

Laboratory Practices and the New York City Experience with CRE

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Objectives

- **At the conclusion of this presentation participants will be cognizant of:**
 - **The classification of β -lactamases including carbapenemases**
 - **The epidemiology of CRE in the greater NYC area**
 - **Methods being employed for the laboratory detection and characterization of carbapenemases**

β -Lactamases and the Genes Encoding Them among Gram-negatives

- Molecular class A (TEM, SHV, ESBLs, CTX-M, KPC)
- Molecular class B (metallo- β -lactamases (IMP, VIM, SPM, NDM))
- Molecular class C (AMP C: SPICE/SPACE bacteria)
- Molecular class D (OXA)

Suggested review:

Bush K. (2013) The ABCD's of β -lactamase nomenclature. *J Infect Chemother* 19:549-59

Carbapenemases

- Class A: KPC, SME, IMI, NMC
→ serine residue at the active site
- Class B: IMP-1 → -53, VIM-1 → -46,
GIM-1 and GIM-2, SPM, SIM,
IND-1 → -15, NDM-1 → -16
→ Zn^{2+} -dependent metallo-enzyme
- Class C: N/A
- Class D: OXA family (OXA-1 → -498)

Class B Plasmid-Mediated Metallo- β -Lactamases

- Zinc containing β -lactamases: not inhibited by clavulanic acid, tazobactam, avibactam, or sulbactam
- Low rates of aztreonam hydrolysis
- Most common in *Pseudomonas aeruginosa*, *Acinetobacter baumannii*, and *Enterobacteriaceae* (outside of US)
- L1 Carbapenemase of *Stenotrophomonas maltophilia* (L2 is a serine cephalosporinase) – both harbored on same plasmid

Class B Plasmid-Mediated Metallo- β -Lactamases

- IMP-1: first identified and reported in *Pseudomonas aeruginosa* in 1991 and later in *Serratia marcescens*
- Variants (IMP-2 \rightarrow -53) identified predominantly in *Pseudomonas aeruginosa*, *Klebsiella pneumoniae*, and *Acinetobacter baumannii* (worldwide)

Class B Plasmid-Mediated Metallo- β -Lactamases

- NDM-1: New Delhi metallo- β -lactamase
- First 3 *bla*_{NDM-1} isolates detected in US were in *E. coli*, *Enterobacter cloacae*, *Klebsiella pneumoniae*
- NDM-1 has quickly spread among non-clonally related isolates: *Citrobacter freundii*, *Morganella morganii*, *Providencia rettgeri*, *Acinetobacter baumannii*, *Providencia stuartii*
- Confers resistance to all β -lactams except aztreonam
- Plasmid also carries other β -lactamases and genes conferring resistance to other classes of antibiotics (3 isolates aztreonam-R due to other β -lactamases)

NDM β -lactamases

- Now NDM-1 \rightarrow NDM-16
- Resistance reliably detected by standard susceptibility testing methods and some by MHT
- Recent NDM-1 blood culture isolate at NYP/WCMC in child from India; successfully treated polymyxin B / continuous infusion meropenem (MIC = 4 μ g/mL) / gut decolonization with gentamicin

NDM-1- β -Lactamases

- “Laboratory ID of carbapenem-resistance mechanisms is not necessary to guide treatment or infection control practices but should be used for surveillance and epidemiologic purposes” - MMWR
- “Clinicians should be aware of the possibility of NDM-1 producing Enterobacteriaceae in patients who have received medical care in India and Pakistan and should specifically inquire about this risk factor when carbapenem-resistant enterics are reported”
- Isolates should be forwarded to CDC for confirmation (caveat)

Comparison of NDM-1 and KPC

	KPC	NDM
β -lactamase type	Serine	Metallo- β -lactamase
Ambler class	A	B
Most commonly affected species	<i>K. pneumoniae</i>	<i>K. pneumoniae</i>
Other species commonly affected	<i>E. coli</i> , <i>E. cloacae</i>	<i>E. coli</i> , <i>E. cloacae</i>
Common MLST types	ST258	Variable
Geographic epicenter	NE USA	India, Pakistan
β -lactam antibiotics affected	Penicillins, cephalosporins, carbapenems	Penicillins, cephalosporins, carbapenems
Phenotypic Detection	Modified Hodge Test (MHT) positive	Unknown (positive MHT likely)
Inhibitors	Boronic acid	EDTA

Verona Integron-Encoded Metallo- β -Lactamase (VIM)

- First report¹ in the US (July 2010) of a VIM carbapenemase in *Klebsiella pneumoniae*
- Patient hospitalized in Greece (where endemic)
- Transferred to US where isolate was recovered from blood collected through a central venous catheter (placed in Greece)
- Nonsusceptible to all antibiotics usually used to treat *K. pneumoniae*
- Patient recovered and discharged after 26 days (line removed)
- Screened 22 other patients for colonization - negative
- Recent isolate confirmed in Indianapolis; no history of travel outside of Indiana

¹MMWR. September 24, 2010. Vol. 59: 1212.

Class D, Chromosomally Encoded Carbapenem Hydrolyzing Enzymes

- OXA-enzymes (oxacillinases) mostly identified in *Acinetobacter baumannii* and *Pseudomonas aeruginosa*
- Usually chromosomally located
- OXA-23: shown to be plasmid-mediated
- OXA-48 and OXA-48-like emerging as major resistance determinants worldwide

Case

- A 48 year old obese female was admitted for elective knee replacement surgery following an automobile accident
- Post-surgery she developed idiopathic heparin-induced thrombocytopenia
- Loss of perfusion to her intestines resulted in small bowel transplant
- Post-surgery # 2 she developed ARDS and was placed on a ventilator
- The patient's condition continued to deteriorate and she developed a nosocomial pneumonia

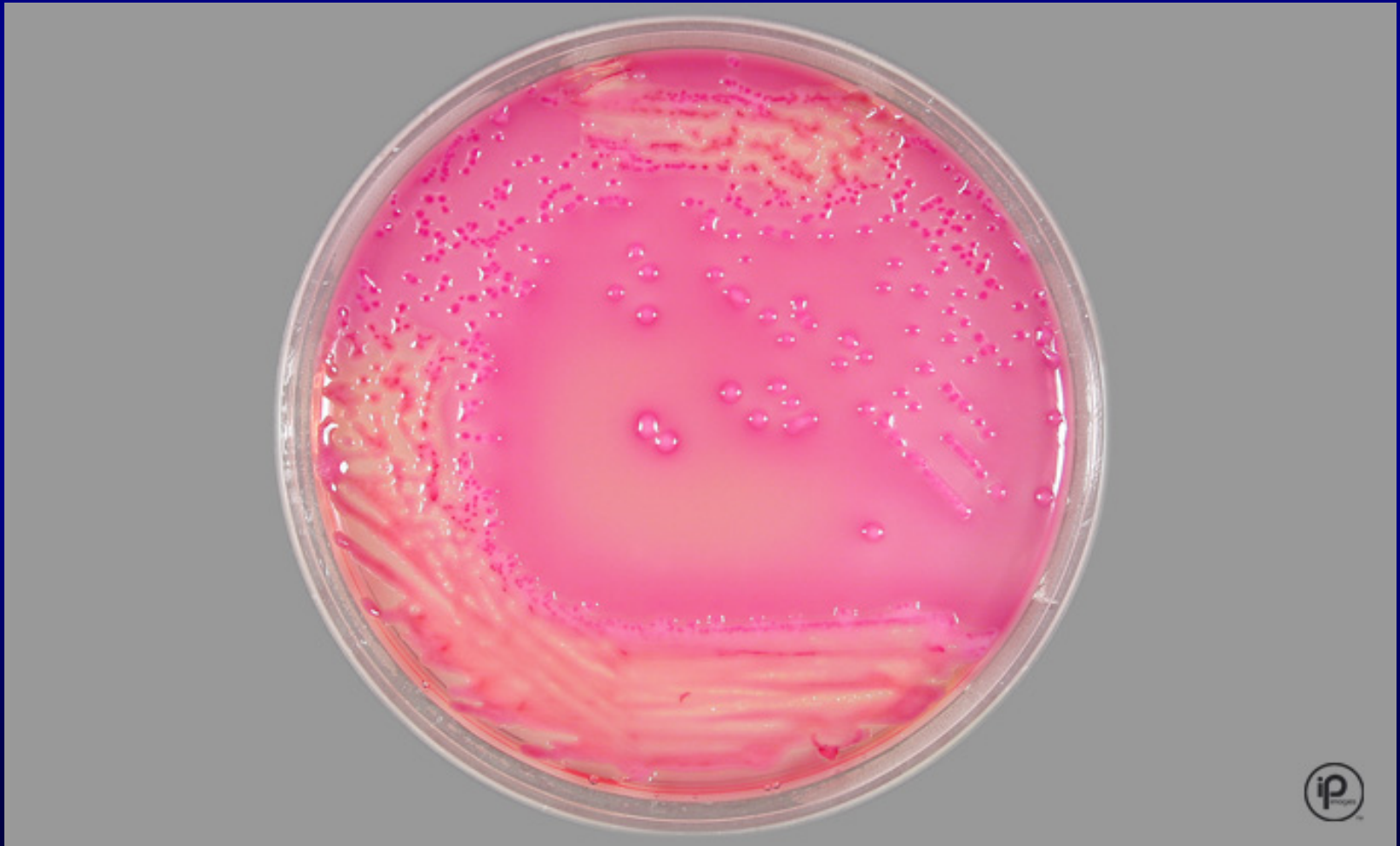
Case

- The antimicrobial susceptibility pattern of the isolate was as follows:
- Resistant to: ampicillin, piperacillin, amoxicillin-clavulanate, ampicillin-sulbactam, ticarcillin-clavulanate piperacillin-tazobactam, aztreonam, cefazolin, cefuroxime, cefotetan, ceftriaxone, cefotaxime, ceftazidime, cefepime, imipenem, meropenem, ertapenem, gentamicin, tobramycin, levofloxacin, ciprofloxacin, chloramphenicol, and trimethoprim-sulfamethoxazole
- Intermediate susceptibility to: amikacin and tetracycline
- Susceptible to: tigecycline and polymyxin B

Case

- What gram-negative was recovered from BAL, an empyema collection, urine, and blood?

