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"Carbapenem Resistance in Enterobacteriaceae - An Infection Control Emergency"

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Patient History (12-30-07)

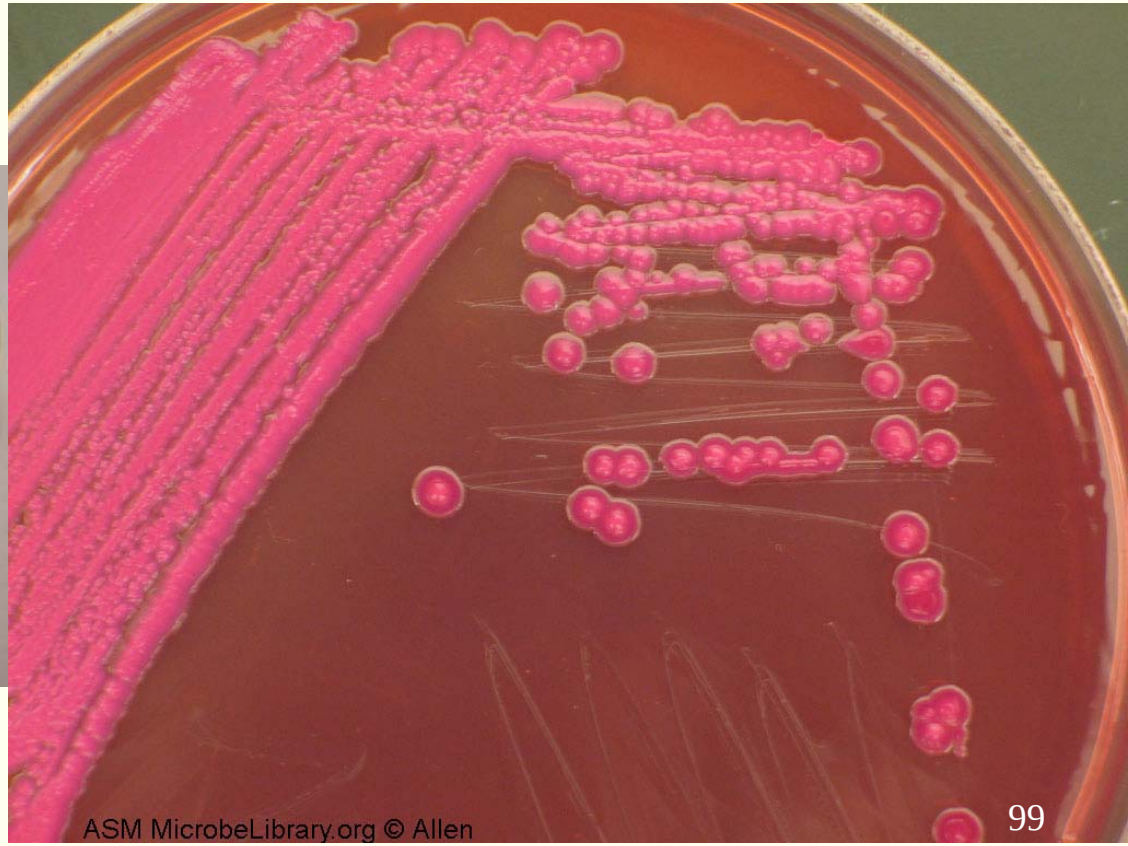
- 58 y/o male
- Morbidly obese (>500 lbs)
- Presented to ER with episode of hypoxia (to 60s) and hypotension during dialysis
- PMH
  - Pt has trach for hypercapnea (COPD and OSA), currently vent dependent
  - Chronic foley catheter
  - Diabetes mellitus type 2
  - ESRD

Patient History continued…

- Exam:
  - Afebrile
  - Multiple decubitus ulcers (sacrum, spine, right leg)
  - Urine is grossly dirty
- CBC:
  - WBC: 8.1
  - Hb: 7.8
  - Plt: 151

