



Carbapenem-Resistant *Enterobacteriaceae* (CRE): Detection and Control

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Outline

- Background
- Mechanisms, Molecular Epidemiology, and Laboratory Detection
- Epidemiology of carbapenem resistant *Klebsiella pneumoniae*
 - NJ-AZ case series
 - Recent outbreak investigations
- Recently approved CDC/HICPAC recommendations on controlling CRE in acute care settings.



Some Background on *Enterobacteriaceae*

- Bacteria in *Enterobacteriaceae* group are common causes of community and healthcare acquired infections.
- *E. coli* is the most common cause of outpatient urinary tract infections.
- *E. coli* and *Klebsiella* species (especially *K. pneumoniae*) are important causes of healthcare associated infections.
 - Together they accounted for 15% of all HAIs reported to NHSN in 2007.



Some Background on *Enterobacteriaceae*

- β -lactam antibiotics (derivatives of penicillin) have long been the mainstay of treating infections caused by *Enterobacteriaceae*.
- However, resistance to β -lactams emerged several years ago and has continued to rise.
 - Extended spectrum β -lactamase producing *Enterobacteriaceae* (ESBLs)
 - Plasmid-mediated AmpC-type enzymes



The Last Line of Defense

- Fortunately, our most potent β -lactam class, carbapenems, remained effective against almost all *Enterobacteriaceae*.

Doripenem, Ertapenem, Imipenem, Meropenem

- Unfortunately, “Antimicrobial resistance follows antimicrobial use as surely as night follows day”



Klebsiella Pneumoniae Carbapenemase

- KPC is a class A β -lactamase
 - Confers resistance to all β -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* (South America)

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 >4µg/ml
Ceftriaxone	R	Colistin	MIC >4µg/ml
Cefepime	R	Tigecycline	S



Carbapenemases in the U.S.

Enzyme	Bacteria
KPC	Enterobacteriaceae
Metallo- β -lactamase	<i>P. aeruginosa</i>
OXA	<i>Acinetobacter</i> spp.
SME	<i>Serratia marcescens</i>



Mechanisms of Carbapenem Resistance in Enterobacteriaceae

- Carbapenemase production
- Cephalosporinase (e.g. ESBL or AmpC-type enzymes) + porin loss



KPC Enzymes

- Located on plasmids; conjugative and nonconjugative
- *bla*_{KPC} is usually flanked by transposon sequences
- *bla*_{KPC} reported on plasmids with:
 - Normal spectrum β -lactamases
 - Extended spectrum β -lactamases
 - Aminoglycoside resistance
 - Fluoroquinolone resistance



