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Changes in the CLSI Standards for Antimicrobial Susceptibility Testing for 2010

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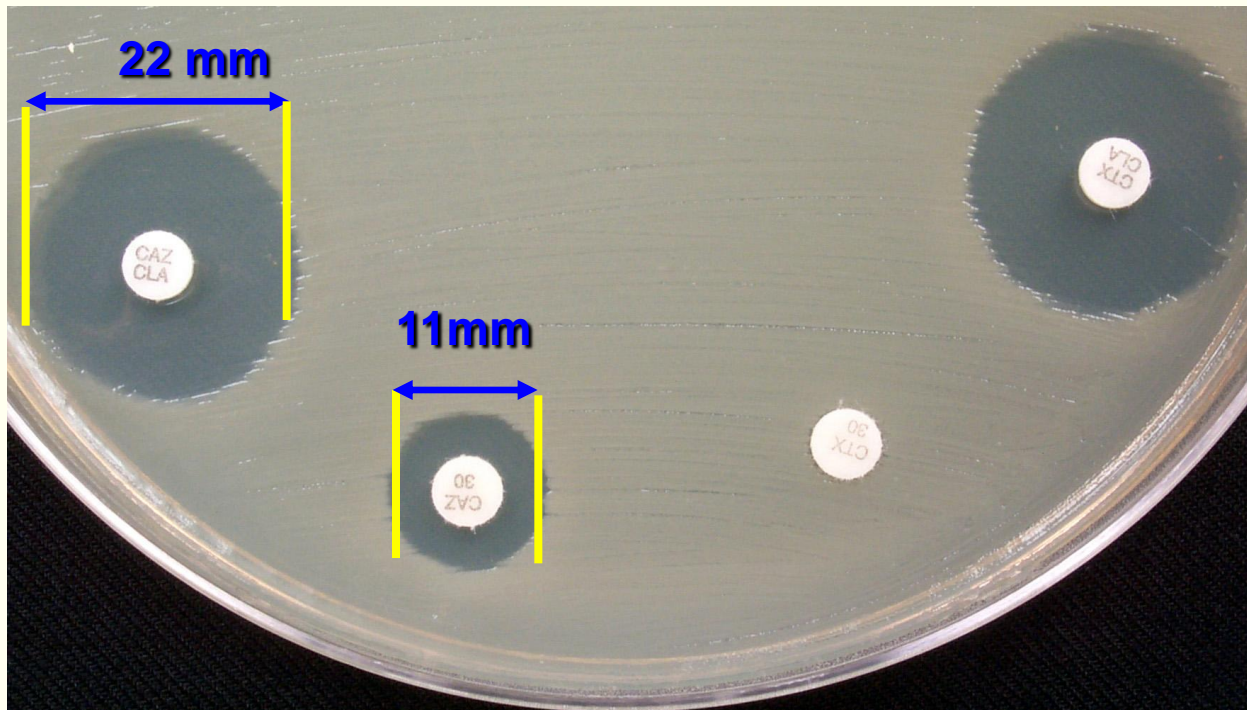
Do Mechanisms Count?

- It is argued that treatment outcomes, e.g. for ESBL producers, KPC producers, etc., can be predicted solely from MICs, irrespective of the resistance mechanism.
- Proponents of this view contend that it is unnecessary for clinical microbiology laboratories to edit susceptibility data on the basis of resistance mechanisms and that these should only be sought, if at all, for purposes of epidemiological surveillance.

Do Mechanisms Count?

- The inherent danger in this approach is that some resistant pathogens may not be recognized because they are falsely susceptible in routine tests and this can lead to patients receiving ineffective antibiotics resulting in adverse clinical outcomes.
- Because susceptibility tests may be unreliable, special tests are required to detect the resistance mechanisms involved so that susceptibility reports can be modified for patient safety.

Combination Disk (CLISI) Method – E.coli with ESBL



CAZ/CLA – 22 mm

CAZ – 11 mm

$22 - 11 = > 5\text{mm}$

= **ESBL**

CLSI Reporting Recommendation

- ESBL confirmed: *E. coli*, *Klebsiella*, *P. mirabilis*
- ◆ *Klebsiella* spp. and *E. coli* Table 2A p. 39 M100-S19
 - Strains of *Klebsiella* spp and *E. coli* that produce ESBLs may be clinically resistant to therapy with penicillins, cephalosporins, or aztreonam, despite in vitro susceptibility to some of these agents. For all confirmed ESBL-producing strains, the test interpretation should be reported as resistant for all penicillins, cephaoporins, and aztreonam.
 - January 2009

ESBLs in organisms other than *E. coli* and *Klebsiella spp.*

- Most labs do not attempt to detect ESBLs in organism other than *E. coli* and *Klebsiella*
- Two Indications for ESBL Testing in Other Organisms
 - ◆ ESBLs detected in *E. coli* or *Klebsiella*
 - ◆ Suspicious phenotype
- How to test?
 - ◆ Use specific (confirmatory) test
 - ◆ Perform Double Disk Diffusion

Prevalence of ESBLs at LUMC

2006 and 2007 (Jan-Sept)

Organism	Total tested	ESBL Pos	% ESBL
<i>C. freundii</i> complex	165	4	2.4
<i>C. koserii</i>	110	6	5.5
<i>E. aerogenes</i>	197	2	1.0
<i>E. cloacae</i>	387	20	5.2
<i>E. coli</i>	5131	96	1.9
<i>K. oxytoca</i>	151	2	1.3
<i>K. pneumoniae</i>	1149	37	3.2
<i>M. morgani</i>	70	4	5.7
<i>P. mirabilis</i>	592	25	4.2
<i>P. stuartii</i>	16	2	12.5

Pitfalls of ESBL Testing

- Recommendation (not CLSI endorsed): Extend CLSI reporting recommendations to all ESBL-producing organisms
- Report all ESBL-producing organisms the same way: resistant to all penicillins, cephalosporins, and aztreonam

Enterobacteriaceae β -Lactam Breakpoints and ESBL Issues

- CLSI is re-evaluating β -lactam breakpoints for Enterobacteriaceae
 - ◆ Example: cefotaxime
 - Current – Susceptible at $\leq 8 \mu\text{g/ml}$
 - Proposed – Susceptible at ≤ 1 or $\leq 2 \mu\text{g/ml}$
 - ◆ Substantial data needed
 - ◆ Goal is to more accurately detect all β -lactamase and other β -lactam resistance mechanisms with revised breakpoints
- Changing breakpoints – commercial systems project it will take 3 years ...**much \$\$\$\$\$!**

Enterobacteriaceae Revised Breakpoints (MIC $\mu\text{g.ml}$)

NEW!!