Patient History

- Concerned that septic => Pan-cultures
  - Urine: *Klebsiella*…



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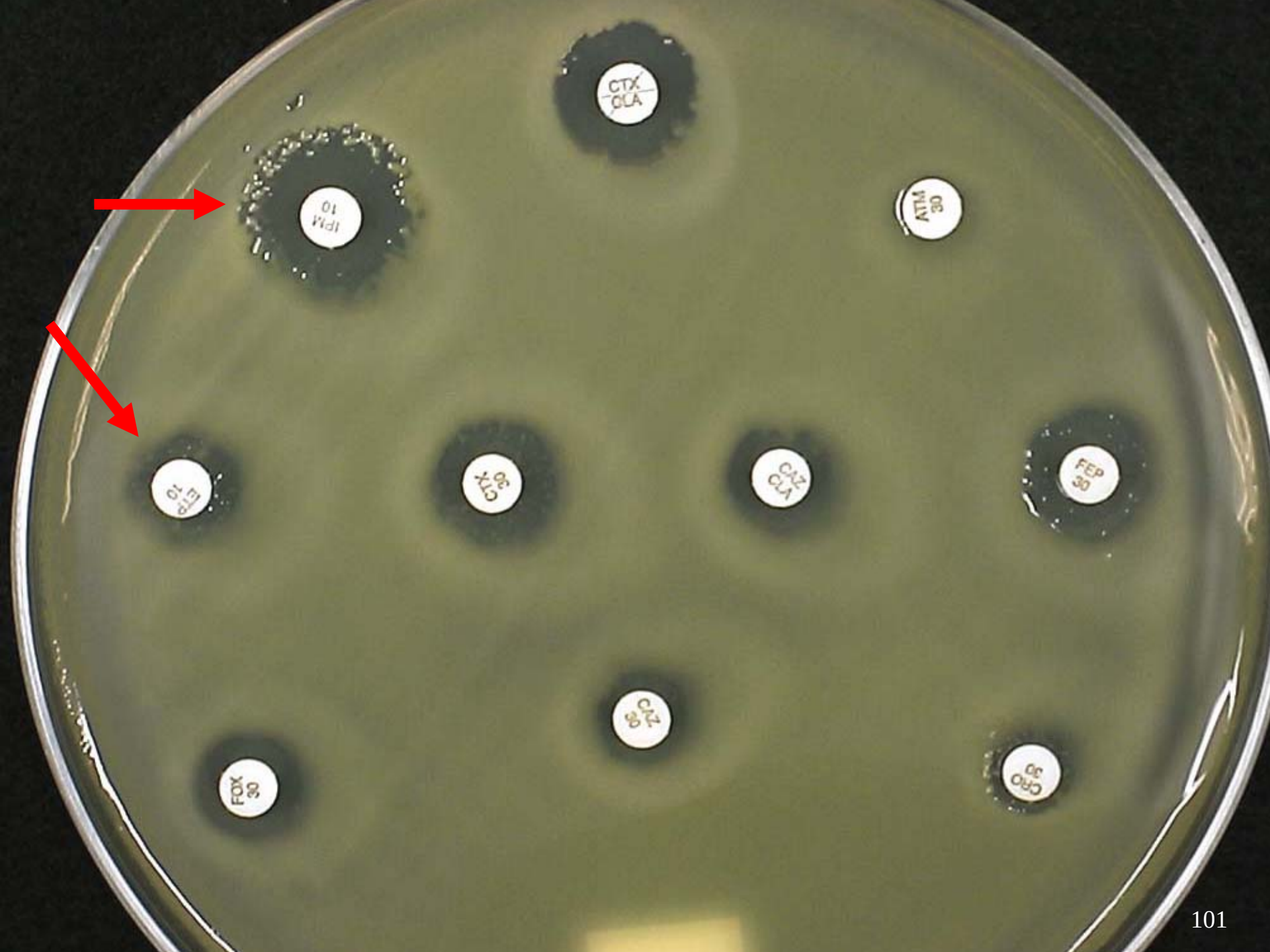
Vitek ID: [redacted] Oxidase -
Type: Gram Negative General Susceptibility 143 (GNS-143)
Status: Final
Elapsed Time: 13 hours
Organism: Klebsiella pneumoniae
Source: Manual
Demographics: [redacted]

	MIC	Instrument	Expert
Ampicillin	>=32	R	
Ampicillin/Sulbactam	>=32	R	
Piperacillin/Tazobactam	>=128	R	
Cefazolin	>=32	R	
Ceftriaxone	>=64	R	
Ceftazidime	>=32	R	
Cefepime	8	S	
Aztreonam	>=32	R	
Imipenem	<=4	S	
Gentamicin	4	S	
Tobramycin	>=16	R	
Ciprofloxacin	>=4	R	
Levofloxacin	>=8	R	
Trimeth-sulfa	>=320	R	
Nitrofurantoin	64	I	
ESBL		Negative	

MIC values in mcg/ml (M1) Wait for All
The presence of other Beta-lactamases (e.g. AmpC, IRT) may mask ESBL production.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Carbapenems

- Ertapenem
- Doripenem
- Imipenem
- Meropenem

Carbapenem-Resistance in Enterobacteriaceae

- Two mechanisms of resistance
  - Carbapenemase (β-lactamase that can hydrolyze carbapenems)
  - Cephalosporinase combined with porin loss
    - Some cephalosporinases (e.g., AmpC-type β-lactamses or certain ESBLs i.e. CTX-M) have a low-level carbapenemase activity
    - Porin loss limits entry of the carbapenem into the periplasmic space

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Carbapenemases in the U.S.

Enzyme	Bacteria
KPC	Enterobacteriaceae
SME	*Serratia marcesens*
Metallo-β-Lactamase	*P. aeruginosa* & *Acinetobacter* spp.
OXA	*Acinetobacter* spp.

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Class A Carbapenemases

- Rare – Enterobacteriaceae
- ***K. pneumoniae* carbapenemase** *(*KPC-type) possess carbapenem-hydrolyzing enzymes most common on East Coast of U.S.
- Enzymes are capable of efficiently hydrolyzing penicillins, cephalosporins, aztreonam, and carbapenems and are inhibited by clavulanic acid and tazobactam
  (ESBL that hydrolyzes carbapenems)

Carbapenemase-Producing Klebsiella pneumonia (KPC)

- "KPC-1" reported in 2001
- Now KPC-2 to KPC-8
- Recovered from isolates of *K. pneumoniae*, other Enterobacteriaceae, *P. aeruginosa.*

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KPC Enzymes

- Located on plasmids
- Active against all β-lactam agents,but may test susceptible to imipenem
- *bla*$_{KPC}$ reported on plasmids with:
  - Normal spectrum β-lactamases
  - Extended spectrum β-lactamases
  - Aminoglycoside resistance [AAC(6')-Ib]
  - Plasmid-mediated fluorquinolone resistance

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Need to Distinguish Between Mechanisms of Carbapenem Resistance – Why?

- Carbapenemase
  - Isolate likely to be resistant to all carbapenems and other β-lactam agents
  - May need to change susceptible reports to resistant for β-lactam drugs
  - Need to implement infection control measures such as contact precautions and possibly active surveillance testing
  - **These are an Infection Control Emergency**

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Need to Distinguish Between Mechanisms of Carbapenem Resistance – Why?