Carbapenem resistance in *K. pneumoniae* NHSN Jan 2006- Sept 2007

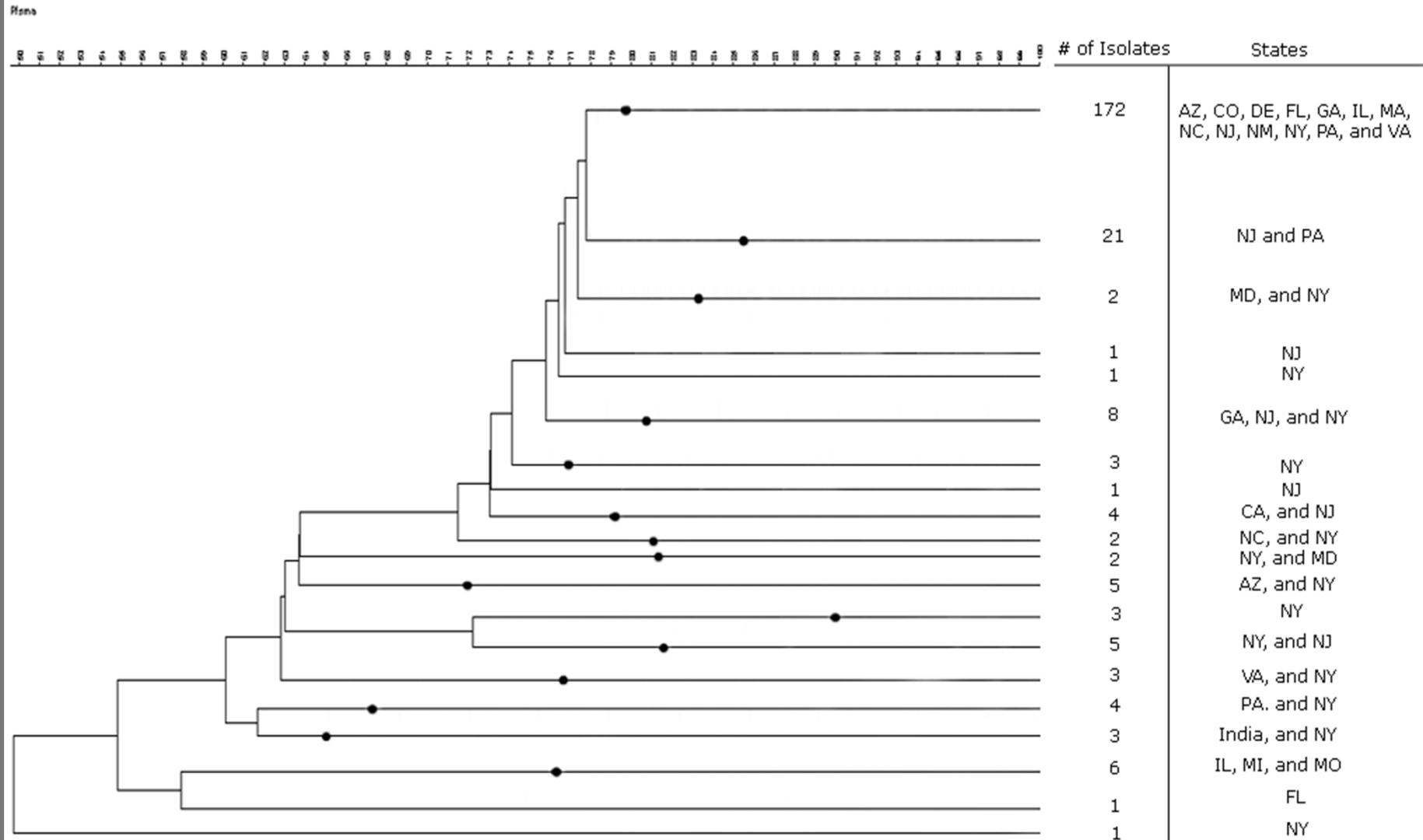


	CLABSI	CAUTI	VAP	Pooled
Carbapenem resistant <i>K. pneumoniae</i>	11%	9%	4%	8%

Hidron, A et al Infect Control Hospital Epidemiol. 2008;29:996

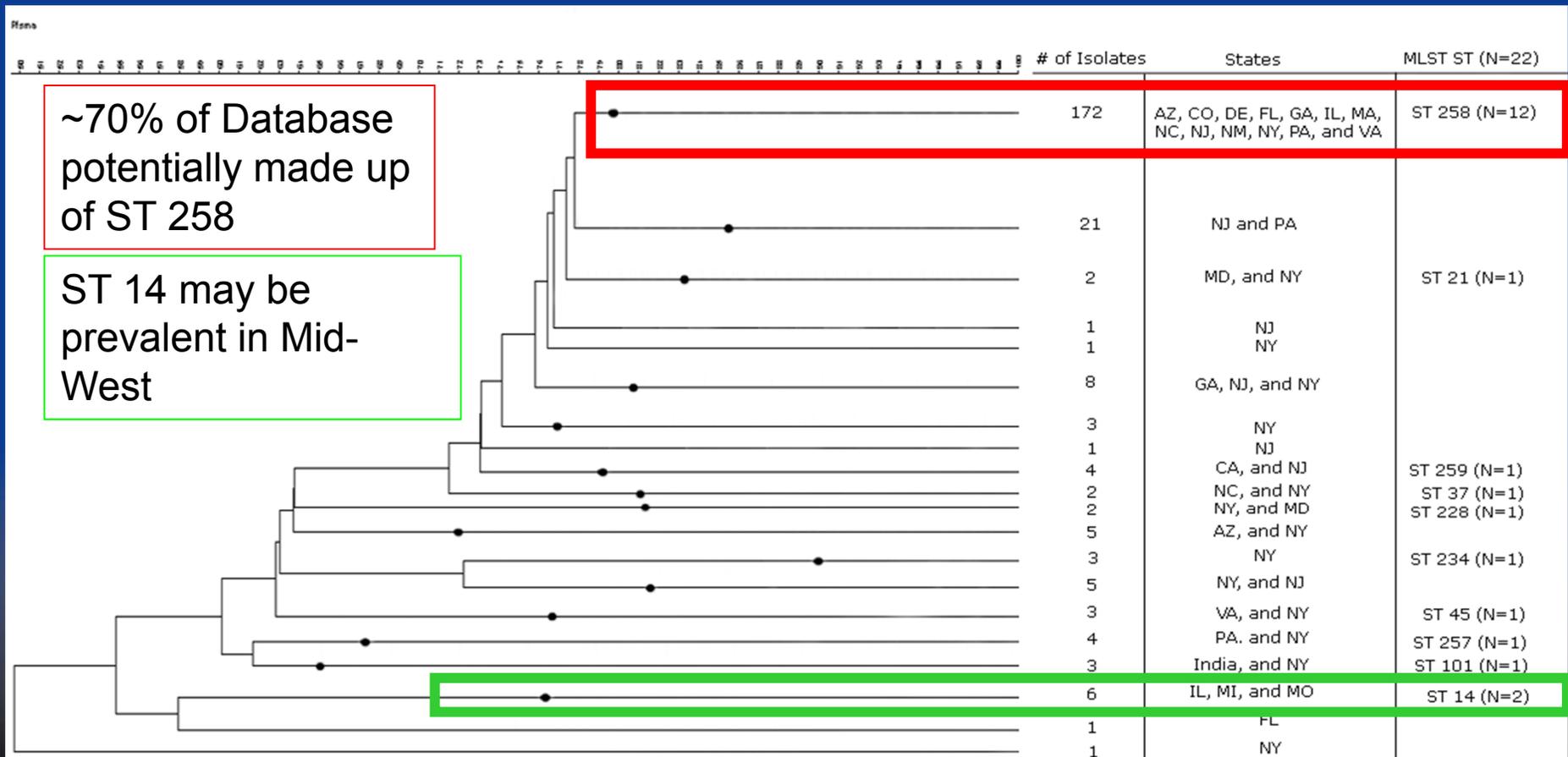


KPC+ *K. pneumoniae*





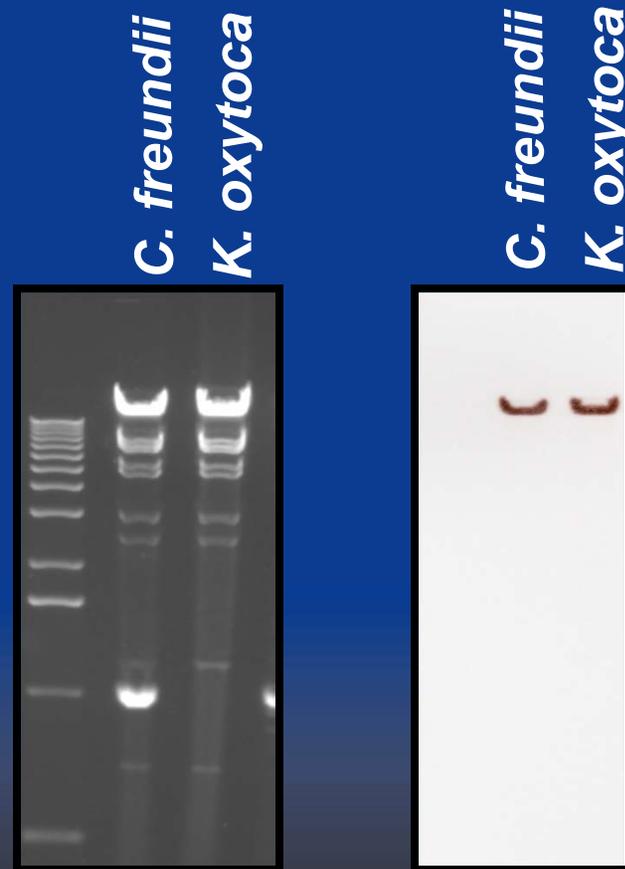
Related KPC+ *K. pneumoniae* Isolates in Multiple States



