The Demise of β-Lactam Antibiotics in New York City

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Northeast Beginnings/Problems

- Methicillin-resistant *Staphylococcus aureus*
- Vancomycin-resistant enterococci
- ESBL-possessing *Klebsiella pneumoniae*

Current Problematic Nosocomial Pathogens

- *Pseudomonas aeruginosa*
- *Acinetobacter baumannii*
- *Klebsiella pneumoniae*

- Resistance Rates, Molecular Epidemiology and Antibiotic Associations
- ? Control Measures

Susceptibility of *P. aeruginosa*

Antibiotic	New York City *Arch Intern Med 2002;162:1515-20*	United States *Clin Inf Dis 2001;32(Suppl2):146-55*
Amikacin	95%	97%
Ceftazidime	77%	78%
Cefepime	71%	83%
Meropenem	**77%**	**91%**
Imipenem	**70%**	**81%**
Piperacillin-tazobactam	83%	87%
Ciprofloxacin	**56%**	**75%**

Susceptibility of *P. aeruginosa* in New York City

Arch Intern Med 2002;162:1515-20

Antibiotic	1999 (n=823)	2001 (n=691)	2003 (n=538)
Amikacin	95%	95%	86%
Ceftazidime	82%	77%	72%
Meropenem	83%	77%	71%
Imipenem	**76%**	**70%**	**60%**
Piperacillin-tazobactam	85%	83%	64%
Ciprofloxacin	**71%**	**56%**	**54%**

Fingerprinting Carbapenem-Resistant *Pseudomonas aeruginosa* from Brooklyn

Arch Intern Med 2002;162:1515-20

Ribotype	Number	Number of Hospitals
A	26 (19%)	12
B	20 (15%)	10
C	17 (12%)	5

Nearly one-half belong to three ribotypes, and evidence of interhospital spread

Antibiotic Usage at Brooklyn Hospitals 1999-2001

- Citywide decrease in number of defined daily doses of beta-lactams (10%), aminoglycosides (41%), carbapenems (10%)
- Increase in number of defined daily doses of fluoroquinolones (18%)
- Significant correlation between carbapenem-resistant *P. aeruginosa* and fluoroquinolone usage

Mechanisms of carbapenem resistance in *P. aeruginosa*

	Carbapenem-susceptible (n=18)	Imipenem resistant (n=6)	Imipenem & meropenem resistant (n=11)	
	mcg/ml of amplified DNA from 10ng RNA			
oprD	33±22	10±1*	24±11	*P<0.01
mexA	39±18	38±16	51±18*	*P<0.05
rpsL	30±6	34±19	35±9	

Carbapenem Resistance in *P. aeruginosa*

- In Brooklyn hospitals, strong correlation between fluoroquinolone use and level of carbapenem resistance; increasing carbapenem resistance during a period of reduced carbapenem consumption (but increased fluoroquinolone usage)
- When using one class of antibiotic, need to consider the impact on resistance to a different class?

Acinetobacter baumannii

- Not among the NNIS reported list of nosocomial pathogens
- 2-10% of all gram negatives from ICUs in Europe

Hanberger et al JAMA 1999;281:67-71

- 10% of all gram negatives Brooklyn

Manikal et al CID 2000;31:101-6

Spread of Multidrug-Resistant *A. baumannii*

2004 IDSA Abstracts

Washington, DC

Dallas

Atlanta

Philadelphia

Susceptibility of *A. baumannii*

	New York City	United States	Latin America
	Arch Int Med 2002;162:1515-20	*Clin Inf Dis 2001;32(Suppl2):S104-13*	
Amikacin	69%	88%	32%
Ceftazidime	31%	67%	26%
Cefepime	35%	68%	34%
Imipenem	**67%**	**96%**	**89%**
Meropenem	47%	94%	89%
Ciprofloxacin	27%	70%	30%

Susceptibility Rates for *A. baumannii* in New York City

Arch Intern Med 2002;162:1515-20

Antibiotic	1999 (n=420)	2001 (n=436)	2003 (n=392)
Ceftazidime	31%	18%	15%
Meropenem	47%	32%	37%
Imipenem	**67%**	**63%**	**44%**
Ciprofloxacin	27%	12%	12%
Amikacin	69%	56%	63%