- Cephalosporins combined with porin-loss
  - Class A ESBL's (CTX-M) + reduced permeability
  - Class C High AmpC + reduced permeability
- These hydrolyze ertapenem more than meropenem or imipenem
  - Not necessarily resistant to all carbapenems (i.e., would not need to change susceptible results to resistant reports for β-lactam drugs
- These isolates are clearly MDR and infection control measures are recommended. Healthcare institutions may reserve more aggressive measures for carbapenemase-producing isolates

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Carbapenemase-Producing *Klebsiella pneumoniae* (KPC)

- Identifying isolates possessing KPC type resistance may be difficult using current methods of susceptibility testing
- The presence of KPC in *K. pneumoniae* may increase the MIC of imipenem, but not to the level of frank resistance
- Therefore, strains carrying this enzyme may only be recognized as ESBL-producing isolates

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CAP Survey D-A 2007 D-05

Carbapenem/test system (no.)[a]	No. reports by category: Susceptible		Intermediate	Resistant	Modal MIC (µg/mL)
Imipenem					
BD Phoenix (22)	2	**9%**	6	14	≥8
MicroScan (541)	174	**32%**	246	121	8
Vitek (377)	290	**77%**	28	59	≤4
Vitek 2 (320)	260	**81%**	38	22	≤4
Meropenem					
BD Phoenix (10)	2		0	8	>8
MicroScan (30)	5		1	24	>8
Vitek (22)	21		0	1	≤2
Vitek 2 (36)	34		1	1	≤2
Ertapenem					
BD Phoenix (0)	-		-	-	-
MicroScan (27)	0		0	27	>4
Vitek (3)	0		0	3	>8
Vitek 2 (49)	0		1	48	>8

a. Reference and referee MIC results were ≥8 µg/ml (resistant or intermediate) for each drug.

Strategy for Laboratory Detection of Carbapenemases

- Establish screening criteria and a confirmatory test
- Necessary when isolates test susceptible to carbapenems, but a carbapenemase is suspected
  - When should a carbapenemase be suspected?
  - What screening criteria should be used?

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Strategy for Laboratory Detection of Carbapenemases

New!!

- CLSI Screening Criteria for KPCs (M100-S-19 Jan 2009)
  - Disk zone of < 22 mm for ertapenem or meropenem
  - MIC of >1 μg/ml for imipenem, ertapenem or meropenem
- CLSI Confirmatory Test (M100-S19, Jan 2009)
  - Modified Hodge Test
- Procedure Notes
  - Imipenem disk test is <u>not</u> a good screen
  - Imipenem MIC does <u>not</u> work as a screen for Proteus/ Providencia/Morganella due to slightly elevated MICs in this group

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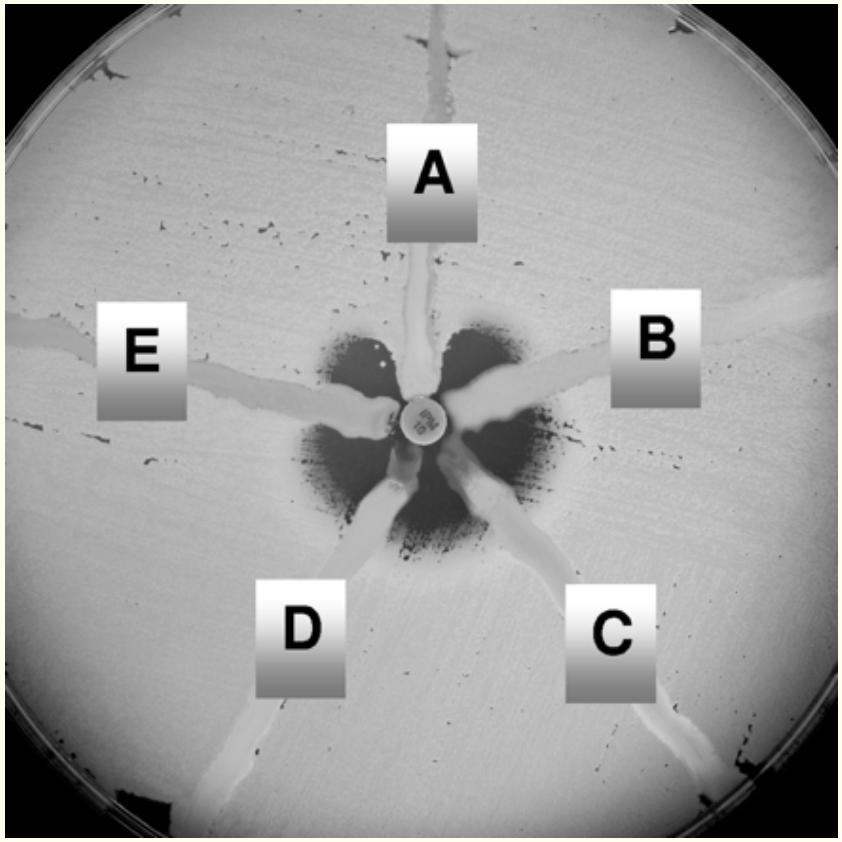
Modified Hodge Test



- Inoculate MH agar with a 1:10 dilution of a 0.5 McFarland suspension of *E. coli* ATCC 25922 and streak for confluent growth using a swab.
- Place 10-µg ertapenem or meropenem (best) disk in center
- Streak each test isolate from disk to edge of plate
- Isolate A is a KPC producer and positive by the modified Hodge test.