~70% of Database potentially made up of ST 258

ST 14 may be prevalent in Mid-West

Inter-Species Plasmid Transfer?





Laboratory Detection of KPC-Producers

Problems:

- 1) Some isolates test susceptible to carbapenems, but the carbapenem MICs are elevated
- 2) Some automated susceptibility testing systems fail to detect low-level carbapenem resistance

FC Tenover, et al. EID 2007

Karen (Kitty) Anderson, et al. JCM 2007



Strategy to Detect Resistance



Done in collaboration with Clinical and Laboratory Standards Institute (CLSI)

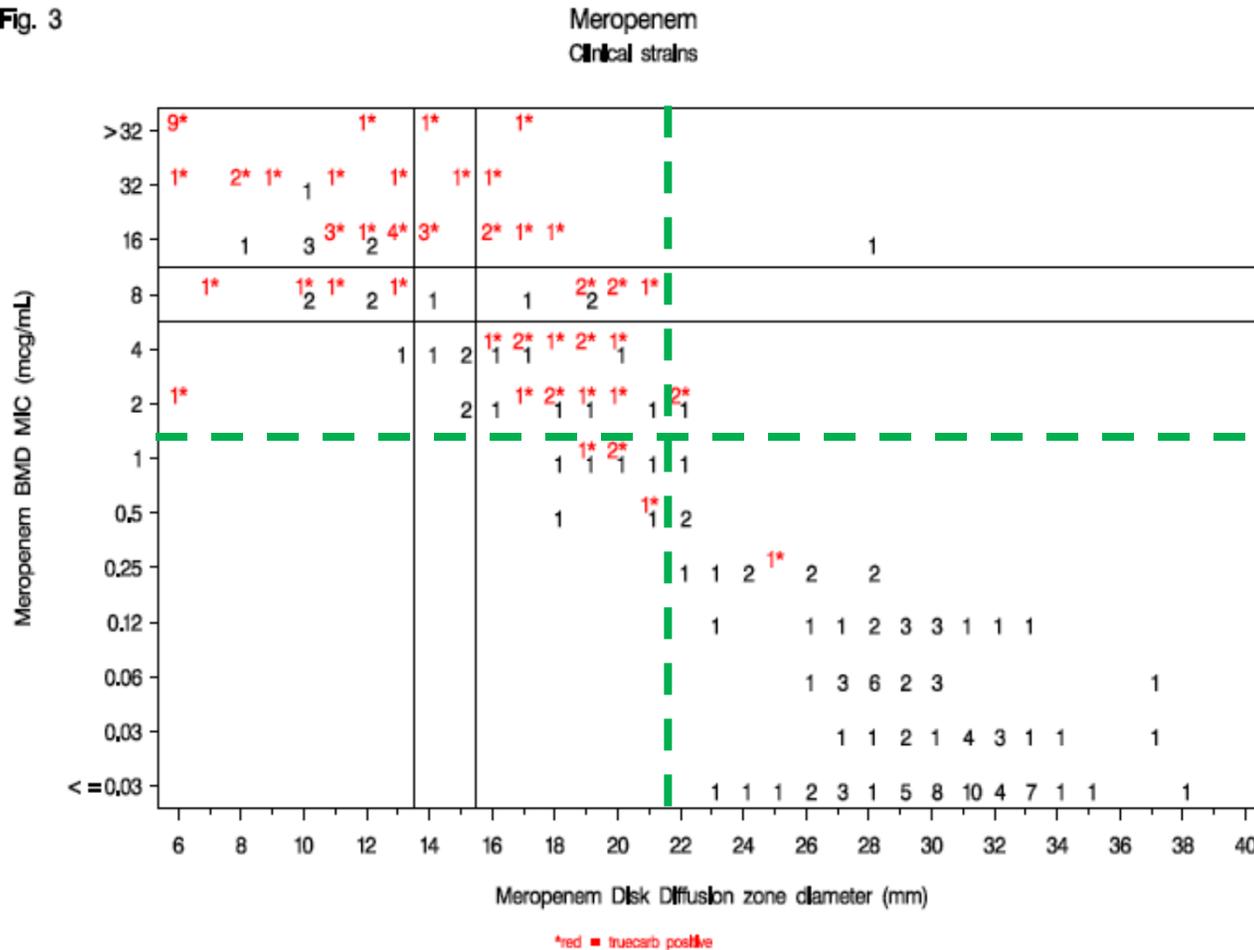
- 1) Identify screening criteria to identify a carbapenemase-producing, carbapenem-susceptible isolate
- 2) Identify a phenotypic test to confirm carbapenemase activity
- 3) Recommend follow-up actions if carbapenemase activity is detected