A. baumannii Carbapenem-Resistance Rates and Antibiotic Use

Arch Intern Med 2002;162:1515-20

	Defined Daily Doses/1000 Patient Days				
Resistance	Ceph (P=.004)	Aminoglycoside	Quinolone	β-Lactamase-inhibitors	Carbapenem
20%	69	30	25	57	7
25%	66	27	31	22	11
31%	145	9	37	33	19
50%	155	55	51	65	6
51%	165	35	15	18	7
54%	186	52	24	33	12
56%	196	42	46	27	3
58%	105	36	39	107	13
62%	136	NA	20	37	15
71%	218	28	47	5	11
73%	173	17	20	85	10
76%	228	49	32	46	16

Acinetobacter - Fingerprinting Results of Carbapenem-Resistant Isolates from New York City (n=224)

Arch Intern Med 2002;162:1515-20

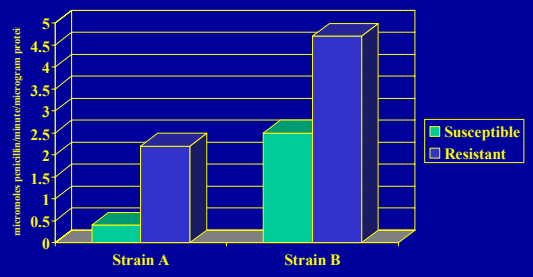
Ribotype	No. Isolates (%)	No. of Hospitals
1	140 (62%)	15
2	43 (19%)	8
3	27 (12%)	7

For the carbapenem-susceptible isolates:

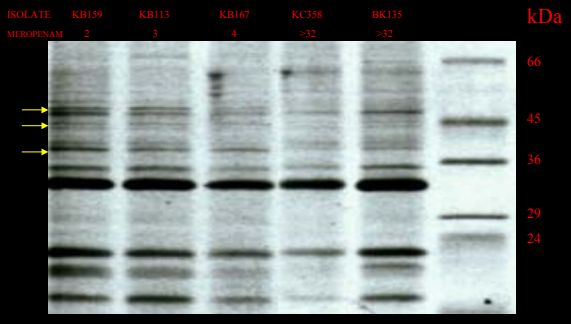
- Cephalosporin-resistant isolates belonged to the same three major ribotypes
- Cephalosporin-susceptible isolates belonged to different ribotypes

Class C β-lactamase Production in *A. baumannii*

Carbapenem susceptible vs. resistant



OUTER MEMBRANE PROTEINS - Strain A



Cephalosporin usage and carbapenem-resistant *A. baumannii*

1. Increased beta-lactam (cephalosporin) use may select isolates with increased expression of chromosomal cephalosporinase
2. Exposure to cephalosporin-resistant isolates to carbapenems leads to diminished porin expression
3. Increased cephalosporinase production + diminished porin production = carbapenem resistance

Summary: Carbapenem-resistant *A. baumannii* in New York City

- Unusually common nosocomial pathogen in New York
- Spread of only a few strains among area hospitals
- Exceedingly high resistance rates; increased cephalosporinase production and diminished porin expression contributes to carbapenem resistance
- No carbapenem-hydrolyzing β-lactamases identified

ESBL-Producing *Klebsiella*

- From 396 ICUs in US: Resistance increased from 3.6% in 1990 to 14.4% in 1993

  Itokazu et al CID 1996;23:779-84
- NNIS data: ceftazidime-resistant *K. pneumoniae* increased from 1.6% in 1986 to 9.4% in 1993

  Monnet et al ICHE 1997;18:492-8
- NNIS data: ceftazidime resistance in 9% of *K. pneumoniae* from ICUs

  CDC AJIC 1999;27:520-32
- European ICUs: Resistance rates to ceftazidime 3-34%

  Hanberger et al JAMA 1999;281:67-71

ESBL-*Klebsiella*: New York City

New York City	Latin America	Western Pacific	Europe	United States	Canada
Clin Inf Dis 2002;35:834-41	Clin Inf Dis 2001;32(Suppl2):S94-103				
34%	45%	25%	23%	8%	5%