Klebsiella pneumoniae



Case

- Polymyxin B MIC = 2 $\mu\text{g/mL}$
(Susceptible?) (ECV; WT/NWT)
- Patient treated with tigecycline and polymyxin B - responded

Antibiotic Susceptibility Testing

Subsequent Stool Isolate

• Isolate	<i>Klebsiella pneumoniae</i>		
• ANTIBIOTICS (µg/mL)	MIC		
•			
• Ampicillin	>16	R	S = Susceptible R = Resistant
• Aztreonam	>16	R	
• Ceftriaxone	>32	R	
• Ceftazidime	>16	R	
• Cefotaxime	>32	R	
• Cefazolin	>16	R	
• Ciprofloxacin	>2	R	
• Cefepime	>16	R	
• Cefuroxime	>16	R	
• <u>Amikacin</u>	<u>32</u>	<u>R</u>	
• Imipenem	>8	R	
• Meropenem	>8	R	
• Ertapenem	>4	R	
• <u>Polymyxin B</u>	<u>2</u>	<u>S (?)</u>	
• Gentamicin	8	R	
• Levofloxacin	>4	R	
• Meropenem	>8	R	
• Trimethoprim-Sulfamethox	>2/38	R	
• <u>Tetracycline</u>	<u>>8</u>	<u>R</u>	
• Tobramycin	>8	R	

The Patient Developed a Second Pneumonia Related to:



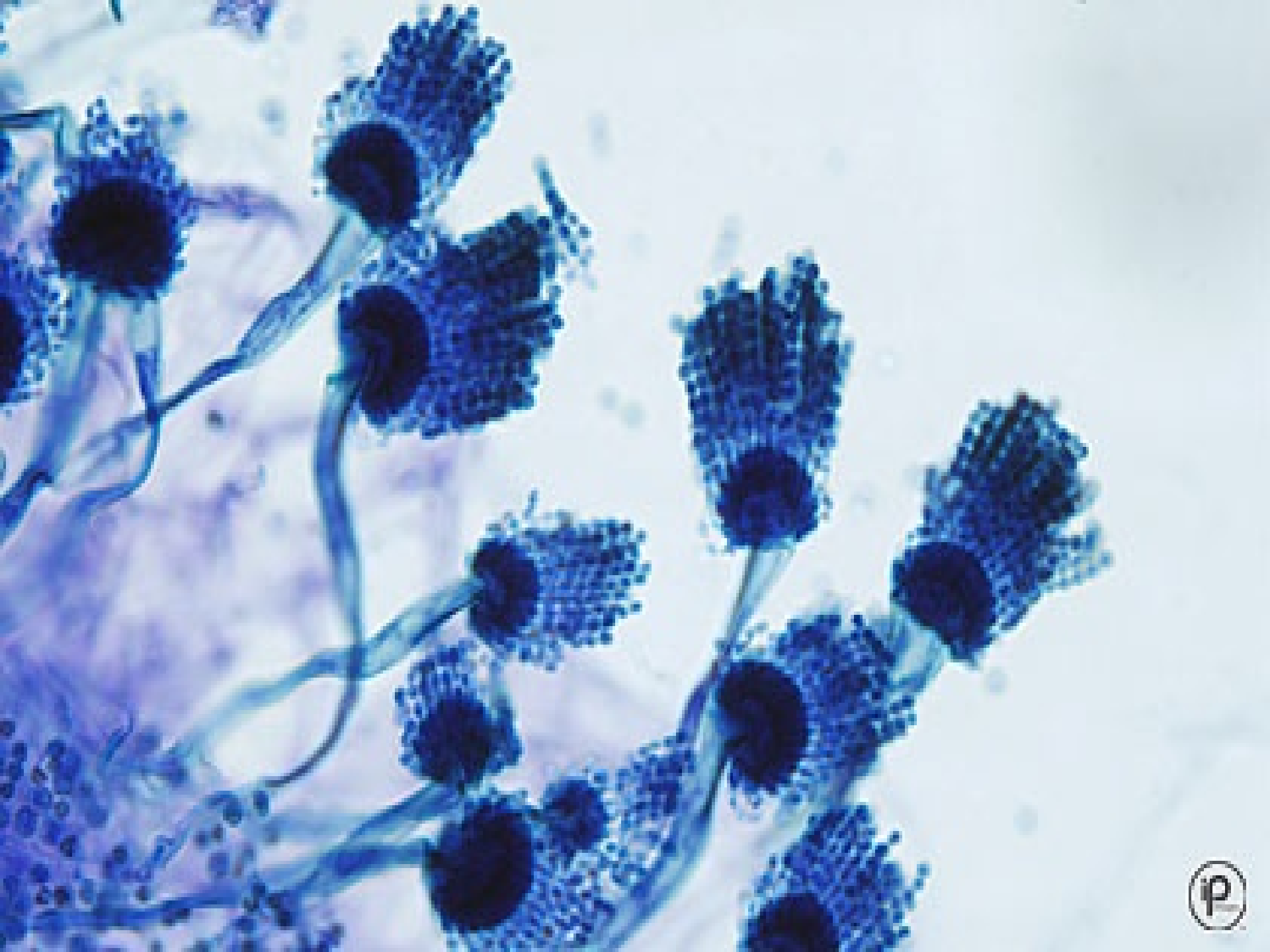
Follow-up

Hyperinfestation with *Strongyloides stercoralis*

Follow-up

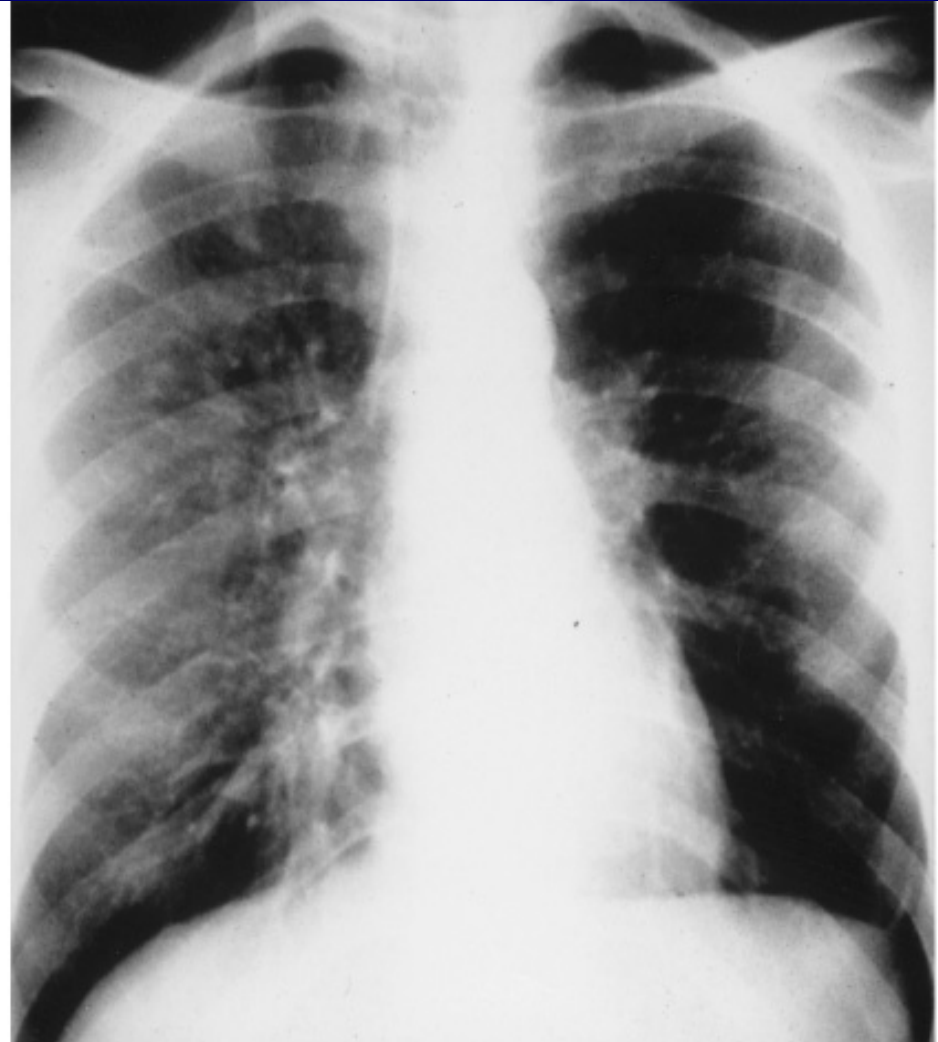
Treated using subcutaneous injections of a veterinarianian preparation of ivermectin and recovered, only to develop a new pneumonia with:





Follow-up

- *Aspergillus fumigatus*
- Again responded to therapy (voriconazole), but developed bilateral CMV pneumonia



Follow-up

**Controlled with high-dose gancyclovir,
but became septic with:**



Multi-drug resistant strain of *Acinetobacter baumannii*

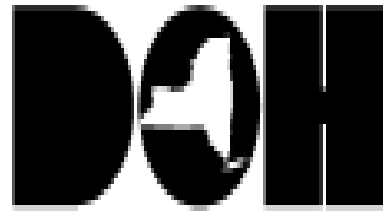
- β -lactam (including imipenem), aminoglycoside, and fluoroquinolone resistant
- Expired 13 months after initial surgery

KPC

- Klebsiella pneumoniae carbapenemase
- Mostly found in *K. pneumoniae*, but also in other enteric bacteria.
- KPC_{bla} resides in plasmids.
- Hydrolyze all of the β -lactam antibiotics including cephalosporins and monobactams (as well as the carbapenems) → Very few therapeutic options
- Endemic in NYC; spreading across nation / world

Class A, KPC Carbapenem-hydrolyzing Enzymes

- KPC-1; *Klebsiella pneumoniae* - North Carolina
- KPC-2; *Klebsiella pneumoniae* - Maryland, Brooklyn/Queens, New York, *Salmonella enterica* serotype Cubana - Maryland, *Klebsiella oxytoca* - New York, *Enterobacter cloacae* - Massachusetts, *Enterobacter aerogenes* - New York
- KPC-3, *Enterobacter cloacae* - New York, *Escherichia coli* - New Jersey
- Now KPC-1 → KPC-24
- KPC-positive isolates often possess additional beta-lactamases (average=3.5)



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Reporting Cases of Klebsiella spp. Infection or Colonization

1. The New York State Sanitary Code mandates prompt reporting of hospital-associated clusters of infectious disease and single cases of emerging pathogens to the NYSDOH and the local health department. Please report using a DOH 4018 form, available on <http://www.health.state.ny.us/nysdoh/infection/infectreport.pdf>:
 - a. Clusters of cases of *Klebsiella* spp. infection or colonization; and/or
 - b. Single cases of carbapenem-resistant *Klebsiella* spp. infection or colonization.
2. The DOH 4018 form should be faxed to the Regional Epidemiology Program at 518-408-1745. Local health departments can be notified by telephone (a confidential case report does not need to be completed).

Advice from the Canadian Medical Association: Beware of US Hospitals



Elderly Canadians who spend their winters in Florida face and pose the most serious risk because they are more likely to find themselves in United States hospitals, in which carbapenem-resistant *Klebsiella pneumoniae* is rampant.

Susceptibility Testing

Frequency of Very Major, Major, and Minor Errors

Testing Method	Number (%) of Isolates with Indicated Result		
	<u>Very Major</u>	<u>Major</u>	<u>Minor</u>
	<u>2010 CLSI Meropenem Interpretive Criteria</u>		
Etest	1 (2.2)	0 (0)	1 (2.2)
Vitek 2	11 (23.9)	0 (0)	18 (39.1)
Sensititre	3 (6.5)	0 (0)	12 (26.1)
Microscan	0 (0)	0 (0)	1 (2.2)
<u>Pre-2010 Meropenem Interpretive Criteria</u>			
Etest	1 (2.2)	0 (0)	7 (15.2)
Vitek 2	27 (58.7)	0 (0)	8 (17.4)
Sensititre	27 (58.7)	0 (0)	12 (26.1)
Microscan	0 (0)	0 (0)	2 (4.3)

MSMC Microscan Results for Carbapenem Resistant *Klebsiella pneumoniae* (n = 531)

	<u>S</u>	(%)	<u>R</u>
Ertapenem	0	0.6	99.4
Meropenem	10.5	7.5	82
Imipenem	11.9	19.2	68.9
Cefepime	3.8	12.4	83.8
Tetracycline	79.1	9.8	11.1
Amikacin	25.6	46.3	28.1
Gentamicin	55.7	15.6	28.6

Carbapenem Resistance in *Klebsiella pneumoniae* in NYC

- Remains endemic, particularly in Brooklyn, although rates have declined
- During peak (2009) at MSMC, 36% of 1163 isolates tested carbapenem-resistant
- The rate held steady ($\approx 16\%$) at NYP/WCMC for past several years until 2016 when dropped to 6%
- 2014 rate at NYP/CPMC was 11% overall; 21% in the ICUs
- For 2008 – 2012, the US rate was 4.7% (N – 5467; SENTRY)¹

¹Rennie RP and Jones RN. 2014. Effects of breakpoint changes on carbapenem susceptibility rates of *Enterobacteriaceae*: Results from the SENTRY Antimicrobial Surveillance Program, United States, 2008 to 2012. Can J Infect Dis Med Microbiol. 25: 285-7



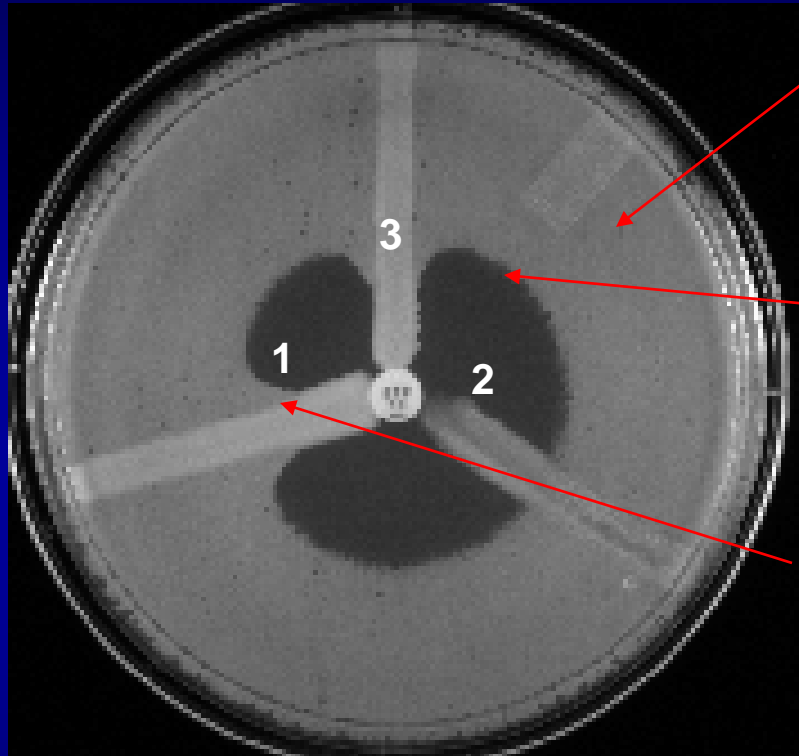
IPM
10

ETP
10

CLSI - Screening and Confirmatory Tests for Suspected Carbapenemase Production in *Enterobacteriaceae*

- **Not necessary to test isolates for a carbapenemase by modified Hodge test (carbapenem inactivation test) when all of the carbapenems that are reported by a laboratory test either intermediate or resistant (i.e., these carbapenem susceptibility results should be reported as tested)**
- **However, modified Hodge test may still be useful in such cases for infection control and epidemiologic purposes**

Modified Hodge Test (Carbapenem Inactivation Test)



E. coli ATCC® 25922

Inhibition of *E. coli* ATCC® 25922 by ertapenem

Enhanced growth of *E. coli* ATCC® 25922. Carbapenemase produced by *K. pneumoniae* D-05 destroyed ertapenem that diffused into the media. Thus, there is no longer sufficient ertapenem to inhibit *E. coli* ATCC® 25922 and an indentation of the zone is noted.

The MHT performed on a small MHA plate.

- (1) *K. pneumoniae* D-05, positive result;
- (2) *K. pneumoniae* 6179, negative result; and
- (3) a clinical isolate, positive result