Screening Criteria



Fig. 3



Betty Wong, et al., CLSI AST Subcommittee Mtg, June 2008



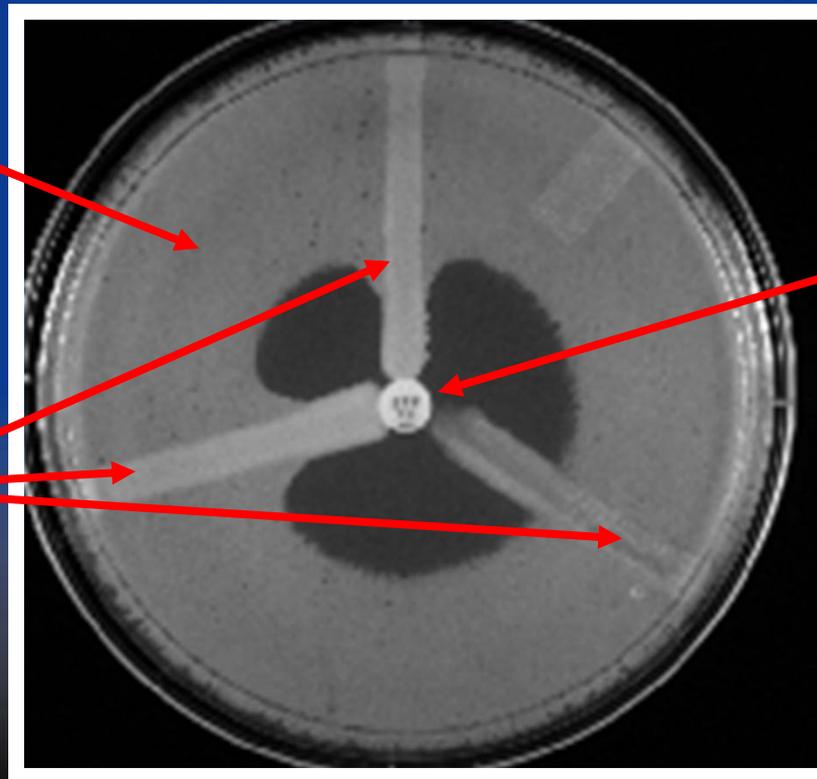
Test for Carbapenemase Detection

Modified Hodge Test (MHT)
Carbapenem Inactivation Assay

Susceptible
E. coli

Carbapenem Disk

Test Isolate





Evaluation of the MHT for Detection of Carbapenemase-Production in Enterobacteriaceae



Drug used in MHT	% Sensitivity	% Specificity
Ertapenem	95.5	90.7
Imipenem	96.7	88.5
Meropenem	94.3	94.0

Betty Wong, et al., CLSI AST Subcommittee Mtg, June 2008



Implementation of Recommendations

- For carbapenems that test intermediate or resistant – report the susceptibility with out additional testing
- Logic – the intermediate or resistant result is sufficient to signal a treatment and an infection control alert
- Could perform a carbapenem-inactivation test for epidemiological or infection control reasons



When Should a Lab Test for Carbapenemase?

- When an isolate test susceptible to a carbapenem, but meets the screening criteria
- MIC Screening Criteria:
 - Ertapenem MIC = 2 $\mu\text{g/ml}$
 - Imipenem or Meropenem MIC is 2 or 4 $\mu\text{g/ml}$



Susceptibility Report if the MHT is Positive

- Report the carbapenem MIC without an interpretation
- Add the comment: “This isolate demonstrates carbapenemase production. The clinical efficacy of the carbapenems has not been established for treating infections caused by *Enterobacteriaceae* that test carbapenem susceptible but demonstrate carbapenemase production *in vitro*.”



Why Report an MIC Without an Interpretation?



- Lack of data on clinical outcome for infections with isolates that have a carbapenemase, but test susceptible to carbapenems
- Limited treatment options
- Unpublished reports that treatment with high-dose carbapenem administered by continuous infusion may possibly be effective



Can Laboratory Detection of Carbapenemase-R be Improved?



- CLSI will reconsider carbapenem breakpoints in June, 2009
- Lower breakpoints may decrease the need for additional testing



New Challenge for Clinical Microbiology Laboratories



- Carbapenemase-producing Enterobacteriaceae are a significant infection control concern
- Identification of patients colonized with carbapenemase-producing Enterobacteriaceae to prevent transmission
- Colonization in the GI tract
- No FDA-approved methods