Susceptibility rates of *K. pneumoniae* in New York City

Clin Infect Dis 2002;35:834-41

Antibiotic	**1999**	**2001**	**2003**
ESBL Positive	34%	38%	45%
Amikacin	86%	84%	76%
Imipenem	99.6%	97%	97%
Piperacillin-tazoactam	84%	75%	66%
Ciprofloxacin	80%	69%	56%

Rate of ESBL-*Klebseilla* and Antibiotic Usage at Brooklyn Hospitals: Correlation with Cephalosporin Usage

J Antimicrob Chemother 2000;45:895

Defined daily doses/1000 patient days

ESBL Rate	B-lactam Inhibitor	3rd Cephalosporin	Carbapenem	Quinolone	Aminoglycoside
71%	18	215	8	5	48
68%	52	172	7	24	68
50%	30	170	15	28	9
46%	10	146	7	N/A	36
44%	23	82	12	4	29
36%	47	135	1	8	49
33%	42	219	18	1	30
33%	24	134	6	24	N/A
33%	34	70	6	24	18
30%	89	71	18	43	36
5%	12	73	4	10	53

ESBL-*K. pneumoniae* (n=264) Fingerprinting Results

Clin Infect Dis 2002;35:834-41

Ribotype	No. Isolates (%)	Hospitals (no.)
1	54 (20%)	13
2	40 (15%)	11
3	13 (5%)	5
4	13 (5%)	4
5	12 (5%)	4
6	9 (3%)	6
7-87	123 (47%)	Most 1-2 each

Beta-lactamases in *K. pneumoniae* (n=49)

Clin Infect Dis 2002;35:834-41

pI value	5.4	5.6	7.0	7.4	7.6	7.8	8.2	9.0
Sequence	TEM-1				SHV-1,2	SHV-7	SHV-5	ACT-1
Percent of ESBL isolates with enzyme	92%	12%	37%	22%	41%	6%	75%	14%

Average of ~ 3 beta-lactamases per isolate

Beta-lactamases in *K. pneumoniae* (n=49)

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Resistance Profiles in *K. pneumoniae*

	Typical *Klebsiella*	ESBL-*Klebsiella*	Cephalosporinase *Klebsiella*
Ampicillin	R	R	R
Ticarcillin	R	R	R
Aztreonam	S	R	R
Ceftriaxone	S	I	R
Ceftazidime	S	R	R
Cefoxitin/cefotetan	S	S	R
Piperacillin-tazobactam	S	S	R
Imipenem/meropenem	S	S	S

ESBL-Possessing *Klebsiella*

- Unrelenting increase in the percentage of ESBL-carrying isolates
- Many strains involved, a few ESBLs predominate

KPC Beta-lactamases

- Class A beta lactamases with carbapenem-hydrolyzing activity
- Exist on a transmissible plasmid
- Inhibited by clavulanic acid

KPC Beta-Lactamases

- KPC-1: From *Klebsiella pneumoniae* in North Carolina, reported in 2001
- KPC-2: Found in *Klebsiella pneumoniae* (Maryland and New York – 10 hospitals in Brooklyn, 1 in Queens), *Salmonella* (Maryland), and *Enterobacter cloacae* (Boston), *Enterobacter aerogenes* and *cloacae* (Brooklyn)
- KPC-3: Found in *Klebsiella pneumoniae* (New York), *E. coli* (New Jersey), *Enterobacter cloacae* (Brooklyn)

Resistance Profiles in *K. pneumoniae*

	Typical *Klebsiella*	ESBL-*Klebsiella*	Cephalosporinase *Klebsiella*	Carbapenemase *Klebsiella*
Ampicillin	R	R	R	R
Ticarcillin	R	R	R	R
Aztreonam	S	R	R	R
Ceftriaxone	S	I	R	R
Ceftazidime	S	R	R	R
Cefoxitin/cefotetan	S	S	R	R
Piperacillin-tazobactam	S	S	R	R
Imipenem/meropenem	S	S	S	R