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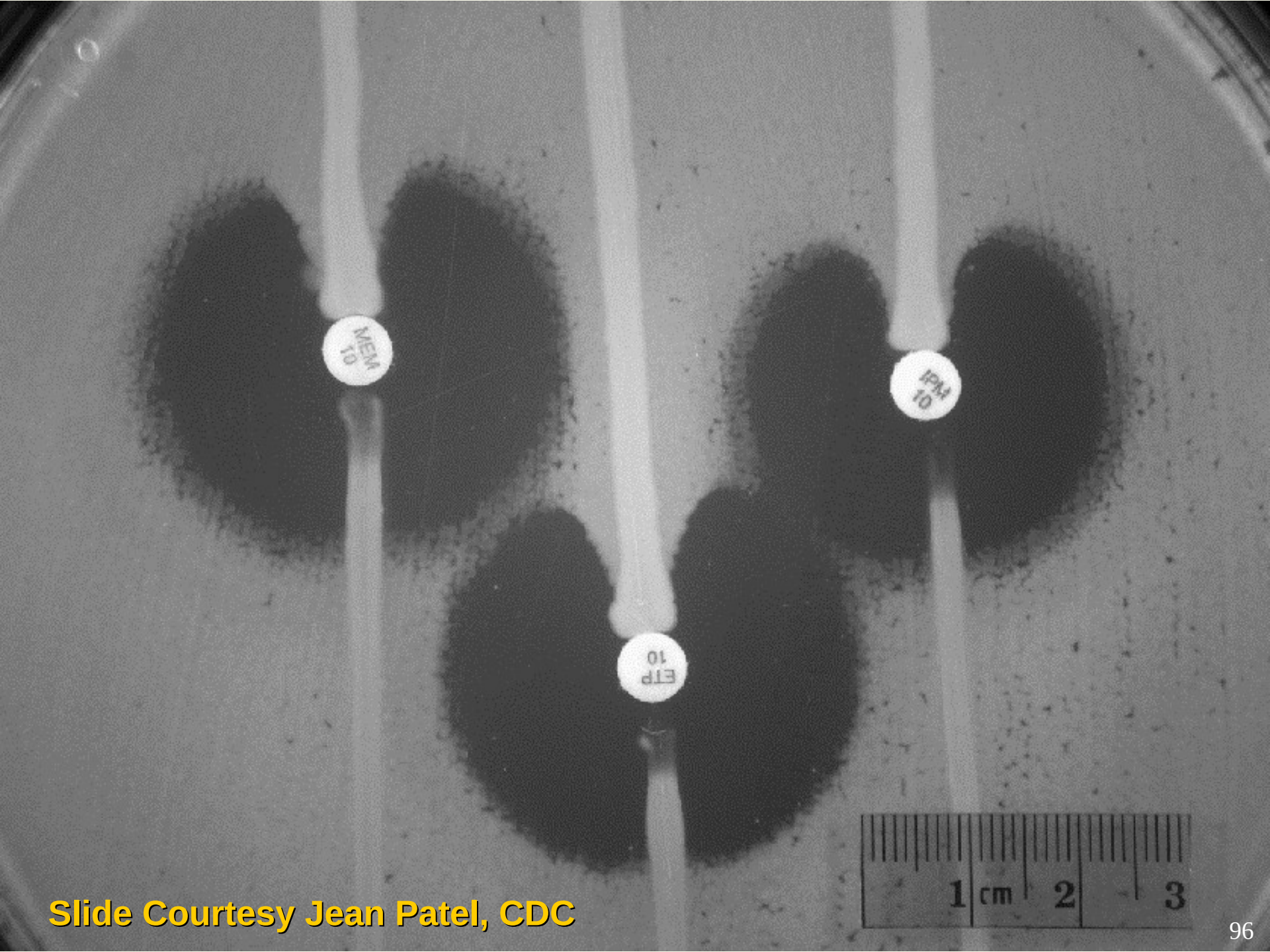
Anderson KF et al. JCM 2007 Aug;45(8):2723-5.



Slide Courtesy Jean Patel, CDC

KPC - Questions

- If I have detected KPC-production, should I change susceptible carbapenem results to resistant?
  - Report MIC without interpretation and add comment warning clinician of possible therapeutic failure with carbapenems
    (CLSI recommendation in the Jan 2009 M100-S19)
  - Suppress MIC value and report carbapenem "R"
  - Suppress MIC value and report carbapenem "I"
  - Report MIC with "I" interpretation if MIC 2, 4, 8 ug/mL
  - Report MIC with "R" interpretation if MIC $\geq$ 16 ug/mL

