19
7	0.14
8	0.27
10	0.50
14	0.19
16	0.38

**NOTE.** FICs of the colistin-resistant strains could not be calculated, because there was no growth even at the lowest concentration of rifampicin (0.125  $\mu\text{g/mL}$ ) used in the FIC measurement.



**Figure 1** Biofilm-forming ability of the paired colistin-susceptible (*black bars*) and colistin-resistant (*gray bars*) strains. The biofilm formation was determined from the optical density at 520 nm (OD<sub>520nm</sub>) of crystal violet–stained biofilm.



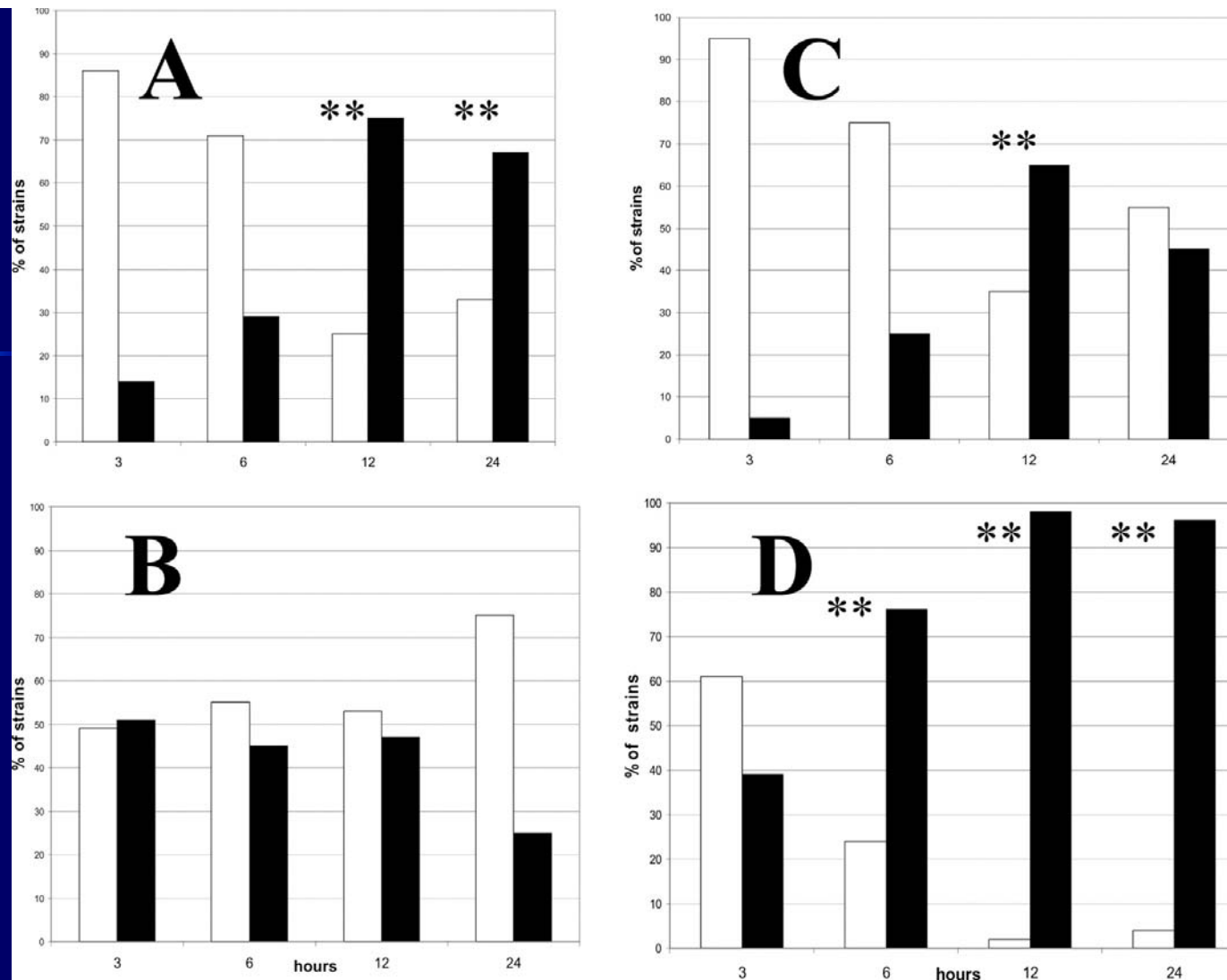
**FIG. 1. *Acinetobacter* isolates resistant to carbapenems (Meropenem Yearly Susceptibility Test Information Collection [MYSTIC], 2004). Data were extracted from the MYSTIC database ([www.mystic-data.org](http://www.mystic-data.org)).**

