CLSI Rationale Document – Carbapenem Breakpoints for *Enterobacteriaceae*: 2011

Background/Introduction:

The carbapenems represent the broadest spectrum class of antibacterials in clinical use and are routinely utilized to manage critically ill patients with severe infections. The oldest of the group, imipenem (combined with the dehydropeptidase inhibitor cilastatin), has been in clinical use since 1986 and until recently resistance to carbapenems within the *Enterobacteriaceae* remained rare. However the emergence of *Klebsiella pneumoniae* carbapenemase (KPC) producing organisms has resulted in a dramatic increase in resistance to the carbapenems amongst the *Enterobacteriaceae*.[1] In addition increasing reports of metallo-beta lactamase production amongst *Enterobacteriaceae* represents a formidable challenge.[2, 3] The issue has been further complicated by the realization that diminished susceptibility to carbapenems within the *Enterobacteriaceae* may also be the result of production of either or both ESBL or AmpC beta lactamases in conjunction with porin alteration.[4, 5] The CLSI originally established the breakpoints for all of the carbapenems with the exception of doripenem utilizing review of population distributions of MICs, available pharmacokinetic data, as well as outcomes data from registration studies. The development of the breakpoints for imipenem and meropenem predated much of the pharmacokinetic/pharmacodynamic (PK/PD) data that are utilized in the current development of breakpoints for new agents or reassessment of older agents. The development and subsequent publication of the ertapenem breakpoints in the 2003 version of the CLSI M100 document did include some preliminary PK/PD data from the sponsor but not the Monte-Carlo simulation data that has become an integral part of recent breakpoint development. The request for review of doripenem by the sponsor (Ortho-McNeil/Johnson and Johnson) at the January 2009 meeting of the CLSI followed initial discussions beginning in 2005 on the need for reevaluation of breakpoints for imipenem, meropenem, and ertapenem. PK/PD analyses presented in 2005 suggested that the CLSI imipenem and meropenem breakpoints might be slightly high, and those for ertapenem could not be justified based upon PK/PD criteria.[6] Applying PK/PD calculations to the application for doripenem, it was recognized that the breakpoints that would be set for doripenem using current methods would result in markedly different breakpoints than those currently in use for imipenem and meropenem.

In addition to the aforementioned PK/PD concerns regarding the current breakpoints for the carbapenems and the *Enterobacteriaceae*, another pressing issue that was integral in the decision of the CLSI to reevaluate the carbapenem breakpoints for the *Enterobacteriaceae* was the detection of *Enterobacteriaceae* producing KPC enzymes. Utilizing the pre 2010 breakpoints, a significant percentage

of KPC producing organisms were identified as being susceptible to the carbapenem being tested, especially imipenem and meropenem. In addition, the 2009 recommendation for utilization of the modified Hodge test for *Enterobacteriaceae* with resistance to any of the 3rd generation cephalosporins and elevated (though usually susceptible) MICs of carbapenems resulted in considerable confusion for clinical microbiologists and clinicians. Concerns were raised that many clinical laboratories were not performing the modified Hodge test and that interpretation of the test was subjective and difficult. The 2007 College of American Pathologists proficiency survey program results revealed that a significant number of clinical laboratories were having difficulties correctly identifying KPC producing *Enterobacteriaceae*.[7] Based upon MIC distributions presented to the committee, it became apparent that by decreasing the carbapenem breakpoints to levels consistent with PK/PD analyses the vast majority of KPC producing *Enterobacteriaceae* (>99%) would be reported as resistant to imipenem, meropenem, and ertapenem and would diminish the need for clinical laboratories to perform the modified Hodge test to guide therapy.

The CLSI utilizes its M23 document to define the requirements for establishment of breakpoints.[8] This document also contains the procedures by which breakpoints may be reevaluated or changed. The discussion surrounding doripenem and the realization of the potential discrepancies that its breakpoints would create due to the differences in types of data required and utilized for the establishment of the breakpoints, as well as the emergence of new resistance mechanisms within the *Enterobacteriaceae* met several of the M23 criteria for reevaluation of the breakpoints. For these reasons a class-wide review of the carbapenem breakpoints for *Enterobacteriaceae* was initiated by the CLSI Antimicrobial Susceptibility Testing Subcommittee.