Agent	CLSI M100-S19 (2009)			CLSI M100-S20 (2010)		
	Susc	Int	Res	Susc	Int	Res
Cefazolin	≤ 8	16	≥ 32	≤ 1	2	≥ 4
Cefotaxime	≤ 8	16-32	≥ 64	≤ 1	2	≥ 4
Ceftizoxime	≤ 8	16-32	≥ 64	≤ 1	2	≥ 4
Ceftriaxone	≤ 8	16-32	≥ 64	≤ 1	2	≥ 4
Ceftazidime	≤ 8	16	≥ 32	≤ 4	8	≥ 16
Aztreonam	≤ 8	16	≥ 32	≤ 4	8	≥ 16

**CLSI M100-S20. Table 2A
January 2010**

Enterobacteriaceae – Evaluated but NOT Revised Breakpoints

Agent	CLSI M100-S20 (2010)		
	Susc	Int	Res
Cefuroxime (parenteral)	≤ 8	16	≥ 32
Cefepime	≤ 8	16	≥ 32
Cefotetan	≤ 16	32	≥ 64
Cefoxitin	≤ 8	16	≥ 32

CLSI Guidance on ESBL Testing

- Will Tests for ESBLs be needed with the new cephalosporin breakpoints for Enterobacteriaceae?
 - ◆ CLSI says **No**. For patient management, tests for ESBLs are not necessary
 - ◆ If requested, tests for ESBLs may be done for Infection Control purposes

New CLSI Guidelines 2010

- When using the new interpretive criteria, routine ESBL testing is no longer necessary before reporting results (eg. it is no longer necessary to edit results for cephalosporins, aztreonam, or penicillins from susceptible to resistant)

New CLSI Guidelines 2010

- This decision was based on evaluation of pharmacokinetics-pharmacodynamics (PK-PD) properties and limited clinical trials
- New interpretive criteria (breakpoints) establish for some (but not all) cephalosporins
- Using new breakpoints treatment decisions can be based solely on MIC alone
- “It’s all about the MIC stupid”

New CLSI Guidelines 2010

- Problem with this approach
 - ◆ Clinical studies show patients with “susceptible” MICs + ESBL fail therapy

Clinical Studies

- No randomized controlled trials have ever been performed that evaluated the use of various comparator antibiotics in treatment of serious infections due to ESBL-producing organisms
- It is unlikely that such studies will ever be performed
- Existing data comes only from retrospective studies

Treatment of ESBL Positive Organisms with Cephalosporins

<u>MIC</u>	<u>FAILURE</u>	<u>DEATH</u>
8	100% (6/6)	33% (2/6)
4	67% (2/3)	0% (0/3)
2	33% (1/3)	0% (0/3)
≤1	27% (3/11)	18% (2/11)

(CLSI breakpoint ≤8 µg/ml)

Case Report

Treatment failure due to ESBL

- 14 YO febrile episode while receiving TPN via CVC
- PMH: Hospitalized 3 months following abdominal sepsis complicated by multiple bowel fistulae
- 2 sets of blood cultures taken and CVC was cultured
- Following day develops signs of pneumonia and *K. pneumoniae* was isolated from all 3 specimens.
- Treated with IV cefotaxime and isolate was reported to be susceptible to CTX by disk diffusion method
- Patient deteriorated and was admitted to ICU
- On 2nd day in ICU patient had not improved and Etest MIC was set up and double disk test performed



**Karas JA et al. *J Antimicrob Chemother.* 1996
*Jan;37(1):203-4.***

Treatment failure due to ESBL

- Double Disk test indicated presence of ESBL
- MIC results:
 - ◆ Cefotaxime 0.75 $\mu\text{g/ml}$ - Susceptible
 - ◆ Ceftazidime >256 $\mu\text{g/ml}$ - Resistant
 - ◆ Cefuroxime 3 $\mu\text{g/ml}$ - Susceptible
 - ◆ Gentamicin >256 $\mu\text{g/ml}$ - Resistant
 - ◆ Ciprofloxacin 0.32 $\mu\text{g/ml}$ - Susceptible
- Therapy with cefotaxime was stopped and patient switched to ciprofloxacin

Treatment failure due to ESBL

- Clinical response was noted the next day and antimicrobial treatment was continued for 7 days
- Removal of CVC did not contribute to resolution of the infection and the patient only improved when cefotaxime was replaced with ciprofloxacin
- Authors' postulate that if an infectious site in a patient has a high concentration of ESBL producing organism (ie $>10^7$ cfu/ml), cephalosporin failure is likely

New CLSI Guidelines 2010

- Problem with this approach
 - ◆ Clinical studies show patients with “susceptible” MICs + ESBL fail therapy
 - ◆ Inoculum used in bmd (10^5) too low and may dilute out resistant subpopulations giving false susceptible results

Pitfalls of ESBL Testing

Effects of Inoculum

MICs in $\mu\text{g/ml}$: SHV-3 producing *Citrobacter freundii*

Inocul. CFU/ml	Cefotaxime	Ceftazidime	Aztreonam	Cefepime
5×10^5	2	1	0.5	0.5

(CLSI breakpoint $\leq 8 \mu\text{g/ml}$)



Thomson KS, Moland ES: Antimicrob Agents
Chemother. 2001 Dec;45(12):3548-54

Pitfalls of ESBL Testing

Effects of Inoculum

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Inocul. CFU/ml	Cefotaxime	Ceftazidime	Aztreonam	Cefepime
5×10^5	2	1	0.5	0.5
5×10^7	256	32	32	>1024

(CLSI breakpoint $\leq 8 \mu\text{g/ml}$)



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Thomson KS, Moland ES: Antimicrob Agents
Chemother. 2001 Dec;45(12):3548-54

Inoculum Effect

- Animal studies also demonstrate an inoculum effect and adverse outcomes when cephalosporins are used to treat ESBL-producing organisms with MICs of cephalosporin in the susceptible range.