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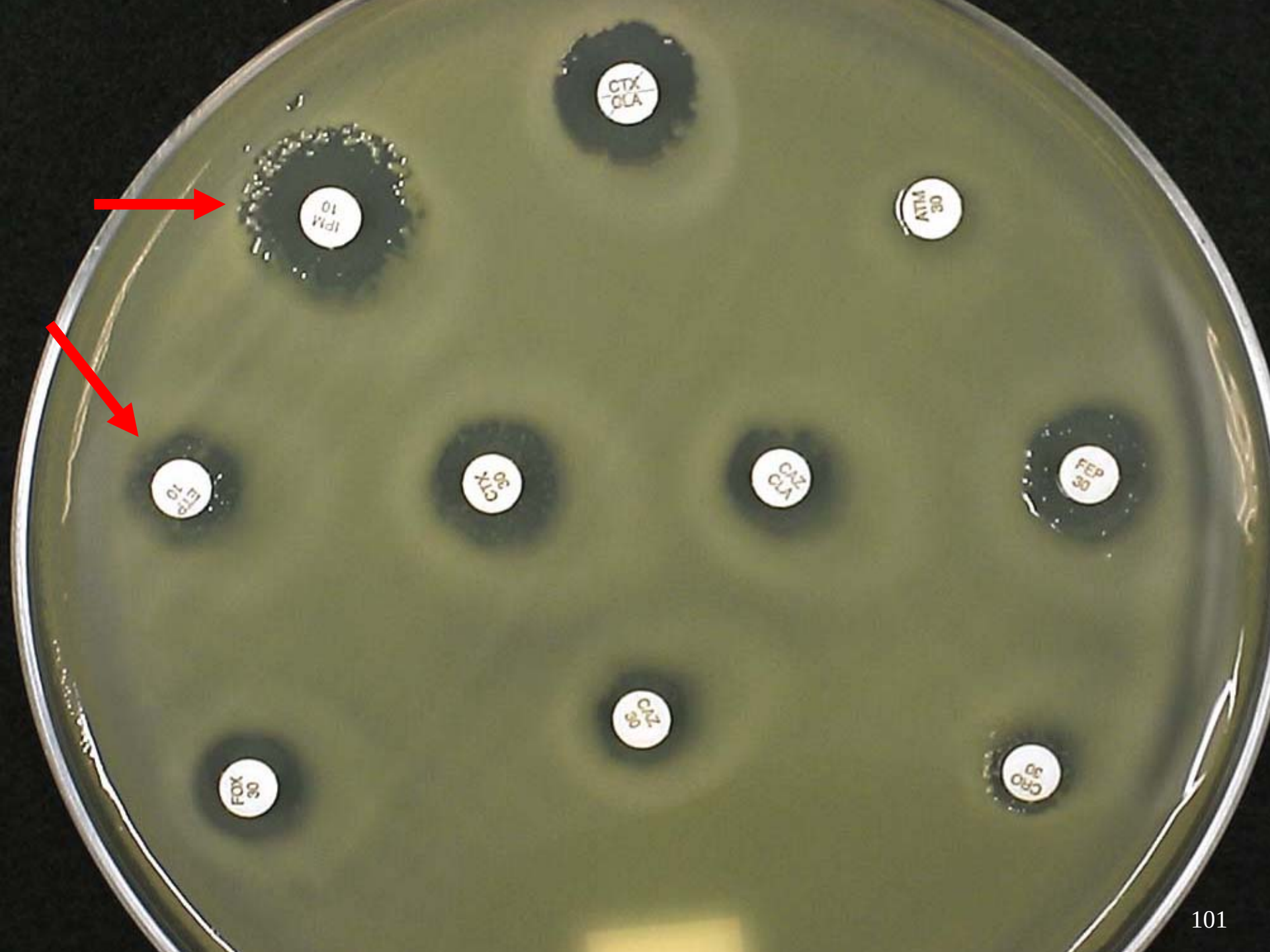
Back to Our Patient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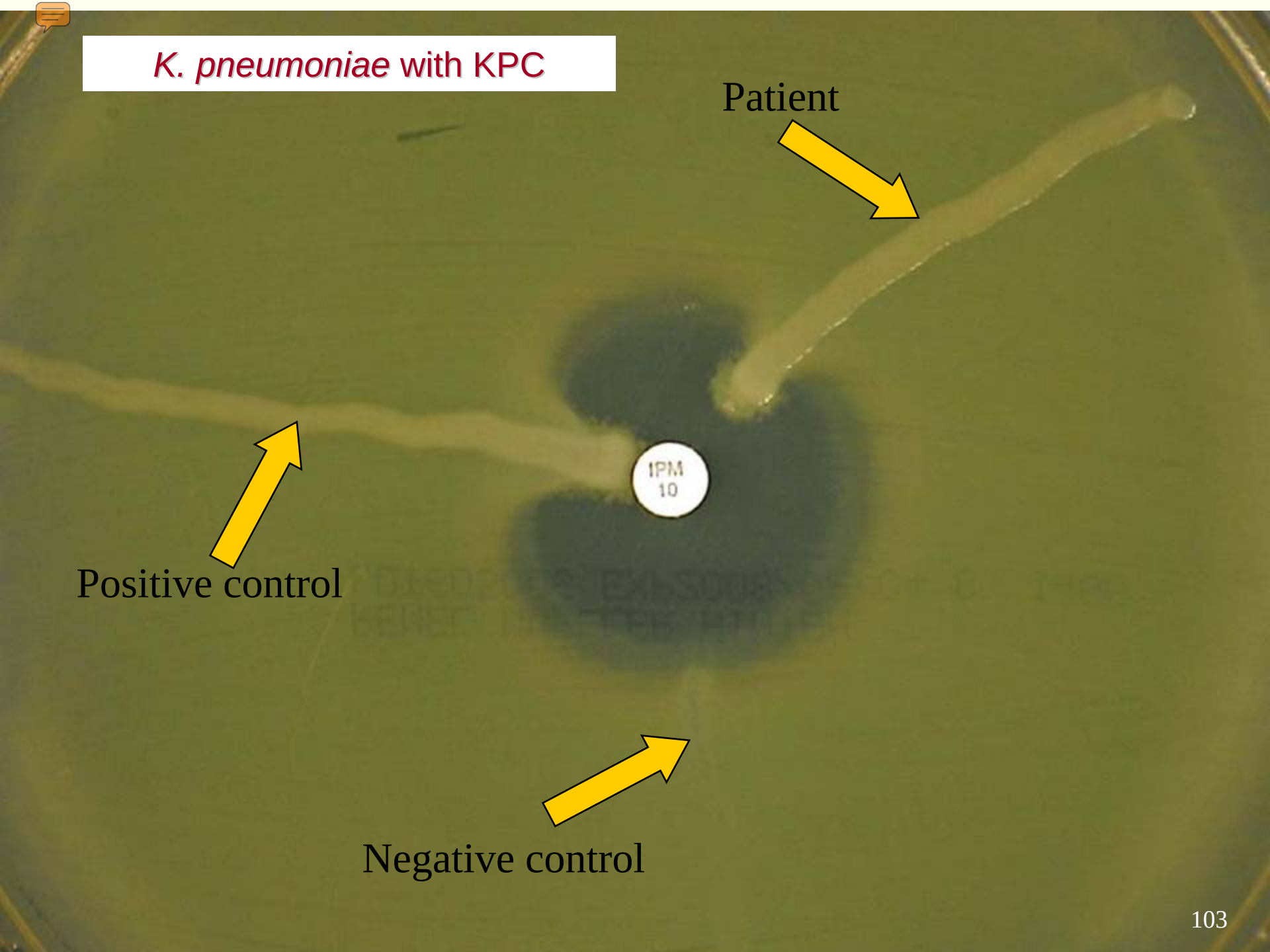
K. pneumoniae with KPC