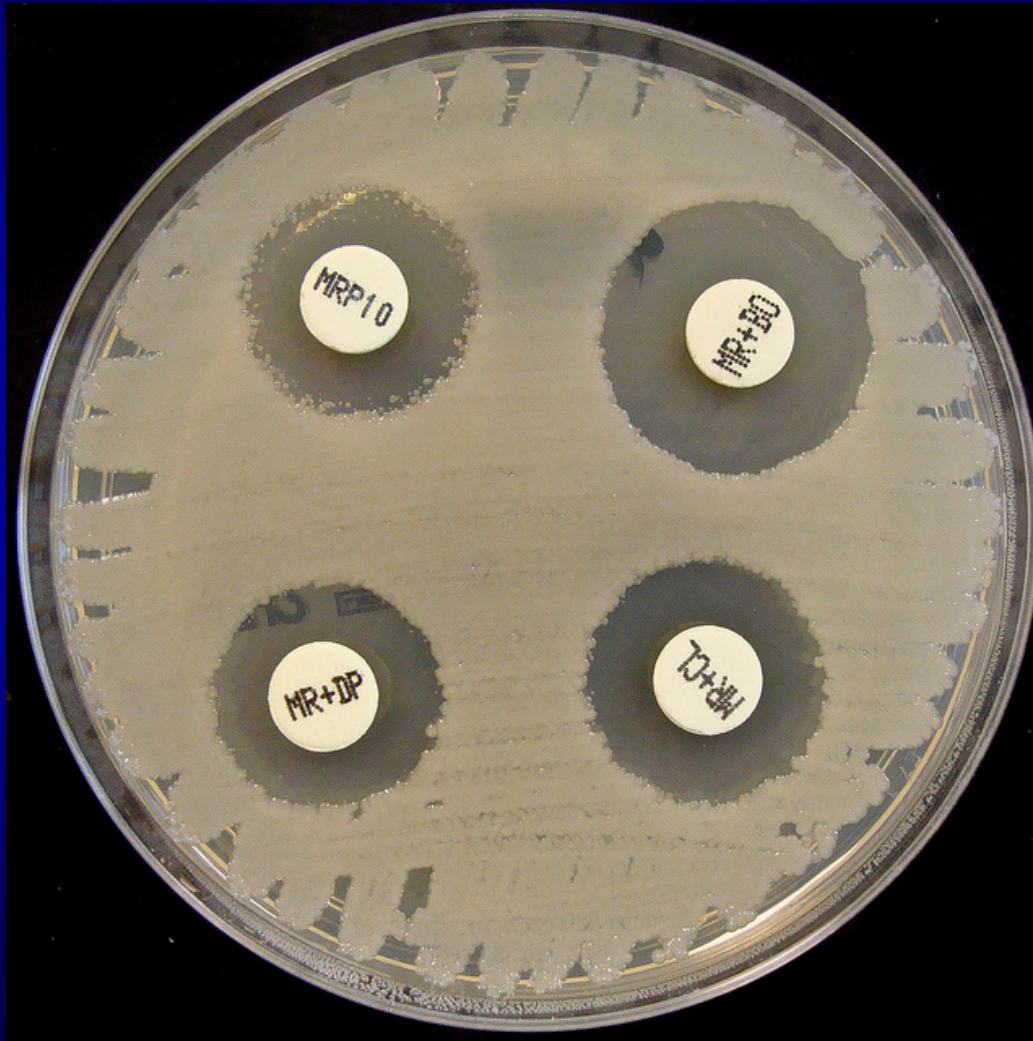
MHT False Positive *Enterobacter cloacae*

Positive Control →



↑
E. cloacae

Positive KPC Test by Boronic Acid Rosco® Method



- Increase in zone of inhibition of ≥ 5 mm for Meropenem (MR) + Boronic Acid (BO) disk, as compared to MR alone, AND
- There must also be a ≤ 3 mm difference for MR versus MR + Clavulanic acid (CL) [AmpC test]
and for MR versus MR + Dipicolinic acid (DP) [Metallo β -Lactamase (MBL) test]

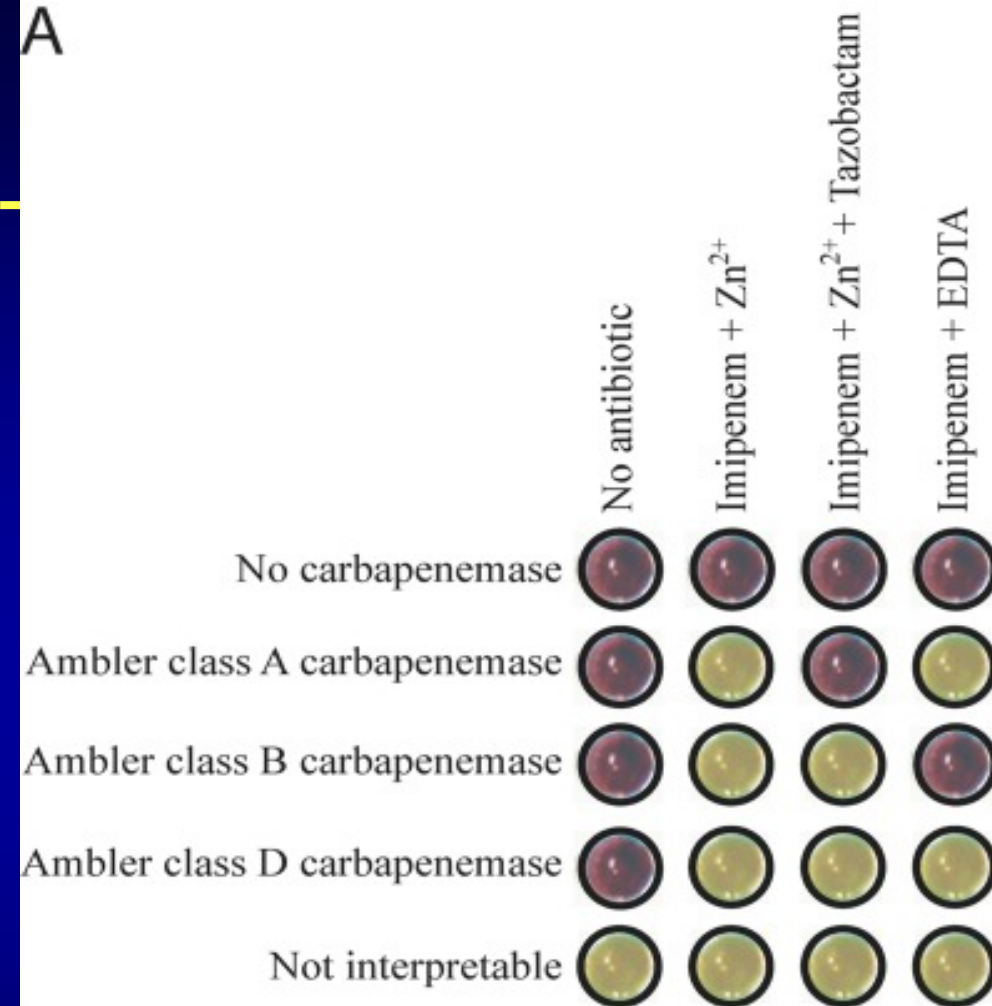
Carba NP Test for Detection of Carbapenemase Production in Enterobacteriaceae and *P. aeruginosa*

- Detects hydrolysis of imipenem
- Isolate suspended in TRIS-HCl lysis buffer, vortexed, incubated for 30 minutes, and centrifuged
- Will be described and included as an alternative to the MHT in the next iteration of CLSI M-100

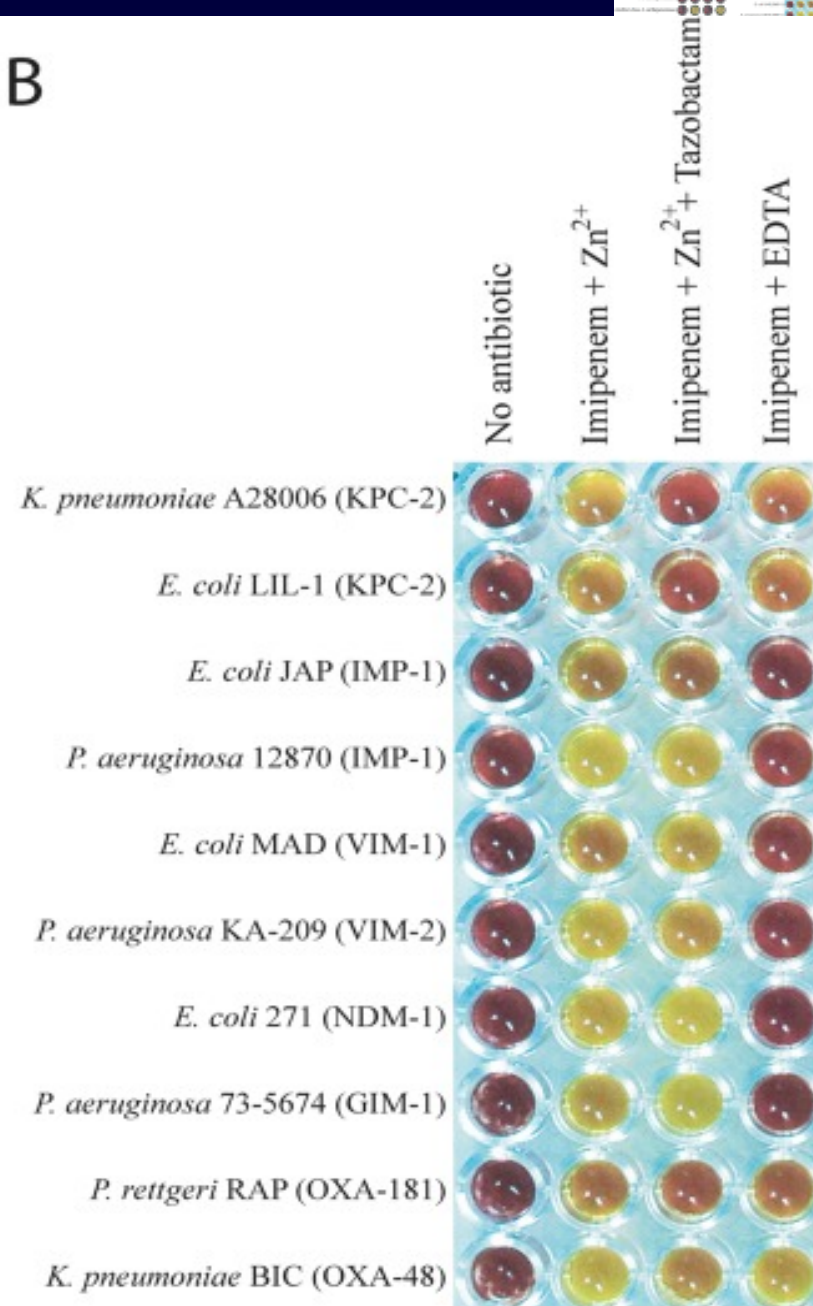
Carba NP Test for Detection of Carbapenemase Production in Enterobacteriaceae and *P. aeruginosa*