Efficacy of different beta-lactams against an ESBL-producing *K. pneumoniae* strain in the rat intra-abdominal abscess model

- Test strain was *K. pneumoniae* 5657 containing TEM-related ESBL obtained from sputum
- Abscess created by intraperitoneal placement of a gelatin capsule containing sterile rat cecal contents, killed *B. fragilis*, and 1:100 dilution of overnight culture of *K. pneumoniae* 5657 (ca. 10^5 CFU)
- Small incision made in left lower quadrant of abdomen and infective capsule placed directly in peritoneal cavity
- Treatment begun by continuous infusion via left internal jugular vein 3-4 hours after placement of capsule and continued 3 days.
- On day 2 and 3 blood samples were collected for determination of serum antibiotic levels
- After 3 days animals were sacrificed, abdominal wall portion of abscess removed and quantitative culture performed

Efficacy of different beta-lactams against an ESBL-producing *K. pneumoniae* strain in the rat intra-abdominal abscess model

Table 1: MICs of various agents for *K. pneumoniae* 5657

Antimicrobial Agent	MIC at inoculum of:	
	10 ⁵ CFU/ml	10 ⁷ CFU/ml
Cefoperazone	2	256
Sulbactam	32	
Cefoperazone-sulbactam (2:1)	0.5	256
Cefotaxime	1	256
Cefpirome	1	>256
Ceftazidime	>256	
Imipenem	0.5	16

Efficacy of different beta-lactams against an ESBL-producing *K. pneumoniae* strain in the rat intra-abdominal abscess model

Table 2: Intra-abdominal abscess treatment outcomes

Antibiotic	No. rats	Mean serum level ($\mu\text{g/ml}$)	Log10 CFU/g of abscess
None	30		8.02 \pm 1.02
Cefoperazone	11	13.5 \pm 4.72	7.41 \pm 0.74 ^a
Cefoperazone-sulbactam	11	8.9 \pm 3.22	5.84 \pm 0.95 ^c
Cefotaxime	18	17.7 \pm 8.42	7.26 \pm 1.02 ^a
Cefpirome	11	28.3 \pm 2.06	7.80 \pm 1.18 ^a
Ceftazidime	10	19.4 \pm 3.09	8.85 \pm 0.64 ^a
Imipenem	19	7.1 \pm 2.08	4.99 \pm 0.97 ^c

^a P>0.05, ^c P<0.05



Rice LB et al. *Antimicrob Agents Chemother.* 1991 Jun;35(6):1243-4.

Efficacy of different beta-lactams against an ESBL-producing *K. pneumoniae* strain in the rat intra-abdominal abscess model

- Conclusions

- ◆ Extend spectrum cephalosporins may be less effective in treating serious infections due to ESBL producing gram-negative bacilli than standard susceptibility tests would imply
- ◆ In vitro studies indicated that the activity of these agents against *K. pneumoniae* 5657 was **highly inoculum dependent**
- ◆ Dramatic improvement of in vivo efficacy of cefoperazone in presence of sulbactam was due at least in part to presence of β -lactamase and may be due to a phenomenon similar to the inoculum effect observed in vitro
- ◆ **Avoid extended spectrum cephalosporins as single agents when treating serious infections with ESBL-producing organisms**

New CLSI Guidelines 2010

- Problem with this approach
 - ◆ Clinical studies show patients with “susceptible” MICs + ESBL fail therapy
 - ◆ Inoculum used in bmd (10^5) too low and may dilute out resistant subpopulations giving false susceptible results
 - ◆ Different susceptibility testing methods give varying results

CAP Survey D-C 2007 D-19

C. freundii with PER-1 ESBL with **MIC 16** µg/ml

Method/system tested (no.)	Reported Cefepime MIC or zone in Susceptible category	Modal MIC
BD Phoenix (24)	Not reported	>16
MicroScan (311)	15%	>16
Vitek (244)	97.2%	≤4
Vitek 2 (230)	85.5%	2
Disk Diffusion (74)	34%	15.5 mm

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 - ◆ Method of inoculum preparation can vary the MIC result

Vancomycin MIC Results, $\mu\text{g/ml}$, for 19 MRSA Isolates, Obtained with 6 Different Testing Methods

Isolate	Frozen Reference	Etest	Turbidity WalkAway		Prompt Inoculation	
			WalkAway	Manual	WalkAway	Manual
11	1	1.5	1	1	2	1
12	1	1.5	2	2	2	2
13	1	2	2	1	2	2
14	1	1.5	1	1	2	1
15	0.5	1.5	1	1	2	2
16	2	2	2	1	2	2
17	1	2	1	1	2	2
18	1	2	2	2	2	2
19	1	1.5	1	1	2	2
Mode	1	2	1	1	2	2

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 - ◆ MIC results are not reproducible and can vary up to >3 dilutions upon repeat testing

CLSI Acceptable Limits ($\mu\text{g/mL}$) for QC Strains Used to Monitor Accuracy

Antimicrobial	E. Coli ATCC 25922	No. of Doubling Dilutions Allowed
Cefazolin	1-4	3
Cefotaxime	0.03-0.12	3
Ceftriaxone	0.03-0.12	3
Ceftazidime	0.06-0.5	4
Aztreonam	0.06-0.25	3
Cefepime	0.015-0.12	8