Culture Method for Isolation of CRE



Sample

Select

Differentiate

TSB +
carbapenem disk

D. Landman et al. JCM. 2005
Kitty Anderson, Betty Wong



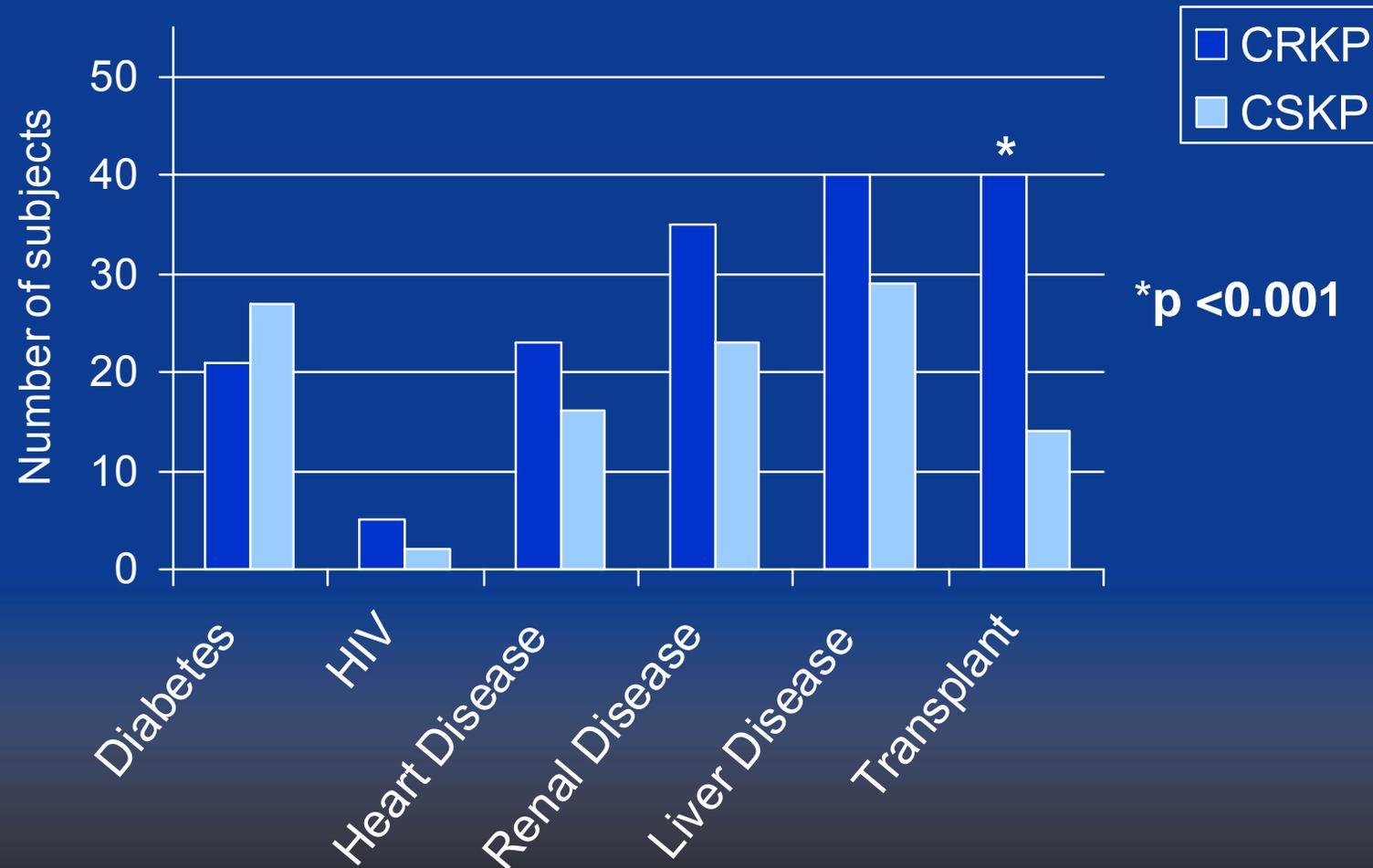
Risk Factors for and Outcomes of CRKP Infections

- Case control studies done by Patel et al. at Mount Sinai in NYC, where CRKP are now endemic.
 - 99 patients with invasive CRKP infections compared to 99 patients with invasive carbapenem susceptible *K. pneumoniae* infections.

Patel et al. Infect Control Hosp Epidemiol 2008;29:1099-1106



Comorbidities



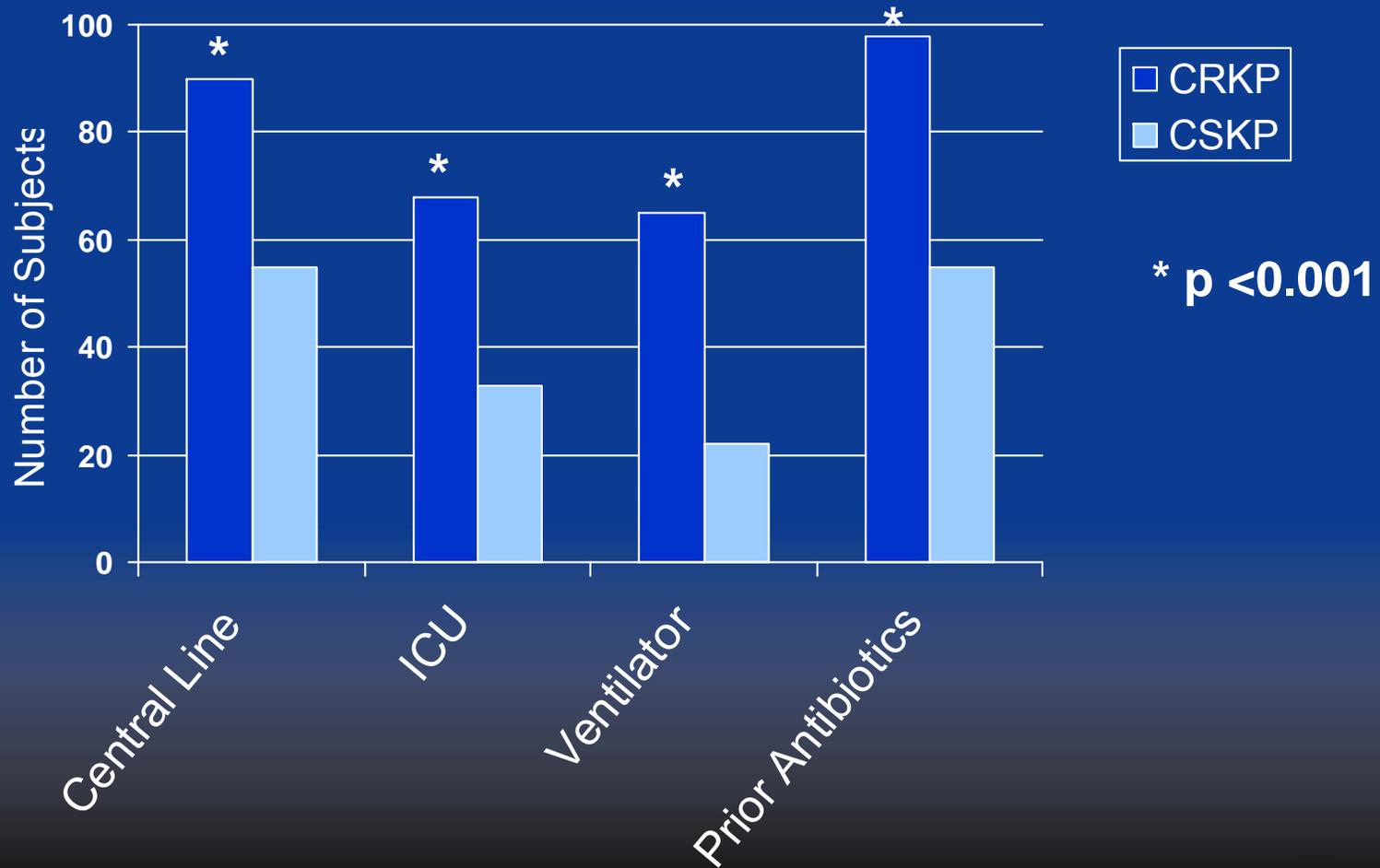


Pre-infection Length of Stay

	CRKP (n=99)	CSKP (n=99)	p-value
Pre-infection LOS			
Mean	25.1 ± 25	6.44 ± 10	
Median	21	1	p<0.001
Range	0-129	0-59	