- Supernatant transferred to 4 wells of a microtiter plate respectively containing:
 - Dilute phenol red solution with ZnSO₄
 - Dilute phenol red solution with ZnSO₄ and imipenem
 - Dilute phenol red solution containing ZnSO₄, imipenem, and tazobactam
 - Dilute phenol red solution containing imipenem and EDTA

A



B

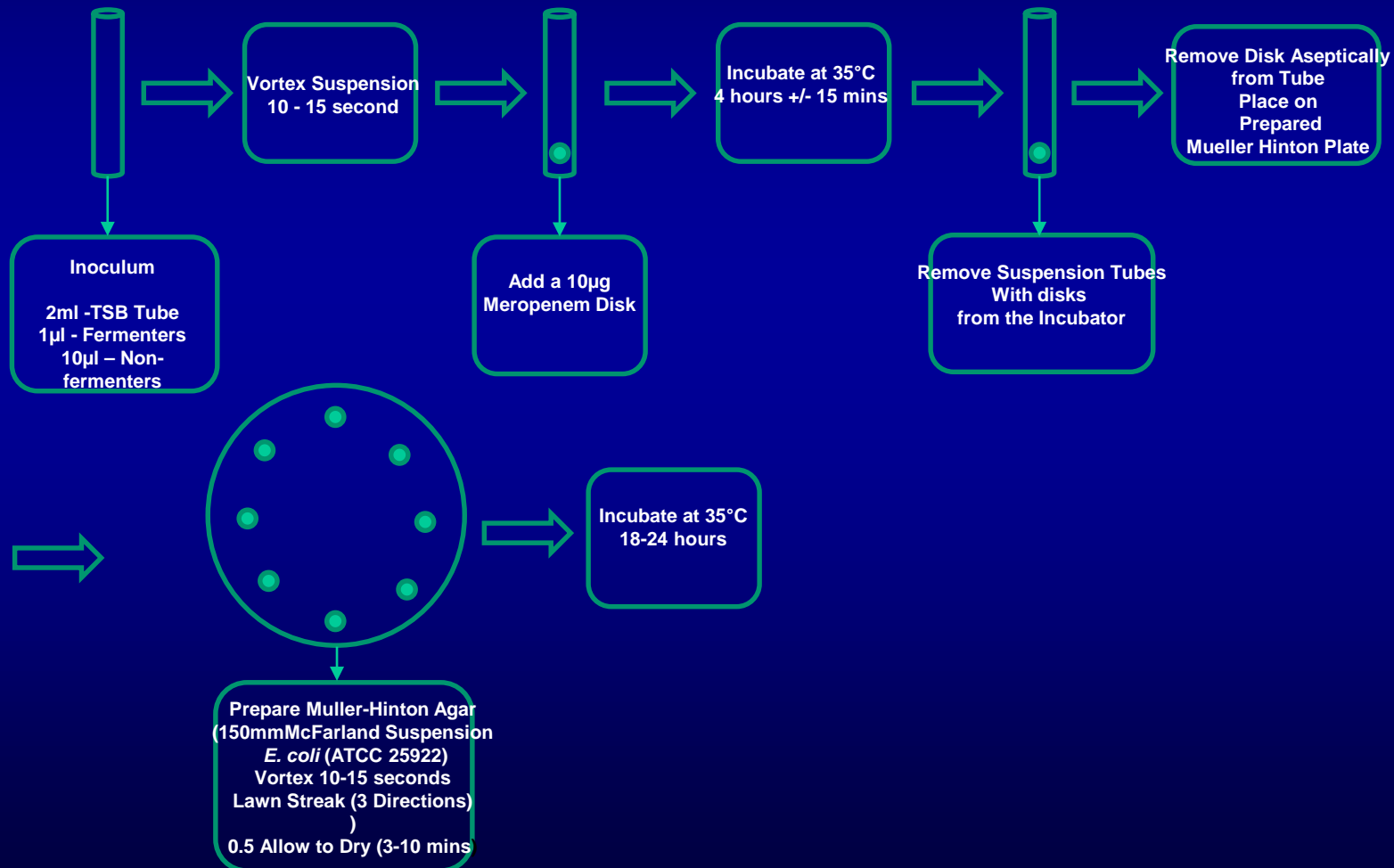


Modified Carbapenemase Inactivation Method (mCIM)

Published this year in CLSI M100

Pierce V, Simner P, Lonsway D, Roe-Carpenter D, Johnson J, Brasso W, Bobenchik A, Lockett Z, Charnot-Katsikas A, Ferraro M, Thomson R, **Jenkins S**, Limbago B, Das S. 2017. The Modified Carbapenem Inactivation Method (mCIM) for Phenotypic Detection of Carbapenemase Production among *Enterobacteriaceae*". *Journal of Clinical Microbiology*. 2017 Apr 5. pii: JCM.00193-17. doi: 10.1128/JCM.00193-17. [Epub ahead of print]

Method



Interpretation of Results

Read for the presence or absence of a zone of inhibition

- ◆ Carbapenemase-positive: If the isolate being tested produces a carbapenemase, the meropenem in the disk will be inactivated allowing uninhibited growth (zones diameter 6 - 10 mm) of the meropenem-susceptible *E. coli* strain (ATCC 25922)
- ◆ Carbapenemase-negative: If the gram-negative rod being tested does not produce a carbapenemase, the meropenem in the disk will not be inactivated resulting in inhibited growth (zone diameter ≥ 20 mm) of the meropenem-susceptible *E. coli* strain (ATCC 25922)
- ◆ Indeterminate: A zone of inhibition (≤ 19 mm but ≥ 11 mm) is an indeterminate result. The presence or absence of a carbapenemase cannot be confirmed. PCR for carbapenemase genes is recommended.
- ◆ Carbapenemase-positive: When small colonies are observed growing in the zone of inhibition around the disk the results are classified as carbapenemase positive. Record as positive and keep note of growth within zone of inhibition

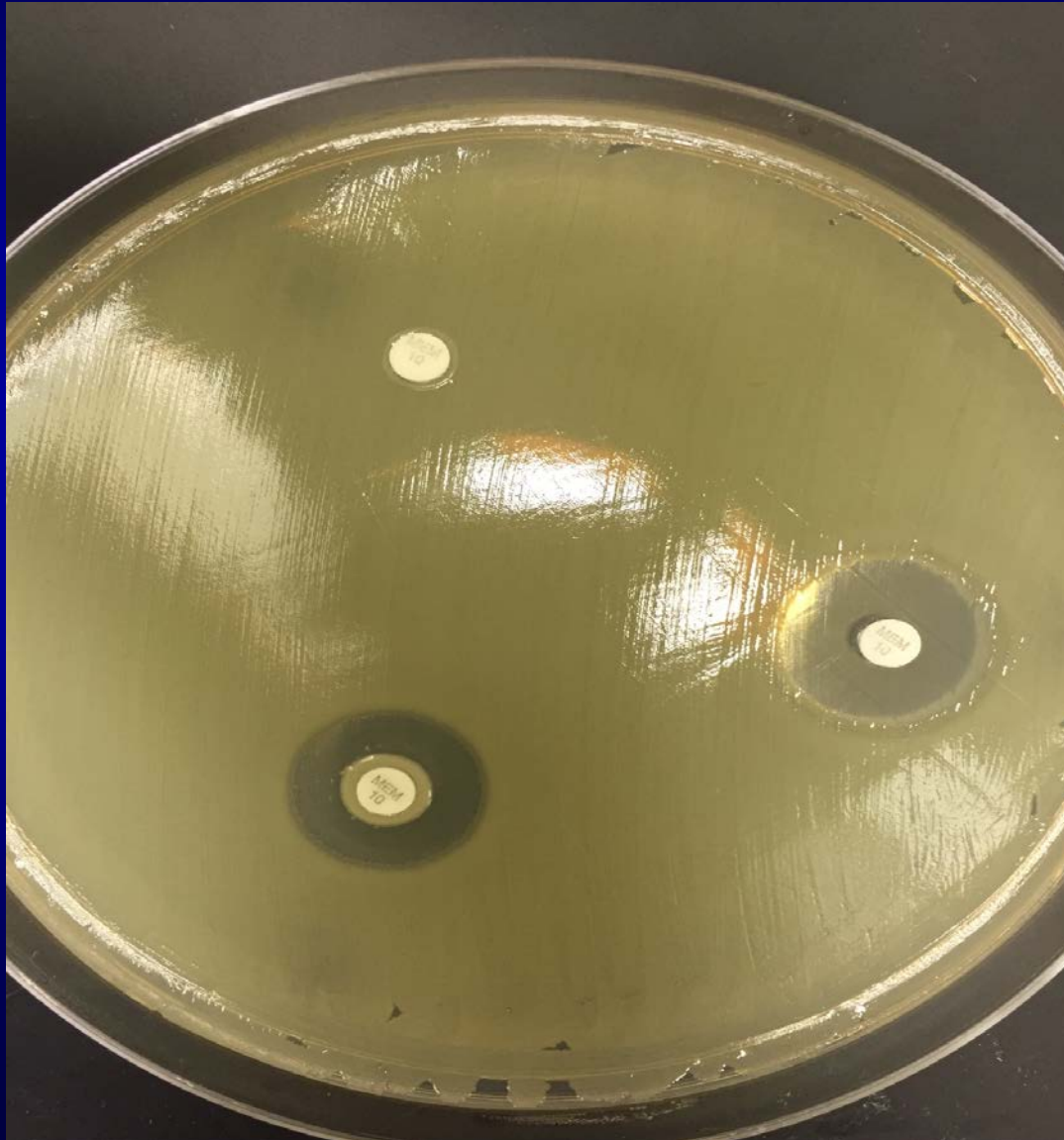
Recommendations

- Enterobacteriaceae (1- μ l loop, TSB, 4 hours)
 - Positive 6 - 15 mm (protocol 6-10 mm)
 - Indeterminate 16 - 18 (protocol ≤ 19 mm but ≥ 11 mm)
 - Negative ≥ 19 mm (protocol ≥ 20 mm)
- *Pseudomonas aeruginosa* and *Acinetobacter baumannii*, zone size ≤ 10 mm 100% positive predictive value (10- μ l loop, TSB, 4 hours)