CLSI M100-S20. Table 4

New CLSI Guidelines 2010

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 - ◆ MIC results are not reproducible and can vary up to 3 dilutions upon repeat testing
 - ◆ **Some cephalosporin breakpoints were not lowered enough and others not lowered at all**

Enterobacteriaceae Revised Breakpoints (MIC $\mu\text{g.ml}$)

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Ceftriaxone	≤ 8	16-32	≥ 64	≤ 1	2	≥ 4
Ceftazidime	≤ 8	16	≥ 32	≤ 4	8	≥ 16
Aztreonam	≤ 8	16	≥ 32	≤ 4	8	≥ 16

CLSI M100-S20. Table 2A

Enterobacteriaceae – Evaluated but NOT Revised Breakpoints

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Cefotetan	≤ 16	32	≥ 64
Cefoxitin	≤ 8	16	≥ 32

CLSI M100-S20. Table 2A

Cephaloporin Breakpoints Following Recent EUCAST and CLSI Revisions

Group	Cefuroxime S≤/R>	Cefotaxime S≤/R>	Ceftriaxone S≤/R>	Ceftazidime S≤/R>	Cefepime S≤/R>
CLSI	8/8	1/2	1/2	4/8	8/16
EUCAST	8/8	1/2	1/2	1/8 ^a	1/8 ^a
EUCAST PK/PD	4/8	1/2	1/2	4/8	4/8

^aCeftazidime and cefepime S breakpoints were adjusted from 4 to 1 ug/ml to ensure that Enterobacteriaceae with clinically important ESBLs were not reported as susceptible

Enterobacteriaceae epidemiologic cut-off values (wild type $\leq X \mu\text{g/mL}$)

	E. coli	K. pneumoniae	K. oxytoca	P. mirabilis
Cefuroxime	8	8	8	4
Cefotaxime	0.25	0.12	0.12	0.06
Ceftriaxone	0.25	0.12	0.12	0.06
Ceftaxidime	0.5	0.5	0.5	0.12
Cefepime	0.12	0.12	0.12	0.12

New CLSI Guidelines 2010

- Problem with this approach
 - ◆ Clinical studies show patients with “susceptible” MICs + ESBL fail therapy
 - ◆ Inoculum used in bmd (10^5) too low and may dilute out resistant subpopulations giving false susceptible results
 - ◆ Different susceptibility testing methods give varying results
 - ◆ Method of inoculum preparation can vary the MIC result
 - ◆ MIC results are not reproducible and can vary up to 3 dilutions upon repeat testing
 - ◆ Some cephalosporin breakpoints were not lowered enough and others not lowered at all
 - ◆ **ESBL enzymes are substrate specific, may miss ESBL resistance if not testing the preferred substrate (eg. CTX-M)**

Vitek ID: [REDACTED] Oxidase -
Type: Gram Negative General Susceptibility 143
Status: Final
Elapsed Time: 6 hours
Organism: Escherichia coli
Source: ID Mate (6004764633)
Demographics: [REDACTED]

	MIC	Instrument
Ampicillin	>=32	R
Ampicillin/Sulbactam	>=32	R
Piperacillin/Tazobactam	<=8	S
Cefazolin	>=32	R
Ceftriaxone	<=8	S
Ceftazidime	<=8	S
Cefepime	<=4	S
Aztreonam	<=8	S
Imipenem	<=4	S
Gentamicin	<=0.5	S
Tobramycin	>=16	R
Ciprofloxacin	>=4	R
Levofloxacin	>=8	R
Trimeth-sulfa	>=320	R
Nitrofurantoin	<=32	S
ESBL		Positive

E. coli with CTX-M ESBL



Why labs should continue to perform ESBL testing on all isolates

- MIC results are inoculum dependent.
- MIC results are not reproducible and can vary by >3 dilutions
- Some ESBLs are inducible, ie. MIC is low initially but cephalosporin will test in resistant range after exposure to antibiotic. Presents a problem especially for Rapid Detection Methods
- Knowing the mechanism of resistance is important. It allows us to modify our reports and implement prompt infection control strategies

Case 1. Unknown #227-2

- Patient is a 40 Y.O. male paraplegic who traveled to New Dehli India for a surgical procedure. 3-4 months after returning to the U.S. patient presents to outpatient center in Chicago with multiple decubitus ulcers and urinary tract infection. Urine collected from foley cath is submitted for culture.

MicroScan Report

Organism Identification:

Organism	% Probability	Footnotes	Special Characteristics
1. E. coli	99.99		

Biochemical Results: (Biochemicals that are bolded and underlined are atypical for the first choice organism)

GLU + RAF - INO - URE - LYS + TDA - CIT - CL4 - ACE - K4 + P4 +
 SUC + RHA - ADO - H2S - ARG - ESC - MAL - CF8 + CET - NIT + TAR -
 SOR + AFA + MEL + IND + CRN + VP - ONPG - OXI FD64 - OF6 + TO4 +