NYC Outbreaks of Imipenem-Resistant *K. pneumoniae*

- Hospital A: August 2003 – February 2004
- 32 patients identified with carbapenem-resistant *K. pneumoniae*
- Eleven resistant isolates examined: all had KPC-2 (two isolates from nursing home patients)
- 10 belonged to Ribotype 1, 1 belonged to Ribotype 2

NYC Outbreaks of Imipenem-Resistant *K. pneumoniae*

- Hospital B: December 2003 – May 2004
- 27 patients identified with carbapenem-resistant *K. pneumoniae*
- Nine resistant isolates characterized: all had KPC-2
- Eight belonged to Ribotype 1, 1 belonged to Ribotype 2

Hospital C

Susceptibility Rates for *K. pneumoniae*

	2001 (n=314)	2002 (n=438)	2003 (n=372)	Jan-Jun 2004 (n=330)
Ceftazidime	71%	71%	57%	49%
Imipenem	97%	99%	91%	74%

Previous antibiotic administration in patients with KPC-*K. pneumoniae*

60 patients reviewed

- 60% received fluoroquinolones
- 60% received beta-lactam/beta-lactamase inhibitor antibiotics
- 25% received aminoglycosides
- 25% received cephalosporins
- 20% received carbapenems

Susceptibility Data for KPC-possessing *K. pneumoniae* (n=97)

- Piperacillin-tazobactam 0%
- Cefotetan 60%
- Ceftazidime 2%
- Cefepime 40%
- Chloramphenicol 7%
- Ciprofloxacin 2%
- Fosphomycin 2%

Susceptibility Data for KPC-possessing *K. pneumoniae* (n=97)

- Doxycycline 64%
- Gentamicin 60%
- Tobramycin 3%
- Amikacin 45%
- Polymyxin 99%

Outcome of patients with KPC-possessing *K. pneumoniae* bacteremia

19 patients reviewed

- Two died the same day
- Nine received ineffective therapy: six died at 14d, two microbiological failures
- Eight patients received "effective" therapy: One died, one microbiological failure

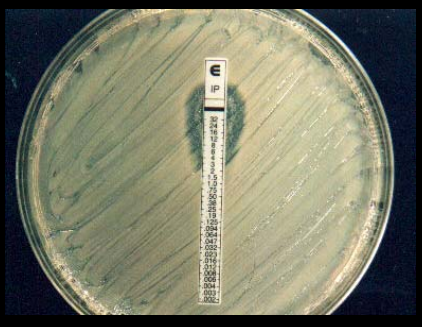
Prevalence of KPC beta-lactamases in *K. pneumoniae* from New York City

Jan – Mar 2003 Surveillance study:

- Of 265 ESBL-possessing isolates, nine (3.3%) were found to possess KPC-2
  - Ribotype 1: three isolates
  - Ribotype 2: four isolates
  - Two isolates unrelated
- Three of the nine isolates were reported as carbapenem-susceptible by the microbiology laboratory

Imipenem susceptibility testing of KPC-possessing *K. pneumoniae*

Isolate	Clinical Laboratory	Broth dilution		Etest
		10^4 cfu/ml	10^5 cfu/ml	10^8 cfu/ml
1	Resistant	0.5	4	>32
2	Resistant	1	8	>32
3	Resistant	>16	>16	>32
4	Susceptible	2	8	>32
5	Resistant	8	>16	>32
6	N/A	16	>16	>32
7	Susceptible	2	4	>32
8	Susceptible	4	>16	>32
9	Resistant	16	>16	>32



KPC-Possessing *Enterobacter* spp. in Brooklyn, NY

- *E. cloacae* with KPC-3 in October 2003
- Of 111 cephalosporin-resistant *Enterobacter* isolates collected during citywide surveillance studies, two were found with KPC-2
- Both KPC-2 isolates were reported as carbapenem-susceptible by microbiology laboratories

Imipenem susceptibility testing of KPC-possessing *Enterobacter* spp.