AND/OR

- Additional Studies and modify the method in one year
 - Increased inoculum *Pseudomonas aeruginosa* and *Acinetobacter baumannii* complex (2 X 10 μ l)
 - Increased incubation time for *Pseudomonas aeruginosa* and *Acinetobacter baumannii* (6 hours)
 - *Acinetobacter baumannii* and *Pseudomonas aeruginosa* – mixed genes; other mechanisms for carbapenemase negative isolates
 - Pilot study data presented at January 2017 meeting – above parameters, all sites, for June meeting

Examples



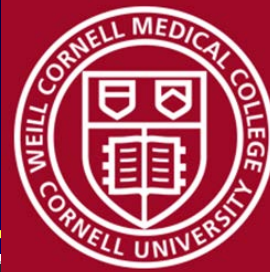
imCIM

- The modified Carbapenem Inactivation Method (mCIM) is a simple phenotypic test that detects carbapenemase production in *Enterobacteriaceae*, but cannot distinguish between serine-based carbapenemases and MBLs
- imCIM employs ethylenediaminetetraacetic acid (EDTA), in conjunction with the mCIM assay to differentiate serine from metallo-carbapenemases (MBLs)

imCIM

- Potentially important from both an epidemiologic and therapeutic perspective

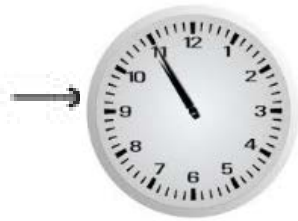
Methods: modified CIM (w/o EDTA)



Suspend 1 µl
loopful of bacteria
in TSB



Add 10 microgram
of meropenem disc



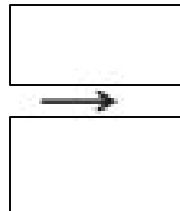
Incubate for 4 hours
at 35° C



Place on Mueller Hinton agar
inoculated with *E. coli* ATCC
25922



Incubate for at least 18
hours at 35° C



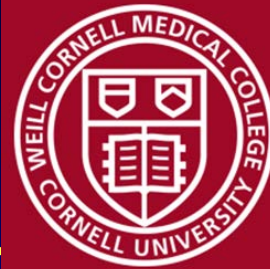
Read presence or absence
of inhibition zone at 18 and
24 hours of incubation



+ mCIM
Carbapenemase activity
present

- mCIM
Carbapenemase activity
absent

Methods: imCIM with EDTA



Suspend 1 μ l loopful
of bacteria in TSB +
0.1 mM EDTA



Add 10 microgram
of meropenem disc



Incubate for 4 hours
at 35° C



Place on Mueller Hinton agar
inoculated with *E. coli* ATCC
25922



Incubate for at least 18
hours at 35° C



Read presence or absence
of inhibition zone at 18 and
24 hours of incubation

- imCIM
Carbapenemase
activity
not inhibited by EDTA

+ imCIM
Carbapenemase activity
inhibited by EDTA

Results: QC testing

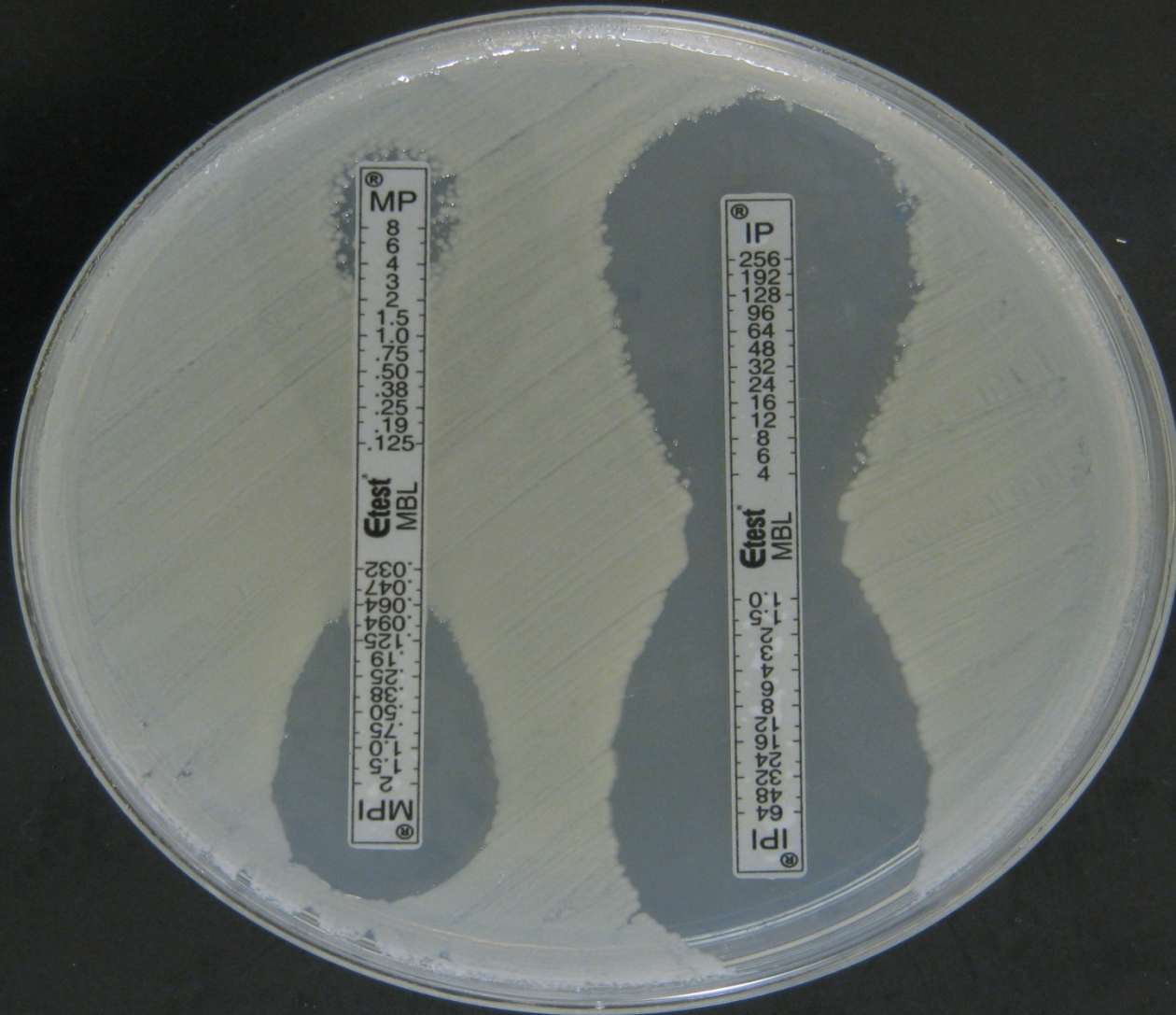
K. pneumoniae ATCC 1705 (KPC+)
K. pneumoniae ATCC 1706 (KPC -)
K. pneumoniae ATCC 2146 (NDM+)

No EDTA



EDTA

Positive MBL Tests by Etest®



Positive MBL Test by Dipicolinic Acid Rosco® Method



- Increase in zone of inhibition of ≥ 5 mm for MR + DP, versus MP alone, AND
- There must also be a ≤ 3 mm difference for MR alone versus MR+BO (KPC) and MR alone versus MR+CL (AmpC)

CARBAPENEMASES - CLSI

- In the setting of limited treatment options, clinicians managing infections due to these isolates may wish to consider maximum approved dosage regimens and/or prolonged intravenous infusions of carbapenems as described in the medical literature
- Each laboratory should develop a mechanism for informing clinicians about such circumstances in a timely manner. This might include a telephone call and/or a comment appended to the laboratory report. Consultation with an Infectious Disease specialist is recommended.

Enterobacteriaceae Carbapenem Breakpoints

Revised CLSI and FDA MIC Breakpoints (µg/mL)

<u>Drug</u>	<u>Susceptible</u>	<u>Intermediate</u>	<u>Resistant</u>
Doripenem	≤ 1 (NA)	2 (NA)	≥4 (NA)
Meropenem*	≤ 1 (4)	2 (8)	≥4 (16)
Imipenem*	≤ 1 (4)	2 (8)	≥4 (16)
Ertapenem*	≤0.5 (2)	1 (4)	≥2 (8)

Revised CLSI and FDA Disc Breakpoints (mm) and FDA

<u>Drug</u>	<u>Susceptible</u>	<u>Intermediate</u>	<u>Resistant</u>
Imipenem	≥23	20-22	≤19
Meropenem	≥23	20-22	≤19
Doripenem	≥22	20-21	≤19
Ertapenem	≥22	19-21	≤18

Previous breakpoints are shown in parentheses

CARBAPENEMS

- **NOTE:** Imipenem MICs for *Proteus* spp., *Providencia* spp., and *Morganella morganii* tend to be higher (e.g., MICs in the intermediate and at the breakpoint of resistance) than those with meropenem or doripenem MICs. These isolates can be imipenem resistant by mechanisms other than production of carbapenemases.