SPECIMEN DESCRIPTION	FOLEY CATH URINE
SPECIAL REQUESTS	NONE
CULTURE RESULTS	>100000 COLONIES / ML KLEBSIELLA PNEUMONIAE MULTIPLE DRUG RESISTANT ORGANSIM. KLEBSIELLA PNEUMONIAE CARBAPENEMASE KPC PRODUCING ORGANISM. TREATMENT WITH ANY BETA LACTAM DRUG INCLUDING CARBAPENEMS IS NOT RELIABLE. PATIENT REQUIRES CONTACT ISOLATION UNUSUAL RESISTANCE PATTERN FOUND, GENTAMICIN REMAINS ACTIVE IN VITRO BUT IN VIVO USE SHOULD BE AVOIDED. RESULTS CONFIRMED BY CDC
REPORT STATUS	FINAL 01/22/2008

SUSCEPTIBILITY

ORGANISM	>100000 COLONIES / ML KLEBSIELLA PNEUMONIAE
METHOD	MIC
AMPICILLIN	>=32 RESISTANT
AMP/SULBACTAM	>=32 RESISTANT
PIP/TAZOBACTAM	>=128 RESISTANT
CEFAZOLIN	>=32 RESISTANT
CEFTRIAXONE	>=64 RESISTANT
CEFTAZIDIME	>=32 RESISTANT
CEFEPIME	>=32 RESISTANT
AZTREONAM	>=32 RESISTANT
IMIPENEM	8 INTERMEDIATE
GENTAMICIN	4 SUSCEPTIBLE
TOBRAMYCIN	>=16 RESISTANT
CIPROFLOXACIN	>=4 RESISTANT
TRIMETHOPRIM/SULFA	>=320 RESISTANT
NITROFURANTOIN	64 INTERMEDIATE
MEROPENEM	>=16 RESISTANT
ERTAPENEM	8 RESISTANT
TETRACYCLINE	<=4 SUSCEPTIBLE
TIGECYCLINE	.75 SUSCEPTIBLE
METHOD	KIRBY BAUER
COLISTIN	SUSCEPTIBLE

Why is Carbapenem Resistance a Public Health Problem?

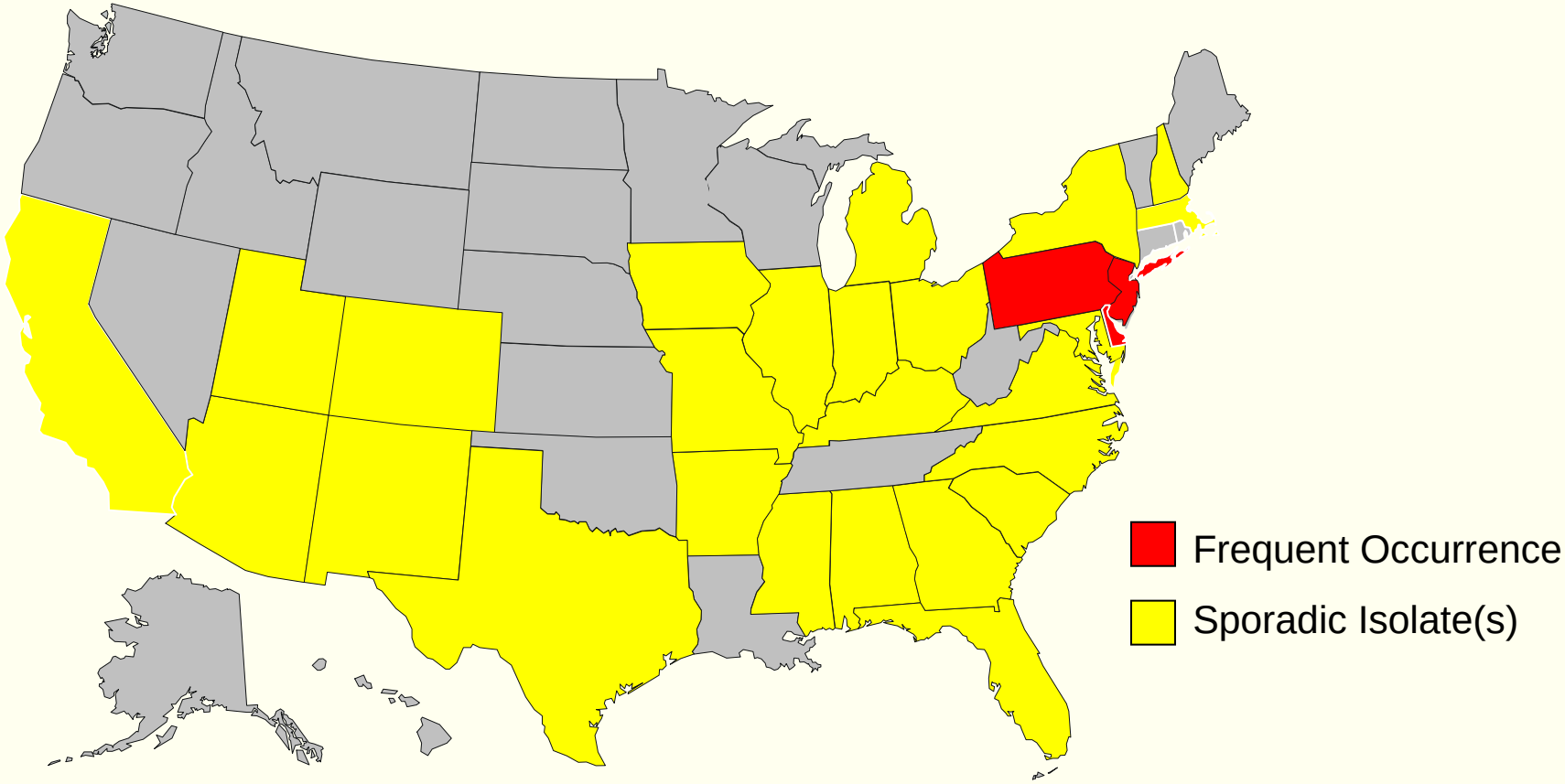
- Significantly limits treatment options for life-threatening infections
- No new drugs for gram-negative bacilli
- Emerging resistance mechanisms, carbapenemases are mobile
- Detection of carbapenemases and implementation of infection control practices are necessary to limit spread