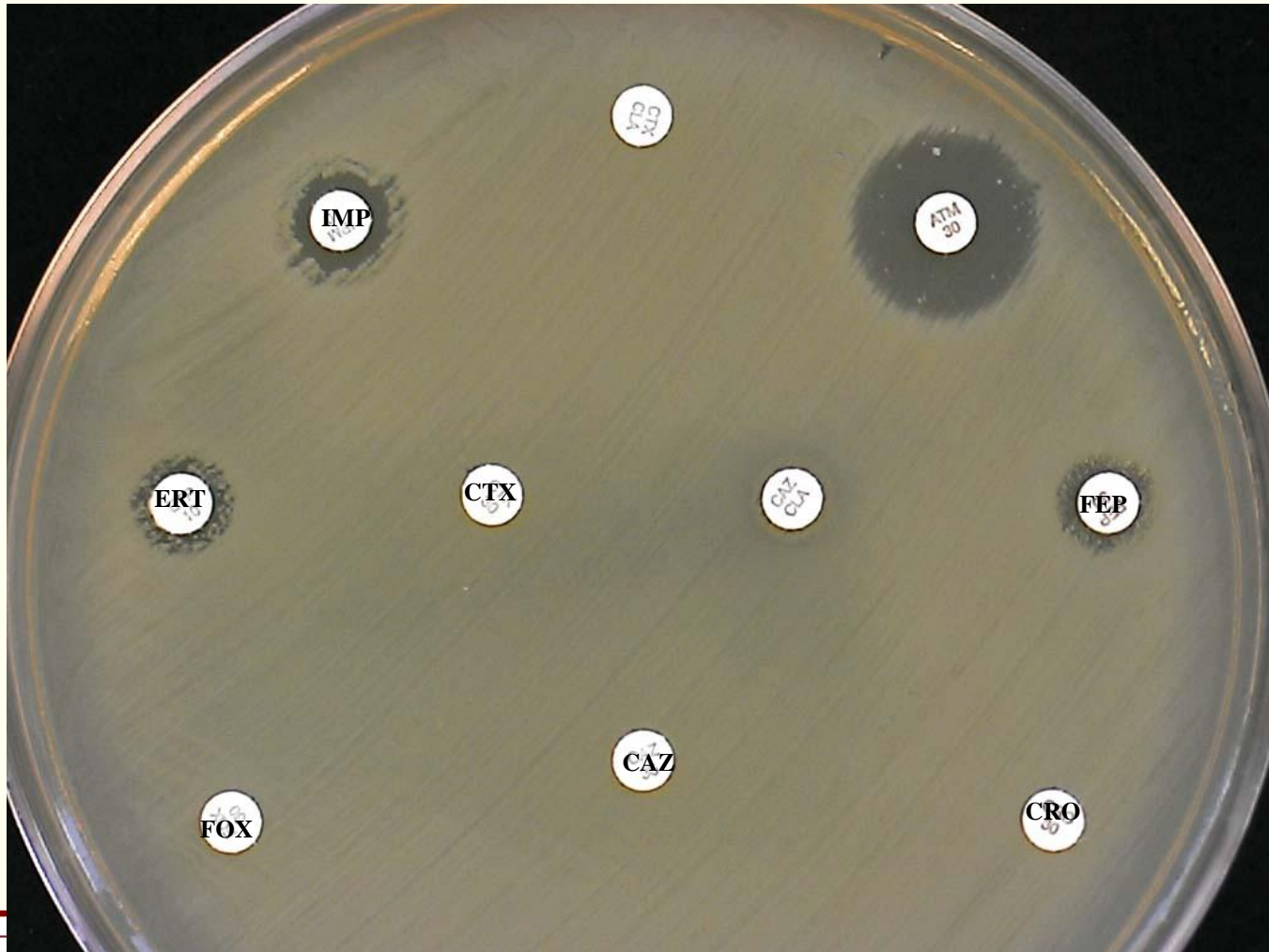
MIC Results: (Antimicrobics marked with "Ø" are suppressed from Long and Short Format Patient Reports)

AM	A/S	PYT	CFZ	GAX	CAZ	CPE	MER	GM	Ø TE	TO	CP	T/S
>16	>16	>64	>16	>32	>16	>16	>8	>8	>8	>8	>4	>2/58
R	R	R	R	R	R	R	R	R	R	R	R	R
CAZ/CA	CFT	CFT/CA	ETP	IMP	Ø AUG	Ø CRM	Ø LVX	Ø MXF	Ø TIM			
>2	>32	>4	>4	4	>16/8	>16	>4	>4	>64			
	R		R	S	R	R	R	R	R			