Screening Cultures for CRKP

- All ICU patients screened weekly and upon admission (rectal swabs)
- Specimens inoculated to 5 mL tube of tryptic soy broth containing 10 µg imipenem disk and incubated overnight at 37° C
- Broth subcultured onto MacConkey agar; imipenem disk placed in the area of heavy inoculum
- Incubated overnight at 37° C
- Suspicious colonies identified and *in vitro* susceptibility to ertapenem, imipenem, and meropenem determined by broth microdilution using Microscan® system; resistant isolates confirmed by E-testing
- 27% of KPC-positive patients detected by screening subsequently became bacteremic with the organism

Calfee DP, Jenkins SG. 2008. Surveillance Cultures to Detect Asymptomatic Colonization with Carbapenem-Resistant *Klebsiella pneumoniae* among Intensive Care Unit Patients. *Infection Control and Hospital Epidemiology*. Vol.10: 966-968.

Mechanisms of Carbapenem Resistance

- In U.S., Harboring KPC enzyme most frequent etiology
- Cross-resistance with fluoroquinolones and aminoglycosides
- Hyper-production of AmpC or CTX-M β -lactamases along with an outer membrane porin mutation^{8,9}; OMP K37?
- Recent multi-center study examined strains of *E. coli* and *K. pneumoniae* resistant to piperacillin-tazobactam, amoxicillin-clavulanate, and ampicillin-sulbactam, but fully susceptible to cephalosporins – mutants with porin deletions and hyperproduction of TEM

⁸Reviews on Medical Micro. 2004;15:63-72

⁹Antimicrob Agents Chemother. 1997;41(3):563-9

Mount Sinai Experience

- 721 patients colonized/infected with carbapenem-resistant *K. pneumoniae* from 1/04 to 4/08
- 97 patients colonized/infected with carbapenem-resistant Enterobacteriaceae other than *Klebsiella pneumoniae* since 2006:
(*Enterobacter* spp. – 73; *Providencia stuartii* – 1; *Morganella morganii* – 1; *Serratia marcescens* – 1; *Klebsiella oxytoca* – 6; *E. coli* – 11; *Citrobacter freundii* – 4)
- 29 in patients concomitantly infected with KPC-producing *K. pneumoniae* (confirmed as KPCs by isoelectric focusing and PCR)

Mount Sinai Hospital: Patients with Carbapenem-Resistant *K. Pneumoniae* by Year

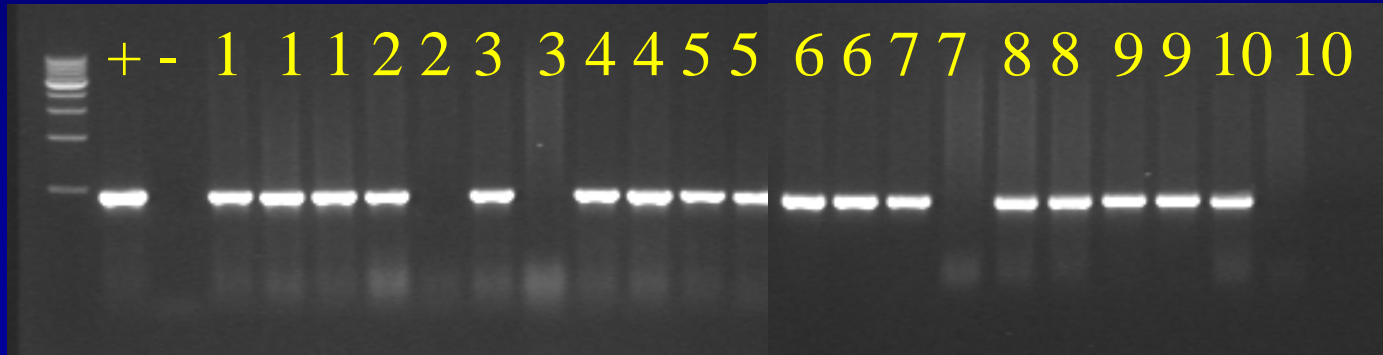
- 1998 – 2
- 1999 – 1
- 2000 – 1
- 2001 – 7
- 2002 – 2
- 2003 – 13
- 2004 – 40
- 2005 – 167
- 2006 – 219
- 2007 – 225
- 2008 – 44 (through 03/21)

Cornell Experience

(Carbapenem-resistant *Enterobacteriaceae* (843) since 2006)

- *Klebsiella pneumoniae* – 668 patients
 - 2007 – 61 2016 – 39 (2/14/16 – 12/31/16)
 - 2008 – 77 2017 – 16 (to date)
 - 2009 – 64
 - 2010 – 79
 - 2011 – 64
 - 2012 – 75
 - 2013 – 120
 - 2014 – 59
 - 2015 – 14 (through 4/30/15)
- *Klebsiella oxytoca* – 8; *E. coli* – 77; *Citrobacter freundii* – 10;
Citrobacter koseri – 1; *Serratia marcescens* – 6;
Enterobacter cloacae - 82; *Enterobacter aerogenes* – 16;
Enterobacter asburiae – 2; *Pluralibacter gergoviae* – 1;
Pantoea spp. – 2; *Providencia rettgeri* – 2; *Providencia stuartii* – 1;
Proteus mirabilis – 1; *Morganella morganii* - 2

10 Patients: Both *K. pneumoniae* and Another Enteric Bacterial Species



- 6 of 10 patients' pairs possess KPC genes confirmed by PCR (patient 1, 4, 5, 6, 8 and 9)

MSSM Study - Prior Antibiotics

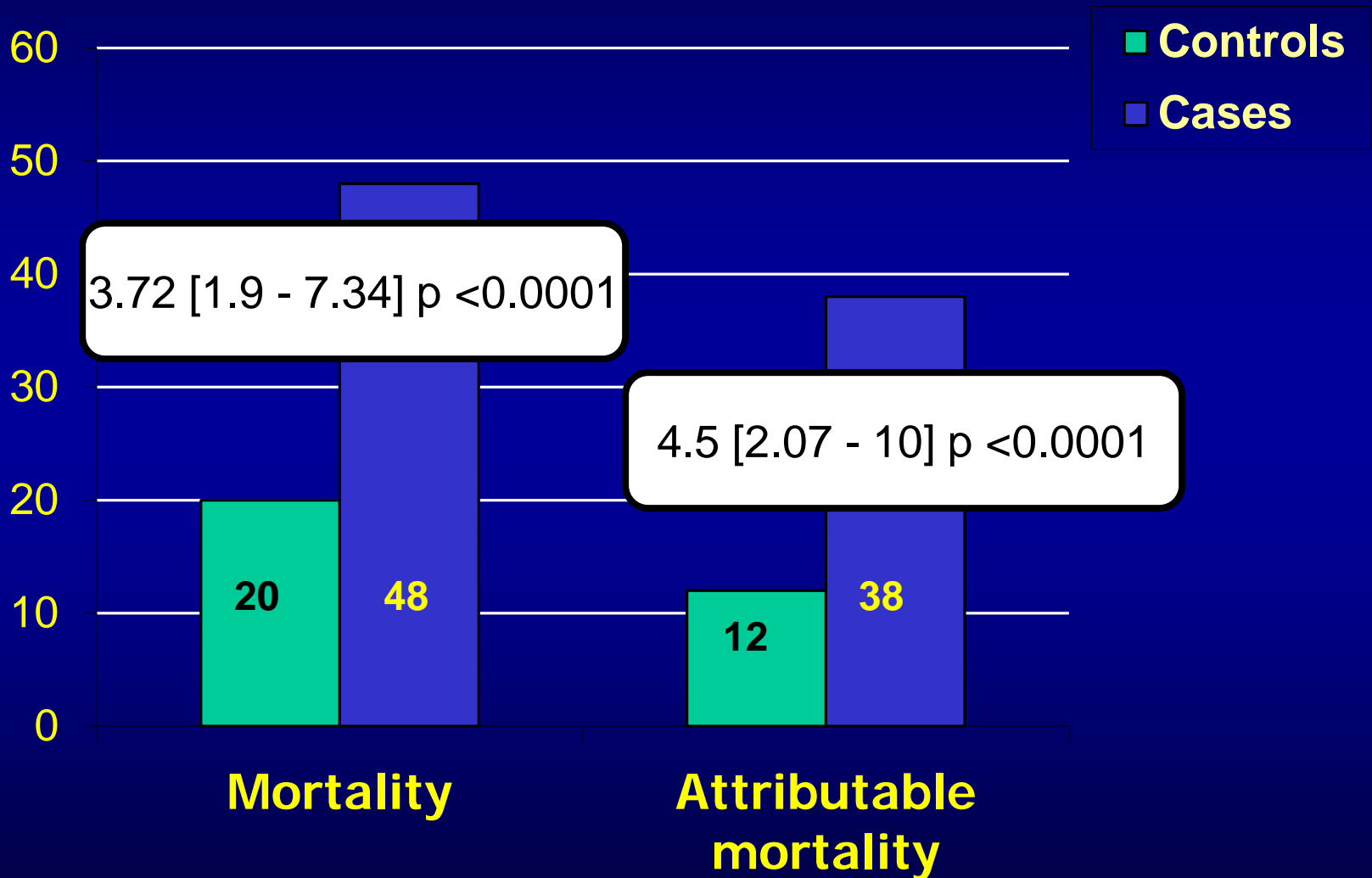
	Cases (n = 99)	Controls (n = 99)	OR [95%CI] P-value
Prior Antibiotics	98	55	78.40 [12.41-3197] p <0.0001
Cephalosporins	63	31	3.84 [2.04-7.25] p <0.00001
Fluoroquinolones	36	23	1.89 [0.97-3.7] p = 0.04
β -lactam/ β - lactamase inhibitor	54	33	2.40 [1.3-4.45] p = 0.0024
Aminoglycoside	14	3	5.27 [1.39-29.35] p = 0.0093
Monobactam	6	1	6.32 [0.73-142] p = 0.054
Carbapenem	54	6	18.6 [7.01-52.16] p <0.00001