Healthcare-Associated Factors





Prior Antibiotics

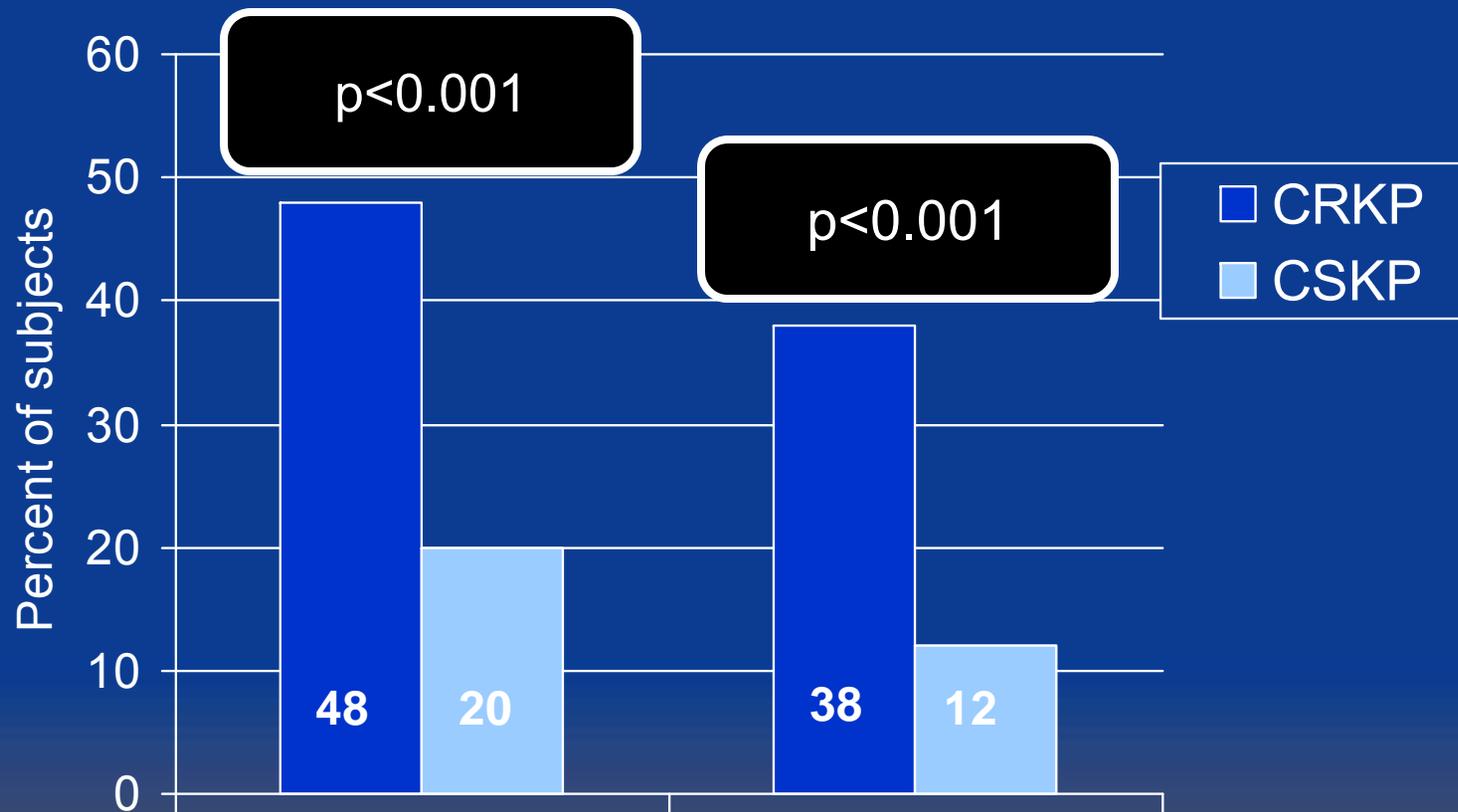


	CRKP (n=99)	CSKP (n=99)	p-value
Cephalosporins	63	31	p<0.001
Fluoroquinolones	36	23	p=0.05
B-lactam/inhibitor	54	33	p=0.005
Aminoglycosides	14	3	p=0.01
Carbapenems	54*	6	p<0.001

- *26 (48%) on carbapenems at time of isolation of CRKP
- *37 (69%) either on carbapenems or completed a course of carbapenems within 2 weeks prior to CRKP isolation



Mortality



Overall Mortality
OR 3.71 (1.97-7.01)

Attributable Mortality
OR 4.5 (2.16-9.35)