Extra Tests: ESBL-

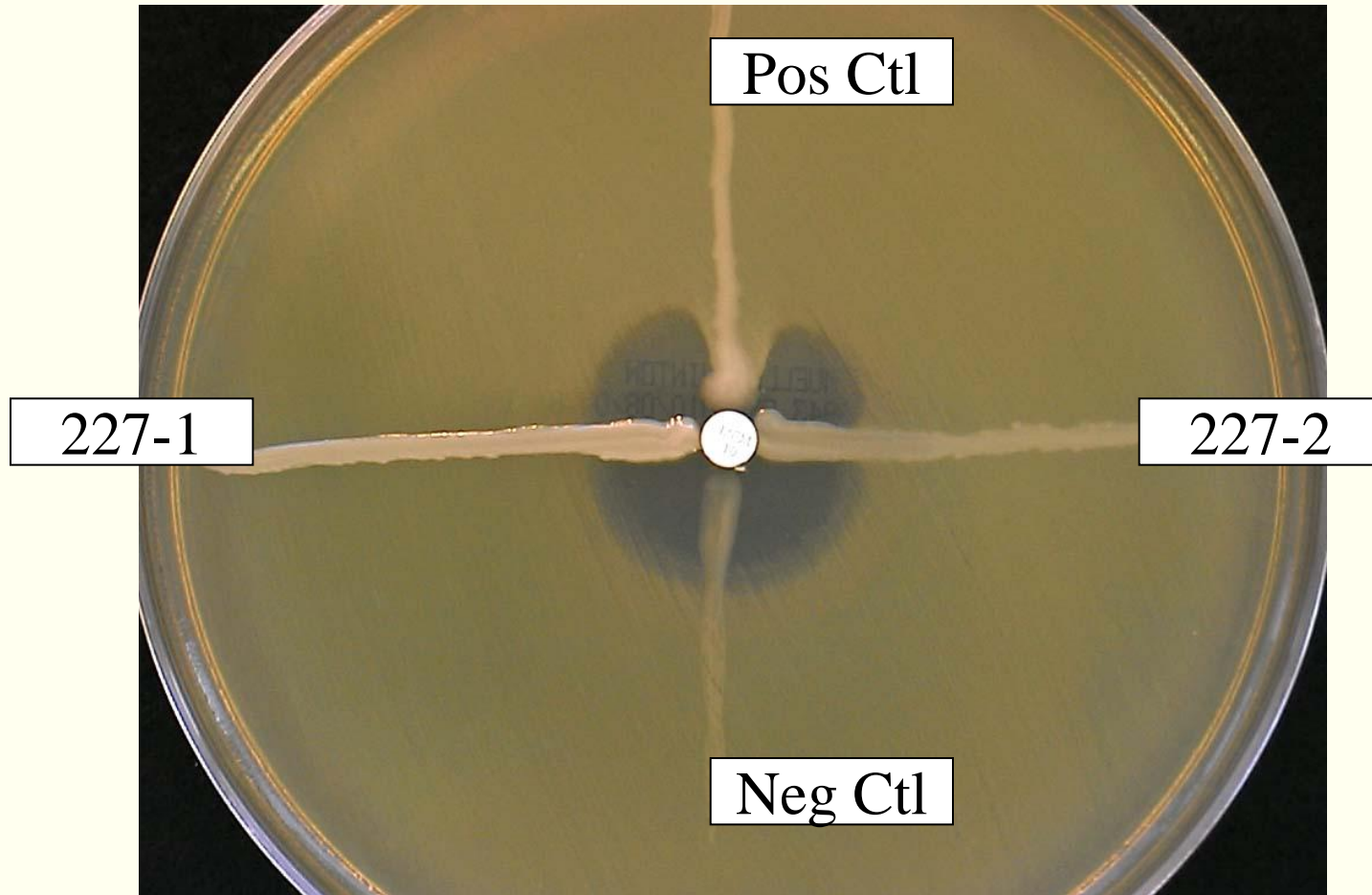
Case Unknown #227-2

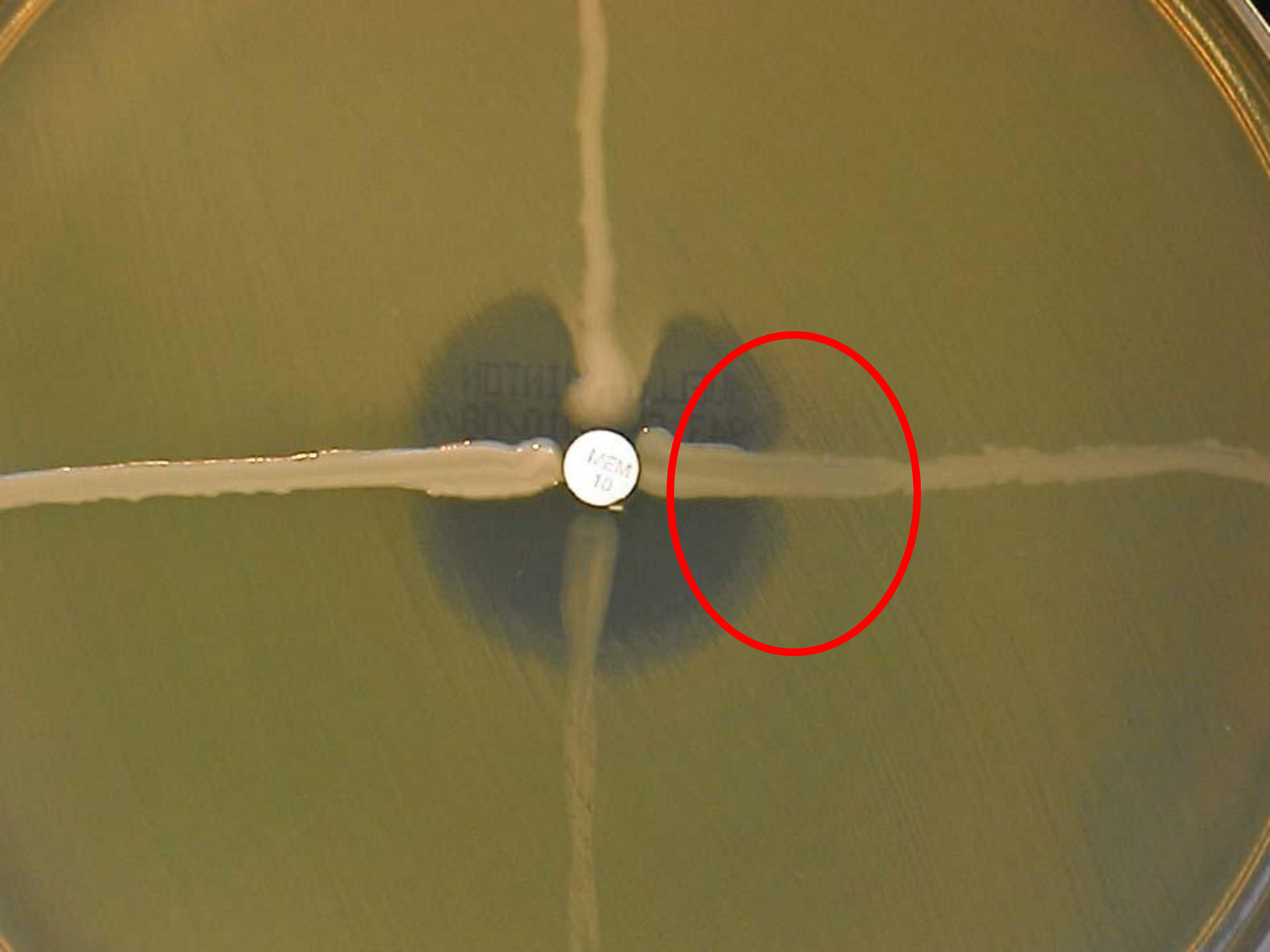
10 Disk



Case Unknown #227-2

Modified Hodge Test

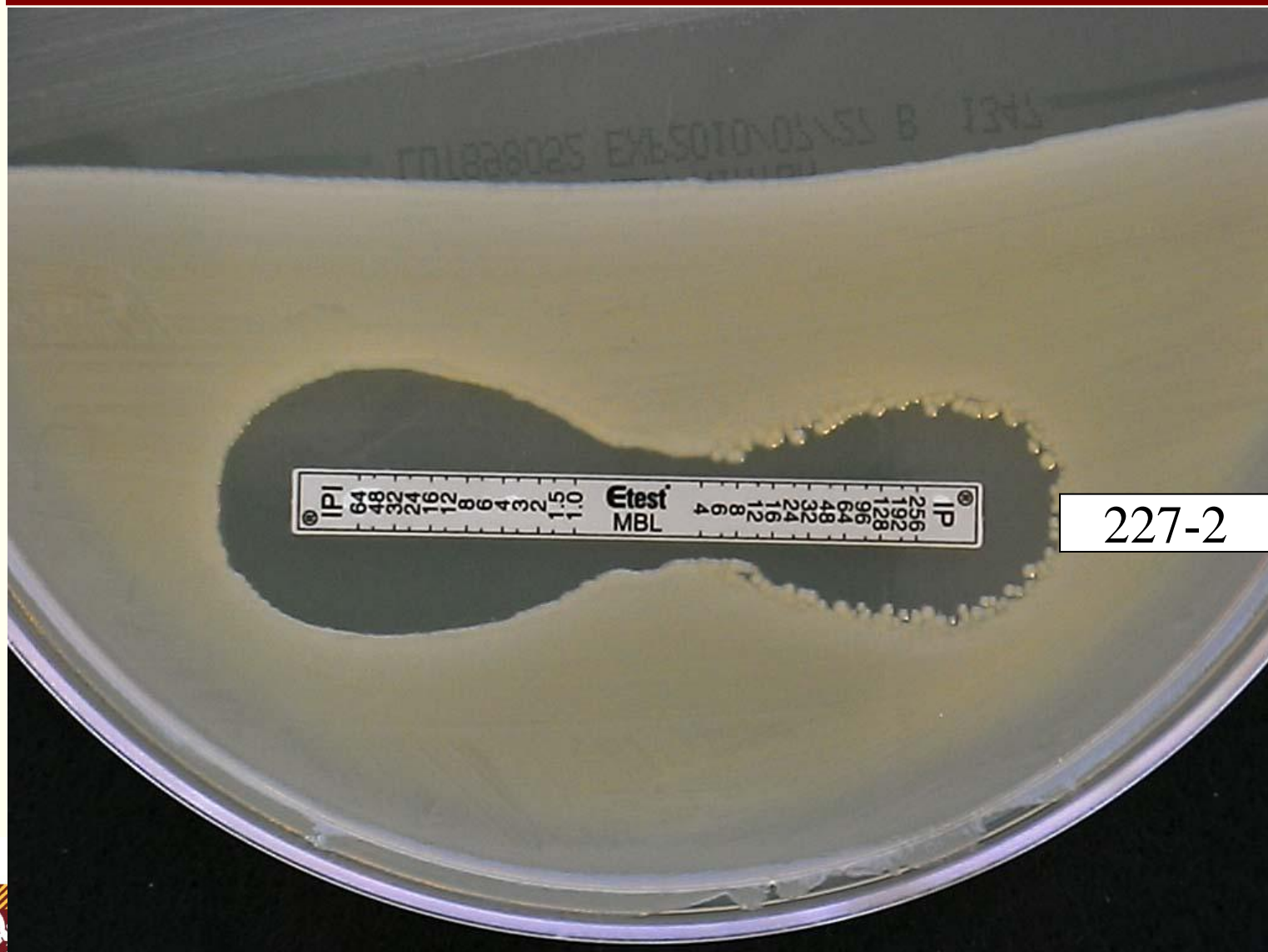




MEM
10

Case Unknown #227-2

MBL Etest for Metallo β -lactamase



And the Answer is

Initial Report of a New Metallo- β -Lactamase, NDM-1

- Swedish patient of Indian origin traveled to New Delhi, acquired a urinary tract infection caused by NDM-1-producing *K. pneumoniae*
- The *bla*_{NDM-1} gene is contained in a complex genetic structure on a 180-kb plasmid that is easily transferable to an *E. coli* recipient
- *bla*_{NDM-1} plasmid contained resistance genes for all antibiotics tested except fluoroquinolones and colistin
- The NDM-1 enzyme shares little identity with other MBLs (~32% identity with VIM-1/VIM-2)

Antimicrobial Agents and Chemotherapy. December, 2009. 53:5046-5054.