Receipt of “Effective” Therapy

	Cases	Controls	OR [95%CI] P-value
Effective Antibiotics	67	95	0.09 [0.03 - 0.28] p <0.00001
Time to therapy			
Mean	3.12	0.76	p <0.001
Median	3	0	
Range	0 - 12	0 - 5	
Adjunct Therapy	73	58	1.98 [1.04 - 3.78] p = 0.024

Effective therapy: Antibiotic to which the isolate is susceptible *in vitro*

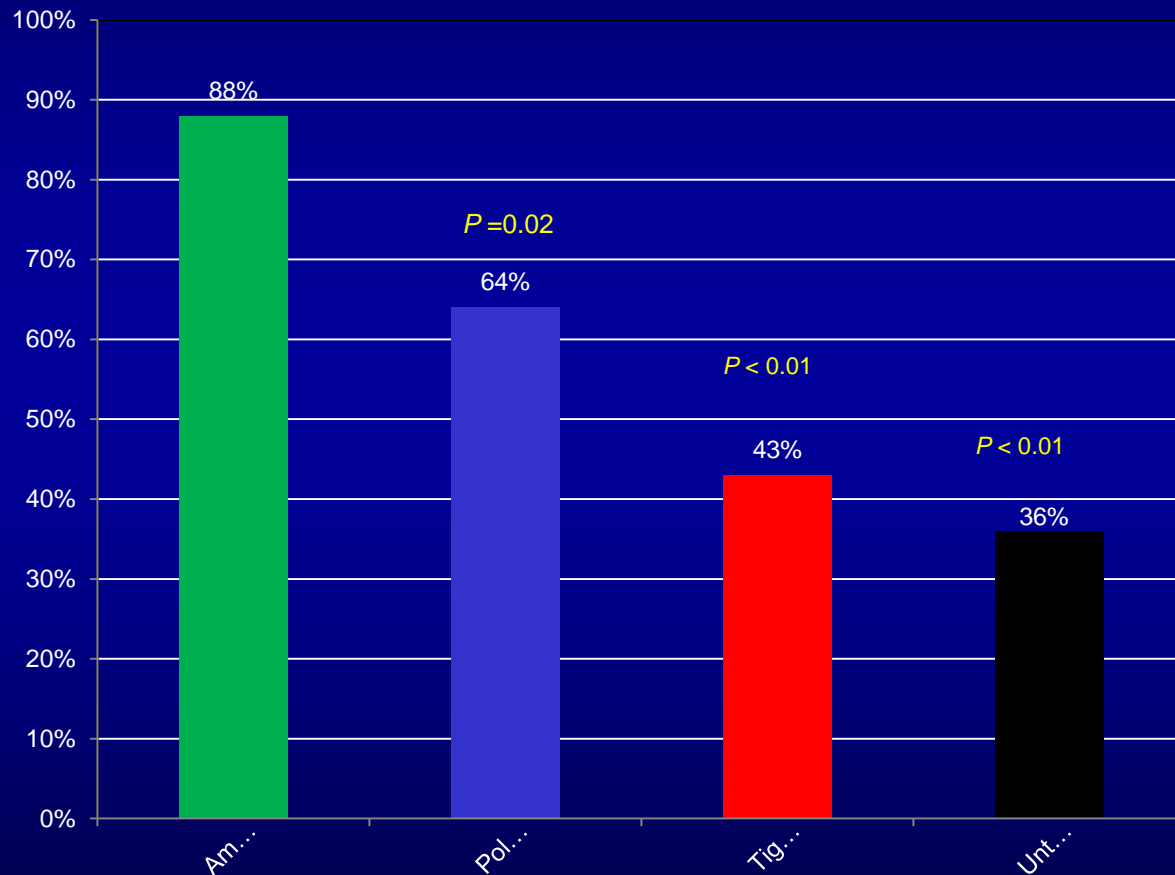
Overall Mortality (%)

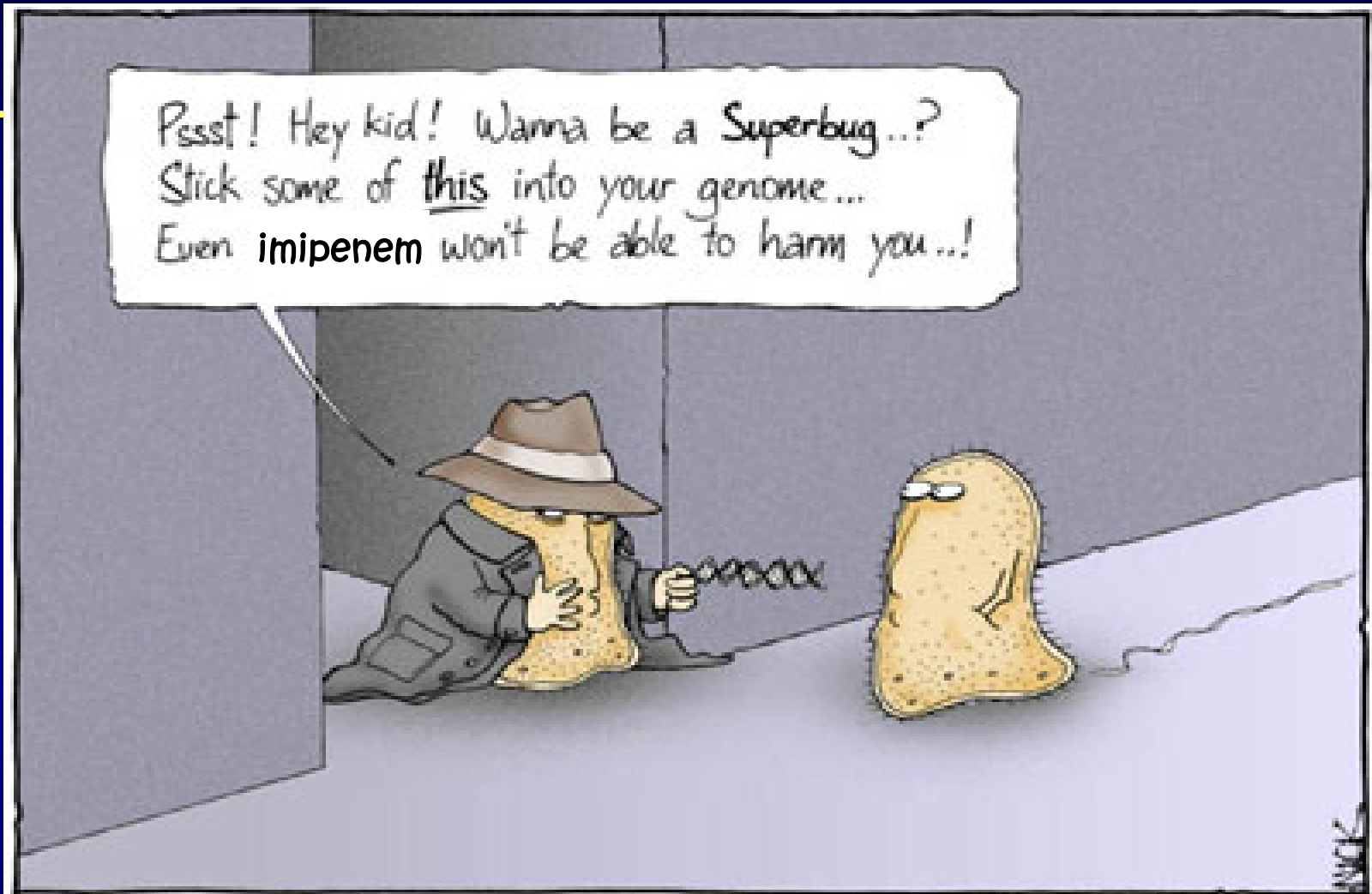


Predictors of Mortality in Cohort (n = 198)

	Expired (n = 68)	Survived (n = 130)	OR [95% CI] p-value
Effective antibiotics	53(78%)	109(84%)	0.68 [0.31-1.52] p = 0.31
Delay to Antibiotics	2.34	1.45	1 [0.81-1.24] p = 0.9891
Adjunct Therapy*	35(51%)	53(41%)	0.30 [0.12 - 0.75] p = 0.0095

Clearance of CRKP Bacteriuria





It was on a short-cut through the **Surgical ICU** that Albert was first approached by a member of the Antibiotic Resistance.

Thoughts?

Questions?