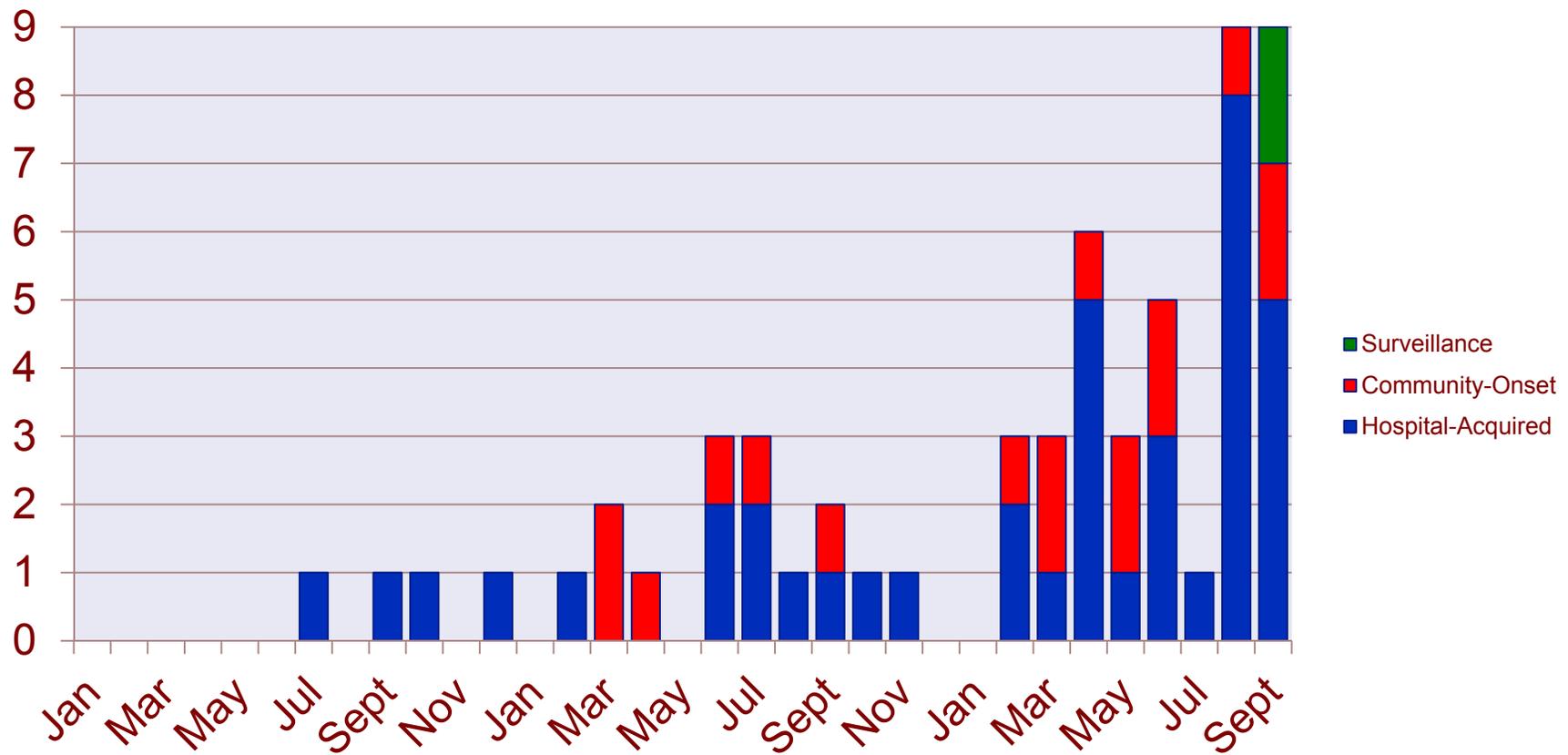
Recent Outbreaks of KPC Producing *Klebsiella*



- September 2008: Acute care hospital in Ponce, Puerto Rico.
- November 2008: Long term care facility in IL.
- Methodology:
 - Review of microbiology data for case finding
 - Review of infection control practices
 - Surveillance cultures of patients who were epidemiologically associated with cases.

Epi-Curve of Carbapenem Resistant Klebsiella- Puerto Rico

Hospital-Acquired, Community-Onset, and Active Surveillance Cases
Jan 2006 - Sept 2008





Infection Control Observations- Puerto Rico and IL

- Staff entering rooms without donning a gown, occasionally no gloves or hand hygiene
- Reuse of gloves between rooms with no hand hygiene.
- Exiting rooms without removing gowns
- Touching patients and equipment without PPE
- Inconsistent PPE use during wound care, respiratory care



Infection Control Assessment- Puerto Rico

BASED ON 50 HOURS OF OBSERVATION

Staff Type	Hand Hygiene		Contact Precautions	
	Entry	Exit	Exit	
Nurse (145)	46%	61%	76%	
Physician (31)	48%	60%	33%	



Active Surveillance Testing

- Refers to the practice of culturing asymptomatic patients for the presence of an organism.
 - Used as part of successful control strategies in healthcare outbreaks of many pathogens.
 - Used as part of endemic control efforts for VRE, MRSA.
- Has been part of KPC control efforts in Israel

KPC Producing Organisms in Israel

- CRE 1st encountered in Israel in 2005, but rarely seen.
- In 2006 there was a nationwide clonal spread of an epidemic KPC producing *K. pneumoniae* strain.
- The emergence was startling rapid.
- Associated mortality was very high- 44%.



Active Surveillance Strategy

- Targeted contacts of CRKP cases defined as “patients treated by the same nurse” or in the same high risk unit (ICU)
 - 4-14 patients usually screened
 - 15% of screened contact patients were positive
 - Repeated screening until one cycle negative
- In non-contact wards 0-1% positivity
- The addition of active surveillance coincided with control of the outbreak.



Point Prevalence Survey- Puerto Rico

- Rectal swabs were obtained from all patients currently hospitalized on SICU and diabetic ward- 20-30 patients.
- 2 patients had unrecognized colonization with CRKP.
- Point prevalence of unrecognized cases: 6.6- 10%



Point Prevalence- IL Long Term Care Outbreak

- Other patients on same floor as initial cases: $20/41 = 49\%$.
- Other epidemiologically related patients:
 - Former 3rd floor patients: $1/8$
 - Former roommates of cases: $0/2$
 - Other dialysis patients: $0/4$
- Epidemiologically unrelated patients
 - Those with long lengths of stay on other floors: $0/8$



CRKP Outbreaks- Lessons Learned



- Healthcare epidemiology/infection control staff at some facilities might not be aware that CRKP are actually present.
- The etiology of outbreaks of CRKP are multi-factorial, but are due in part to:
 - Non-compliance with infection control
 - Unrecognized carriers serving as reservoirs for transmission



Where Are We Now? The Bad News



- CRE, especially carbapenem resistant *K. pneumoniae*, are being encountered more commonly in healthcare settings
- Infections caused by these pathogens are associated with high mortality.
- They are readily transmitted in healthcare settings.
- New treatment options are non-existent.
- These are also commonly encountered pathogens in community infections.