Extent of Problem

- Highly endemic in greater NY area
  - Endemic in ICUs at Columbia, Cornell, St. Vincent's, Mount Sinai, SUNY Downstate (Brooklyn), ……..
  - Officially a reportable disease in New York State
- Still relatively uncommon, now being reported from multiple other regions of U.S.: AZ, NJ, DE, NC, NM, FL, PA, DE, GA, MD, MI, MO, MA, CA, AK, OH, VA…… *and now Illinois*
- Reports from other parts of world: Scotland, Israel, Colombia, China, Brazil, France, Turkey, Greece, Singapore, Korea, Puerto Rico……

AAC. 2005; 49(10): 4423-4; *AAC.* 2006; 50(8): 2880-2; *AAC.* 2007; 5(2): 763-5; 47th ICAAC. Abstract C2-1929.2007; 47th ICAAC. Abstract C2-2063. 2007; 47th ICAAC. Abstract C2-1933. 2007

Geographical Distribution of KPC-Producers



Courtesy of J. Patel, PhD., CDC
1/09

Why Spreading?

- Suboptimal detection
- Molecular factors
- Antibiotic selection pressure

Who is Infected with Carbapenemase-Producing Enterobacteriaceae?

- Hospitalized patients with:
  - Increased number of co-morbid conditions
  - Frequent or prolonged hospitalization
  - Invasive devices
  - Antimicrobial exposure (vancomycin, fluoroquinolones, penicillins, and extended-spectrum cephalosporins)
  - Carbapenemase-producers are most frequently isolated from urine or blood

Esther T. Tan, et al. CID. Submitted

Active Surveillance Cultures to Detect Colonization with KPC in ICUs

- Specimens for surveillance culture were obtained from all patients at ICU admission and on a weekly basis
- ICU nursing personnel collected perianal specimens by using sterile cotton-tipped swabs.
- If a perianal swab specimen could not be obtained, a sputum specimen was collected

Calfee D, Jenkins SG. Use of active surveillance cultures to detect asymptomatic colonization with carbapenem-resistant Klebsiella pneumoniae in intensive care unit patients Infect Control Hosp Epidemiol. 2008 Oct;*29*(*10*):*966-8*.

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Active Surveillance Cultures to Detect Colonization with KPC in ICUs

- Specimens were directly inoculated onto MacConkey agar, onto which an ertapenem disk was subsequently placed
- Incubated at 37C for up to 48 hours.
- Mucoid, lactose-fermenting colonies growing within 15 mm of the disk were identified.

Calfee D, Jenkins SG. Use of active surveillance cultures to detect asymptomatic colonization with carbapenem-resistant Klebsiella pneumoniae in intensive care unit patients Infect Control Hosp Epidemiol. 2008 Oct;*29*(*10*):*966-8*.

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Active Surveillance Cultures to Detect Colonization with KPC in ICUs

- Specimens were inoculated in 5 mL of tryptic soy broth containing a 10-mg imipenem disk and were incubated overnight at 37C.
- The broth was then subcultured onto MacConkey agar and incubated overnight at 37C.
- Mucoid, lactose-fermenting colonies were identified, and ertapenem susceptibility was determined

Calfee D, Jenkins SG. Use of active surveillance cultures to detect asymptomatic colonization with carbapenem-resistant Klebsiella pneumoniae in intensive care unit patients Infect Control Hosp Epidemiol. 2008 Oct;*29*(*10*):*966-8*.

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Active Surveillance Cultures to Detect Colonization with KPC in ICUs

- 215 (2%) of 11,236 patients admitted to participating ICUs were found to be colonized or infected with KPC.
- KPC was first identified by surveillance culture in specimens from 79 (37%) of the 215 patients.
- There were 69 perianal specimens and 10 sputum specimens positive for *K. pneumoniae.*

Calfee D, Jenkins SG. Use of active surveillance cultures to detect asymptomatic colonization with carbapenem-resistant Klebsiella pneumoniae in intensive care unit patients Infect Control Hosp Epidemiol. 2008 Oct;*29*(*10*):*966-8*.