	Agar dilution	Broth dilution			Etest
	10^4 cfu/spot	10^4 cfu/ml	10^5 cfu/ml	10^6 cfu/ml	10^8 cfu/ml
E. cloacae KPC-3	16	2	4	16	>32
E. cloacae KPC-2	4	0.5	2	4	24
E. aerogenes KPC-2	16	0.5	2	8	>32

KPC-Possessing *Klebsiella* and *Enterobacter*

An Infection Control nightmare:

Enzyme located on a transmissible element

Not all isolates with KPC are detected as imipenem-resistant

Controlling Resistance

1. Aggressive Infection Control Protocols
2. Routine Surveillance in High-Risk Areas
3. Reducing Environmental Contamination
4. Antibiotic Controls

Controlling Resistance

1. Aggressive Infection Control Protocols– e.g., targeting all cephalosporin-resistant Enterobacteriaceae, monitoring compliance, routine surveillance cultures

Lucet et al CID 1999;29:1411-8

2. Routine Surveillance in High-Risk Areas

ICU Surveillance Cultures – August 2004

- Cultures placed in McConkey broth with 1mcg/ml meropenem
- 3 ICUs targeted: one med-surg, one medical, one surgical
- 0/30 hand cultures positive

ICU Surveillance Cultures- Gastrointestinal Colonization

	Surg ICU	Med ICU	Med-Surg ICU
	(n=15)	(n=13)	(n=8)
KPC-*K. pneumoniae*	5	3	6
A. baumannii	4	2	2
P. aeruginosa	4	1	2

Unrecognized colonization

- *K. pneumoniae*: 2/14 with prior clinical culture with carbapenem-resistant isolate
- *A. baumannii*: 3/8 with prior clinical culture
- *P. aeruginosa*: 2/7 with prior clinical culture

Surveillance for Resistant Nosocomial Pathogens

- Unrecognized intestinal colonization may be common in outbreak settings
- No commercially-available selective media available for the targeted pathogens

3. Reducing Environmental Contamination

Acinetobacter baumannii

- Widespread environmental contamination:
  - Bedside areas
  - Sinks
  - Temperature probes
  - Air samples
  - Ventilator circuits
- Carried on hands of health care workers

Environmental Cultures performed at Brooklyn Hospitals

Arch Intern Med 2002;162:1515-20

- Approximately 10-15% of bedrails and respirator equipment cultures from high risk areas grew carbapenem-resistant *A. baumannii* or *P. aeruginosa*

ICU Environmental Cultures- August 2004

	IV Poles	BP cuffs	Bedrails
	(n=39)	(n=35)	(n=37)
K. pneumoniae	2	5	2
A. baumannii	2	3	0
P. aeruginosa	0	1	0

Phone cultures – 1/13 grew *K. pneumoniae, A. baumannii*

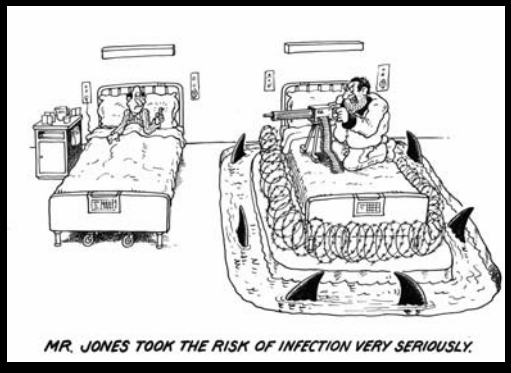
4. Antibiotic controls

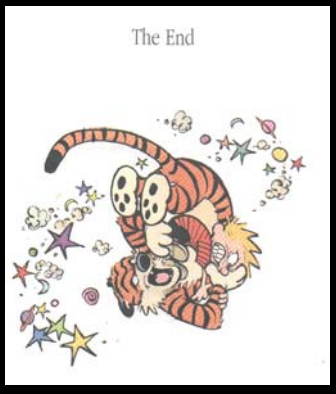
- Beta-lactams (cephalosporins for ESBL-producers, ? *A. baumannii*)
- ? fluoroquinolones for *P. aeruginosa*

Rational Antibiotic Usage – no magic bullet on the horizon

Controlling Antibiotic Resistance- Unresolved Issues

- Improve methods for surveillance and detection
- Improve compliance with infection control protocols
- Effective antibiotic control policies


MR. JONES TOOK THE RISK OF INFECTION VERY SERIOUSLY.


The End