TABLE 4. Combinations of antibiotics demonstrating enhanced activity against carbapenem-resistant *A. baumannii*

Study type	Antibiotic combination (reference[s])
In vitro	Meropenem + ampicillin-sulbactam (90, 92) Imipenem + ampicillin-sulbactam (26) Rifampin + ampicillin-sulbactam (197) Rifampin + polymyxin B (197, 230) Rifampin + colistin (69) Imipenem + polymyxin B + rifampin (230) Imipenem + polymyxin B (230) Cefepime + ampicillin-sulbactam (173)
Animal models	Meropenem + ampicillin-sulbactam (92) Imipenem + ampicillin-sulbactam (226) Imipenem + tobramycin (124) Imipenem + rifampin (124, 226) Rifampin + tobramycin or colistin (124) Rifampin + ampicillin-sulbactam (226)
Clinical experience	Rifampin + colistin (126, 146) Colistin + others <sup>a</sup> (88, 189)

<sup>a</sup> Imipenem, meropenem, ampicillin-sulbactam, piperacillin-tazobactam, cefepime, quinolones, and aminoglycosides.





**FIG. 1. Time-kill synergy studies of meropenem combined with ciprofloxacin (A) and colistin (B) against 51 isolates of *P. aeruginosa* and of meropenem combined with ciprofloxacin (C) and colistin (D) against 41 and 51 strains of *A. baumannii*, respectively. In each pair of bars, the one on the left represents an additive effect and the one on the right represents synergy<sup>57</sup>. \*\*, Significantly higher percentage of organisms showing synergy ( $P < 0.001$ ).**

# **Treatment of MDR *Acinetobacter* sp.**

**carbapenem or A/S susc: monotherapy with either imipenem, meropenem (? doripenem) or A/S**

**carbapenem (non-MBL) resistant: colistin + rifampin + imipenem**

**carbapenem (MBL) resistant: colistin + rifampin (+/- tigecycline) (? +/- nebulized colistin for VAP)**

## Other agents for treatment of MDR *Acinetobacter*?

**Doripenem (MIC<sub>50</sub> 0.5, MIC<sub>90</sub> 16 µg/ml; 76%  
susc MIC ≤ 4)**

**cationic membrane – active peptides: rBPI<sub>2</sub>**

**Cecropin P1**

**BAL 30072 (monobactam)**

# Colistin-resistant *A. baumannii*

Increased susceptibility (vs colistin-sensitive, in absence of colistin) to:  $\beta$  lactam/lactamase inhibitors, cephalosporins, quinolones, AGs (tobra, amik), rifampin, fusidic acid, erythromycin, teichoplanin, Q-D

Li R, et al. Clin Infect Dis 2007; 45:594-8

# Testing Other Drugs

- **Tigecycline:**

- Test by Etest if possible – disk diffusion tends to overcall resistance
- No CLSI breakpoint, but there are FDA breakpoint
  - Susceptible  $\leq 2$  mg/ml
  - Intermediate = 4 mg/ml
  - Resistant  $\geq 8$  mg/ml

# Testing Other Drugs

## ■ Polymixin B or Colistin

- Could test either, but colistin used clinically
- Disk diffusion test does not work – don't use!
- Etest – works well, but not FDA cleared
- Broth microdilution – reference labs
- Breakpoints - none
  - $\text{MIC} \leq 2 \text{ mg/ml}$ , normal MIC range
  - $\text{MIC} \geq 4 \text{ mg/ml}$  indicates increased resistance

**J Clin Microbiol. 2001. Vol. 39 (1): 183-190**

# **Proposed Definitions Of Panresistant And Extreme Drug Resistant (XDR) Gram-negative Bacilli**

**Panresistant: ctz, cef, imi, mero, pip/tazo, cipro, levo**

**XDR: all of the above plus ticar/clav, amp/sulb, AGs (gent, tobra, amik), tigecycline (MIC  $\geq$  0.75 for blood isolates), polymyxins**

**note: uses EUCAST, not CLSI breakpoints**

**Clin Infect Dis 2007; 45:1179-81**

**As these organisms become increasingly prevalent, treatment of health care-associated infections most likely will become more difficult or even impossible. These circumstances eventually may limit the ability to offer therapeutic interventions associated with a high risk of infection, such as solid organ and bone marrow transplantation and chemotherapy, and could make the hospital environment unsafe even to the general population undergoing simple and elective procedures. In addition, infections acquired in the community, even those occurring in young, healthy individuals, including such conditions as pyelonephritis and perforated appendicitis, may become untreatable and therefore life-threatening.**

**JAMA Dec 2008; 300:2911**