Changes to Gram-negative Susceptibility Reporting:

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In early July 2014 the Clinical Microbiology Laboratory will introduce a new antibiotic susceptibility panel for gram-negative pathogens. This change was precipitated by new Clinical Laboratory Standards Institute (CLSI) interpretive guidelines for expanded-spectrum cephalosporins, aztreonam and carbapenems pertaining to the Enterobacteriaceae (**Table 1**). The new susceptibility breakpoints were determined based on a number of factors including: drug characteristics; distribution of MIC values in large representative microbiologic samples; animal model data, pharmacokinetic and pharmacodynamic (PK/PD) data and its correlation with efficacy; the correlation of MIC values with clinical outcomes; and the impact of known resistance mechanisms on MIC values.

Table1: CLSI minimum inhibitory concentration (MIC) interpretive standards for expanded-spectrum cephalosporins, aztreonam and carbapenems for *Enterobacteriaceae*.

Agent	**Previous MIC Interpretations**			**New MIC Interpretations**		
	Sensitive	Intermediate	Resistant	Sensitive	Intermediate	Resistant
Cefazolin	≤ 8	16	≥ 32	≤ 2	4	≥ 8
Cefotaxime	≤ 8	16-32	≥ 64	≤ 1	2	≥ 4
Ceftazidime	≤ 8	16	≥ 32	≤ 4	8	≥ 16
Ceftriaxone	≤ 8	16-32	≥ 64	≤ 1	2	≥ 4
Aztreonam	≤ 8	16	≥ 32	≤ 4	8	≥ 16
Ertapenem	≤ 2	4	≥ 8	≤ 0.5	1	≥ 2
Imipenem	≤ 4	8	≥ 16	≤ 1	2	≥ 4
Meropenem	≤ 4	8	≥ 16	≤ 1	2	≥ 4

Some specific points of note are included below.

The laboratory will continue to test for and report the detection of extended-spectrum beta-lactamase (ESBL) as these results have both therapeutic and epidemiologic implications.

- If ESBL (+), all 3rd generation cephalosporins, cefepime, aztreonam, and piperacillin/tazobactam will be changed to resistant regardless of MIC
  - A comment will state that an ESBL has been detected
- If ESBL (–), interpretation will be per the new breakpoints

The lab will continue to evaluate for the presence of carbapenemases as these results have both therapeutic and epidemiologic implications.

- When an isolate is intermediate or resistant to ertapenem or meropenem the susceptibility results will be reported with a comment that further testing for the presence of a carbapenemase is in progress
  - Carbapenems should be used with caution in this situation as if a carbapenemase is present treatment failure is likely
- PCR based testing for the presence of the *kpc* and *NDM-1* gene will be performed on weekdays by the Nebraska Public Health Lab

- If either PCR is positive all beta-lactam results will have interpretations adjusted to resistant and a comment will be added identifying the specific carbapenemase identified
- If both PCR tests are negative a comment will be added that the isolate tested negative for these 2 genes and interpretations will not be adjusted
- Other non-validated tests will also be performed to determine the presence of other beta-lactamases. If significant results are obtained from this the results will be entered as a progress note by the clinical microbiology lab, antimicrobial stewardship, or infection control.

Nitrofurantoin will no longer be available for testing in gram-negative pathogens.

- Currently 97% of *E. coli* are susceptible to this agent (2013 antibiogram) and testing for this agent is available upon specific clinician request.

Cefotaxime will no longer being tested in gram-negative pathogens.

- Ceftriaxone susceptibility results can be used to predict susceptibility to cefotaxime within the Enterobacteriaceae (*E. coli*, *Klebsiella* species, *Enterobacter*, etc.).

Some *Pseudomonas aeruginosa* isolates will have ceftazidime MIC results that will be interpreted as non-susceptible.

- This indicates that the isolate is either intermediate or resistant and ceftazidime should not be used.

Some concerns have been expressed in the literature regarding the implementation of the new MIC breakpoints including: a lack of clinical data supporting use of extended-spectrum cephalosporins in treating ESBL-producing pathogens; the loss of identification of epidemiologically important mechanisms of resistance which have been associated with nosocomial outbreaks; and the lack of accord with FDA breakpoints. Due to these concerns the Clinical Microbiology Lab in concert with the Antimicrobial Stewardship program have chosen to implement the new breakpoints while maintaining the identification of ESBL and carbapenemase enzymes and adjusting interpretation of results when these enzymes are detected. These changes are likely to result in significant changes in antimicrobial reporting and susceptibility, and clinical questions regarding treatment can be addressed by the ID consult services.

Questions regarding interpretation may be directed to Paul D. Fey, Ph.D. D(ABMM), Medical Director, at (402) 559-2122, Amy Crismon, Microbiology Manager, at (402) 552-3313, Trevor Van Schooneveld, MD, Medical Director Antimicrobial Stewardship at (402) 559-8376, or by calling the Clinical Microbiology Laboratory at (402) 552-2090.

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C	G	P4	GLU	RAF	INO	URE	LYS	TDA	CIT	TAR	OF/G
NIT	K4	CI4	SUC	RHA	ADO	H2S	ARG	ESC	MAL	ACE	OF/B
2/38 T/S	Fd64	Cf8	SOR	ARA	MEL	IND	ORN	VP	ONPG	CET	DCB
4	4/2	8/4	16/8 A/S	4	8	16 Crm	1	2	4	8	16 Cpe
8	4	8	16 Am	4	8	16 Cfz	1	2	4	8 Cax	LOC
16 Azt	1	8 Caz	0.5	1	2 Cp	1	2	4 Lvx	8	16	32 Ak
2	16 Cft	0.5/4	4/4 Cft/CA	0.25/4	2/4 Caz/CA	16	32	64 P/T	2	4	8 To
1	2	4	8 Mer	0.5	1 Etp	2	4	8 Te	2	4	8 Gm

Antimicrobial Agents	Dilutions	Antimicrobial Agents	Dilutions
Amikacin – Ak	8 – 32	Cefuroxime – Crm	4 – 16
Ampicillin – Am	4 – 16	Ciprofloxacin – Cp	0.5 – 2
Ampicillin/Sulbactam – A/S	4/2 – 16/8	Ertapenem – Etp	0.5 – 1
Aztreonam – Azt	4 – 16	Gentamicin – Gm	2 – 8
Cefazolin – Cfz	4 – 16	Levofloxacin – Lvx	1 – 4
Cefepime – Cpe	1 – 16	Meropenem – Mer	1 – 8
Cefotaxime – Cft	2, 16	Piperacillin/Tazobactam – P/T	16 – 64
Cefotaxime/K Clavulanate – Cft/CA	0.5/4, 4/4	Tetracycline – Te	2 – 8
Ceftazidime – Caz	1, 8	Tobramycin – To	2 – 8
Ceftazidime/K Clavulanate	0.25/4, 2/4	Trimethoprim/Sulfamethoxazole – T/S	2/38
Ceftriaxone – Cax	1 – 8		