Where Are We Now? The Good News

- CRE are not endemic in in the vast majority of the United States.
 - The occurrence is mostly sporadic
- Simple infection control interventions have been very successful in controlling the transmission of CRKP.
 - Hand hygiene
 - Contact precautions
 - Identification of unrecognized carriers

A Call To Action



Carbapenem-Resistant Enterobacteriaceae A Potential Threat

Mitchell J. Schwaber, MD, MSc

Yehuda Carmeli, MD, MPH

AFTER MORE THAN 7 DECADES OF ANTIBIOTIC USE, A RECURRENT pattern of antimicrobial resistance spread is evident among certain bacterial pathogens. In this pattern, resistance occurs first among the most severely ill hospitalized patients, then spreads to involve other

tant among these are carbapenemases, primarily the serine β -lactamase KPC and the metallo- β -lactamase VIM.³ The genes coding for these enzymes are carried by plasmids that often carry other resistance factors as well, resulting in extensively drug-resistant (XDR) bacteria. Moreover, plasmids carrying resistance genes also may carry virulence factors, thus leading to severe infections. Since plasmids are readily transferred, these resistance genes can easily spread within species and even from species to species of Enterobacteriaceae.

“An effective intervention at containing the spread of CRE should ideally be implemented before CRE have entered a region, or at the very least, immediately after its recognition. Policy makers and public health authorities must ensure the early recognition and coordinated control of CRE.”

JAMA December 2008;300:2911



A Call To Action- Answered

- CDC agrees that the time to act to control CRE is now.
- This fall, CDC began working on infection control recommendations for CRE.
- In December, these recommendations were approved by the Healthcare Infection Control Practices Advisory Committee.



Infection Control

- All acute care facilities should implement contact precautions for patients colonized or infected with CRE or carbapenemase-producing *Enterobacteriaceae*. No recommendation can be made regarding when to discontinue Contact Precautions.



Comment

- Contact precautions have been useful in controlling outbreaks of resistant *Enterobacteriaceae*, including CRKP.



Laboratory- I

- Clinical microbiology laboratories should follow Clinical and Laboratory Standards Institute (CLSI) guidelines for susceptibility testing and establish a protocol for detection of carbapenemase production



Comment

- Given the presence of the KPC enzyme in isolates that have elevated, but susceptible, MICs to carbapenems, ensuring that labs can detect the enzyme will be critical to this early control effort for CRE.



Laboratory- II

- Clinical microbiology laboratories should establish systems to ensure prompt notification of infection prevention staff of all *Enterobacteriaceae* isolates that are non-susceptible to carbapenems or test positive for a carbapenemase.



Comment

- Laboratory identification must be paired with rapid implementation of infection control interventions.



Surveillance-I

- All acute care facilities should review clinical culture results for the past 6-12 months to determine if previously unrecognized CRE have been present in the facility.



Rationale

- In some cases, cases of CRE occur, but are not reported to healthcare epidemiology and infection control.
- Knowing whether CRE are already being encountered will help facilities establish optimal control plans and will help direct detection efforts.



Surveillance- II

- If this review does not identify previous CRE, continue to monitor for clinical infections.



Surveillance- III

- If this review identifies previously unrecognized CRE, perform a single round of active surveillance testing (point prevalence survey) to look for CRE in high risk units (e.g., units where cases were hospitalized, intensive care units or other wards where there is high antibiotic use) and follow screening recommendations if CRE is found.



Surveillance- IV

- If a single clinical case of hospital-onset CRE or carbapenemase-producing *Enterobacteriaceae* is detected **OR** if the point prevalence survey reveals unrecognized colonization, the facility should investigate for possible transmission by:



Surveillance- V

- Conducting active surveillance testing of patients with epidemiologic links to the CRE case (e.g., those in the same unit)
- Continuing active surveillance periodically (e.g., weekly) until no new cases of colonization or infection suggesting transmission are identified
- If transmission of CRE is not identified following repeated active surveillance testing in response to clinical cases, consider altering the surveillance strategy to the performance of periodic point prevalence surveys in high-risk units



Surveillance- VI

- In areas where CRE are endemic in the community, there is an increased likelihood of importation of CRE; hence the approach described above may not be sufficient to prevent transmission. Those facilities should monitor clinical cases and consider additional strategies to reduce rates of CRE as described in Tier 2 of the MDRO guidelines.



Conclusions

- CRE, for now predominantly KPC producing *K. pneumoniae*, pose a major clinical and infection control challenge.
- However, we appear to be early in the emergence of this problem.
- An aggressive control strategy implemented now may help curtail the emergence of CRE.
 - “Where there is great challenge, there is great opportunity”



Acknowledgments

- Esther Tan, MD
- Rebecca Sunenshine, MD
- Chris Gregory, MD, MPH
- Eloisa Llata, MD
- Nicholas Stine
- Carolyn Gould, MD, MPH
- Kay Tomashek, MD
- Jonathan Duffy, MD, EISO
- Sara Schillie, MD, EISO
- Alex Kallen, MD
- Tara Maccannell
- Mike Bell, MD
- J. Kamile Rasheed, PhD
- Brandon Kitchel
- Karen (Kitty) Anderson
- Betty Wong
- David Lonsway
- Linda McDougal
- Angela Thompson
- Jana Swenson
- Brandi Limbago, PhD
- Betty Jensen
- Roberta Carey, PhD
- Fred Tenover, PhD



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