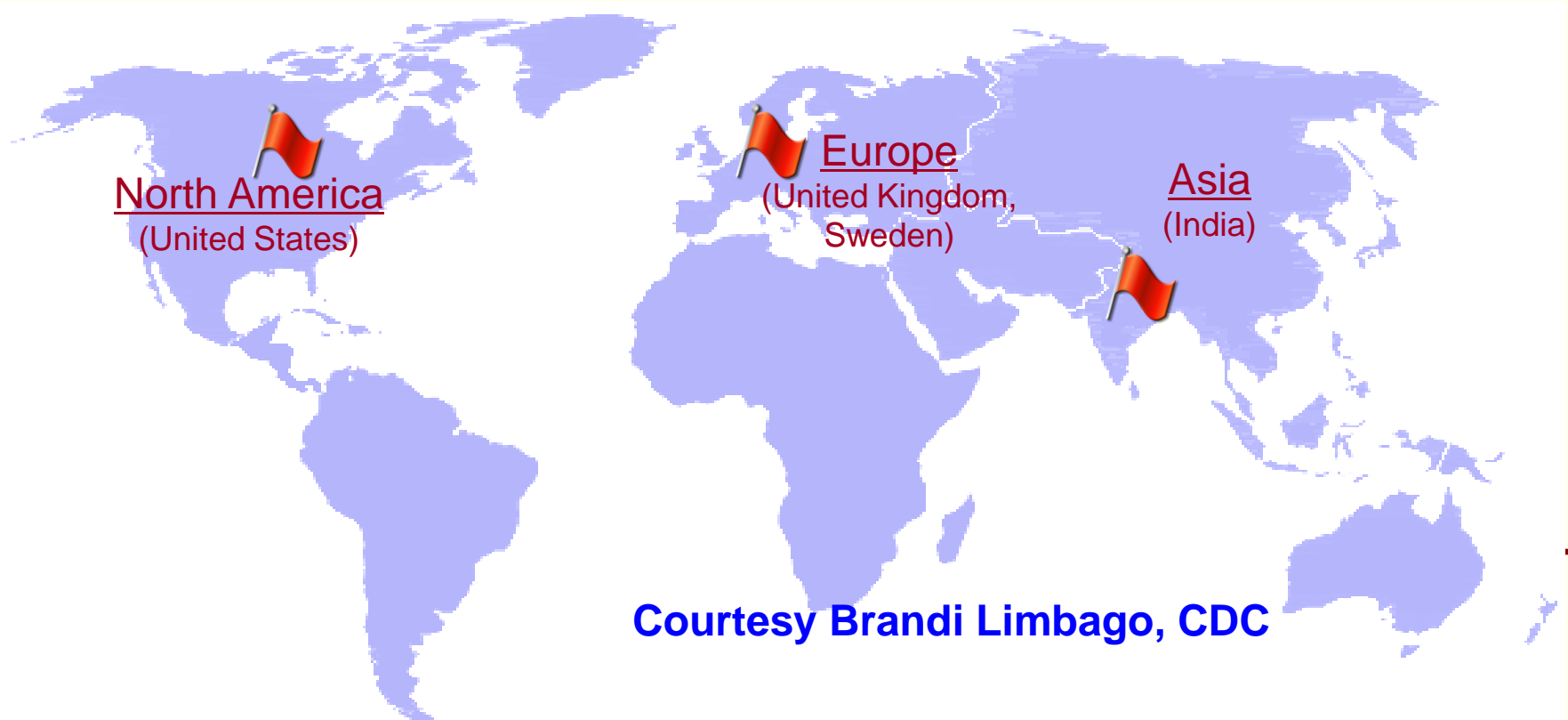
Courtesy Brandi Limbago, CDC

Class B: Metallo- β -Lactamases

- MBLs hydrolyze all β -lactams, including carbapenems, penicillins, extended-spectrum cephalosporins, but not aztreonam
- MBLs pose a serious threat in terms of infection control because of their high mobility
- MBLs require zinc for enzymatic activity which is not diminished by serine β -lactamase inhibitors but is inhibited by EDTA and other chelators of divalent cations

NDM-1 Goes Global

- In 2007 in the UK, more than 100,000 people traveled abroad for treatments ranging from heart operations to plastic surgery
- Potentially >200,000 this year



NDM-Producing Isolates in the U.S.

Location in U.S.	Organism	Date of Isolation	Site	Relevant Patient History
MA	<i>E. cloacae</i>	04/29/2009	Urine	Indian citizen. Hospitalized in India (surgery, chemotherapy, and dialysis) before coming to U.S.
CA	<i>K. pneumoniae</i>	12/29/2009	Urine	Patient was in automobile accident in India and hospitalized before coming to the U.S.
IL	<i>E. coli</i>	05/12/2010	Urine	Patient traveled to India 3-4 months prior with active medical issues incl. decubitus ulcers, urinary catheter



Courtesy Brandi Limbago, CDC

Message from Brandi Limbago

- We're trying to encourage people, especially infection control, to take all CRE very seriously. Our impression is that many are not following the guidance re. CRE detection, isolation and surveillance recommended in the 2009 MMWR. Although NDM is the newest mechanism, all CRE should initiate some sort of alert.
- Guidance: <http://www.cdc.gov/mmwr/preview/mmwrhtml/mm5810a4.htm>

Enterobacteriaceae - Revised Carbapenem Breakpoints (MIC $\mu\text{g.ml}$)

NEW!!

Agent	CLSI M100-S19 (2009)			CLSI M100-S20 (2010) Supplement		
	Susc	Int	Res	Susc	Int	Res
Doripenem	-	-	-	≤ 1	2	≥ 4
Ertapenem	≤ 2	4	≥ 8	≤ 0.25	0.5	≥ 1
Imipenem	≤ 4	8	≥ 16	≤ 1	2	≥ 4
Meropenem	≤ 4	8	≥ 16	≤ 1	2	≥ 4

CLSI. Performance Standards for Antimicrobial Susceptibility Testing: Twentieth Informational Supplement (June 2010 Update). CLSI document M100-S20-U. Wayne, PA; 2010

Enterobacteriaceae - Revised Carbapenem Breakpoints (disk mm)

NEW!!

Agent	CLSI M100-S19 (2009)			CLSI M100-S20 (2010)		
	Susc	Int	Res	Susc	Int	Res
Doripenem	-	-	-	≥ 23	20-22	≤19
Ertapenem	≥ 19	16-18	≤15	≥ 23	20-22	≤19
Imipenem	≥ 16	14-15	≤13	≥ 23	20-22	≤19
Meropenem	≥ 16	14-15	≤13	≥ 23	20-22	≤19

CLSI. Performance Standards for Antimicrobial Susceptibility Testing: Twentieth Informational Supplement (June 2010 Update). CLSI document M100-S20-U. Wayne, PA; 2010

Recommendations

- Apply new (lower) breakpoints to clinical isolates as soon as testing capability becomes available
- Perform Hodge Test and MBL Etest on all Enterobacteriaceae with carbapenem MIC > 1 mg/ml and resistance to 3rd generation cephaloporins
- Report MIC and Change AST result to I or R when resistant mechanism detected
- Report Resistant mechanism to clinicians and infection control practitioners
- **LEARN MORE:** Kumarasamy KK et al. Emergence of a new antibiotic resistance mechanism in India, Pakistan and the UK: a molecular, biological and epidemiological study. *Lancet Infect Dis.* 2010 Sep;10(9):597-602