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Active Surveillance Cultures to Detect Colonization with KPC in ICUs

- KPC colonization was more frequently detected by surveillance culture than by clinical culture
- ICUs in which surveillance cultures were performed both at ICU admission and weekly, vs. only at ICU admission had significantly higher isolation rates 58% (62/107) vs. 15% (10/68); *P* <.001).

Calfee D, Jenkins SG. Use of active surveillance cultures to detect asymptomatic colonization with carbapenem-resistant Klebsiella pneumoniae in intensive care unit patients Infect Control Hosp Epidemiol. 2008 Oct;*29*(*10*):*966-8*.

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Active Surveillance Cultures to Detect Colonization with KPC in ICUs

- The median time from hospital admission to detection of KPC by surveillance culture was 18 days (range, 0–118 days).
- KPC was isolated from the first surveillance culture sample for 36 (46%) of the 79 patients for whom colonization was detected by surveillance culture.

Calfee D, Jenkins SG. Use of active surveillance cultures to detect asymptomatic colonization with carbapenem-resistant Klebsiella pneumoniae in intensive care unit patients Infect Control Hosp Epidemiol. 2008 Oct;*29*(*10*):*966-8*.

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Active Surveillance Cultures to Detect Colonization with KPC in ICUs

- Of 79 patients with KPC detected by surveillance culture 36 patients (46%) resulted in isolation of carbapenem-resistant *K. pneumoniae* by clinical culture and 43 patients (54%) were discharged without a subsequent clinical culture positive for carbapenem-resistant *K. pneumoniae*

Calfee D, Jenkins SG. Use of active surveillance cultures to detect asymptomatic colonization with carbapenem-resistant Klebsiella pneumoniae in intensive care unit patients Infect Control Hosp Epidemiol. 2008 Oct;*29*(*10*):*966-8*.

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Active Surveillance Cultures to Detect Colonization with KPC in ICUs

- Among those with a subsequent clinical culture positive for this organism, the median duration of time from the positive surveillance culture result to the positive clinical culture result was 9 days (range, 0–160 days).
- Twenty-one (27%) of the 79 patients with KPC identified by surveillance culture had at least 1 subsequent episode of KPC bacteremia during the index hospitalization.

Calfee D, Jenkins SG. Use of active surveillance cultures to detect asymptomatic colonization with carbapenem-resistant Klebsiella pneumoniae in intensive care unit patients Infect Control Hosp Epidemiol. 2008 Oct;*29*(*10*):*966-8*.

Healthcare Infection Control Practices Advisory Committee (HICPAC)

- Recommendations for CRE Acute Care Facilities

A. Infection Control:

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

Siegel JC et al. Guideline for Isolation Precautions: Preventing Transmission of Infectious Agents in Healthcare Setting 2007. http://www.cdc.gov/ncidod/dhqp/pdf/guidelines/Isolation2007.pdf

Healthcare Infection Control Practices Advisory Committee (HICPAC)

- Recommendations for CRE Acute Care Facilities

B. Laboratory:

- Clinical Laboratories should follow CLSI guidelines for susceptibility testing and establish a protocol for detection of carbapenemase production (eg. perform MHT)
- Clinical 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

Healthcare Infection Control Practices Advisory Committee (HICPAC)

- Recommendations for CRE Acute Care Facilities

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

- If review identifies previously unrecognized CRE, perform a single round of active surveillance testing to look for CRE in high risk units (e.g. units where cases hospitalized, ICU or other wards with high antibiotic use)
- If this review does not identify previous CRE, continue to monitor for clinical infections

Healthcare Infection Control Practices Advisory Committee (HICPAC)

- Recommendations for CRE Acute Care Facilities

C. Surveillance: If a single case of hospital-onset CRE is detected **OR** if point prevalence survey reveals unrecognized colonization, the facility should investigate for possible transmission by:

- Conducting A.S. testing of patients with epidemiologic links to the CRE case
- Continuing A.S. periodically (e.g. weekly until no new cases are identified
- If transmission not identified with repeated A.S., consider altering surveillance strategy to periodic point prevalence surveys in high-risk units

Laboratory Protocol for Detection of KPC from Rectal Swabs

Step 1 Day One	Place one 10 μg ertapenem or meropenem disc in 5 ml TSB. Immediately inoculate TSB with rectal swab. Incubate overnight at 35 C ambient air
Step 2 Day Two	Vortex and subculture 100 μl inoculated broth culture onto MacConkey Agar. Streak for isolation. Incubate 35 C ambient air
Step 3 Day Three	Exam Mac for lactose-fermenting colonies. Screen representative colonies using phenotypic test for CRE, e.g. MHT
Step 4 Day Four	For CRE and/or MHT-positive isolates, perform species level ID

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Landman D, Salvani JK, Bratu S, Quale J. Evaluation of techniques for detection of carbapenem-resistant Klebsiella pneumoniae in stool surveillance cultures J Clin Microbiol. 2005 Nov;43(11):5639-41.

Summary

- Carbapenem-resistant Enterobacteriaceae are increasingly recognized as the cause of sporadic and outbreak infections in the U.S.
- These organisms cause severe infections among residents of long-term-care facilities and are not easily detected in the clinical microbiology laboratory
- Tigecycline and polymyxins including colistin have been used with variable success
- Aggressive infection-control practices are required in aborting these outbreaks

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QUESTIONS