CLSI carbapenem MIC (µg/mL) breakpoints for *Enterobacteriaceae* Prior to 2010 and Current

Antimicrobial Agent	$S_{pre2010}/S_{current}$	$I_{pre2010}/I_{current}$	$R_{pre2010}/R_{current}$
Imipenem	≤4/≤1	8/2	≥16/≥4
Meropenem	≤4/≤1	8/2	≥16/≥4
Ertapenem	≤2/≤0.5	4/1	≥8/≥2
Doripenem	NA/≤1	NA/2	NA/≥4

Standard Doses & Pharmacokinetic Data

Table 1: Standard Doses Utilized for Breakpoint Determination

Drug	Dose
Imipenem	500mg every 6 hours or 1gm every 8 hours
Meropenem	500mg every 6 hours or 1gm every 8 hours
Doripenem	500mg every 8 hours
Ertapenem	1gm every 24 hours

The doses in table 1 were utilized in determining the breakpoints for the carbapenems and represent the most commonly used doses in clinical settings, as well as FDA approved doses for indications that include *Enterobacteriaceae*. It is important to note that infusion times of all carbapenems at the doses listed in the table were 30 minutes with the exception of doripenem which utilized a 1 hour infusion according to FDA-approved labeling. Extended infusion regimens were not utilized in establishing the current breakpoints.

The pharmacokinetic data utilized to evaluate the four carbapenems and develop the new breakpoints are provided in Tables 2 through 5. Protein binding estimates were obtained from the prescribing information of the approved drug label of each carbapenem.

Table 2 – Imipenem pharmacokinetics

Dose	1 gram infused over 30 minutes
Mean volume of the central compartment	9.66 liters (SD= 5.54)
Mean K central compartment	5.98 $hours^{-1}$ (SD=7.00)
Mean K peripheral compartment	5.05 $hours^{-1}$ (SD=6.46)
Mean total body clearance	12.08 liters/hour (SD=3.51)
Mean AUC	82.73 mg*hours/liter (SD=24.0)

*Adapted from [9]

Table 3 – Meropenem pharmacokinetics

Dose	2 dosing regimens used in calculations
Mean volume of the central compartment	12.4 liters (SD= 3.51)
Mean K central compartment	1.21 $hours^{-1}$ (SD= 1.79)
Mean K peripheral compartment	4.03 $hours^{-1}$ (SD= 8.18)

Mean total body clearance	16.3 liters/hour (SD= 3.08)

*Adapted from [10]

Table 4 – Doripenem pharmacokinetics

Dose	4 dosing regimens used in calculations
Mean volume of the central compartment	9.43 liters (SEM= 6.4%)
Mean volume of the peripheral compartment	5.88 liters (SEM= 6.7%)
Mean intercompartmental clearance	9.69 liters/hour (SEM= 20.3%)
Mean total body clearance	14.5 liters/hour (SEM= 2.6%)

*Adapted from [11]

Table 5 – Ertapenem pharmacokinetics

Dose	1 gram infused over 30 minutes
Mean volume of the central compartment	5.15 liters (SD= 0.5)
Mean total body clearance	0.024 liters/hour/kg (SD=0.004)
Mean AUC	586 mcg*hours/milliliter (SD=50.4)

*Adapted from [12]

Pharmacodynamic Data

Pharmacodynamic studies utilizing the mouse thigh model suggested that the percentage of time that the free carbapenem serum concentration must remain above the MIC of the infecting *Enterobacteriaceae* in order to achieve a static effect was 30-40%.(Craig - Data presented to the CLSI *Enterobacteriaceae* working group 1/2009) This appears to be true irrespective of KPC production by the infecting organism.(Craig - Data presented to the CLSI *Enterobacteriaceae* working group 1/2009) A summary of the 5000 patient Monte Carlo simulation data utilized to evaluate the new breakpoints for each agent is presented in table 6.

Table 6: Monte-Carlo simulation probability of target attainment at New *Enterobacteriaceae* Breakpoints utilizing inflated variance.

	MIC (μg/mL)	f%T>MIC ≥30	f%T>MIC ≥35	f%T>MIC ≥40	f%T>MIC ≥45
Imipenem	1	0.976	0.946	0.914	0.881

500mg Q6h					
Meropenem 1gm Q8h	1	0.969	0.927	0.874	0.794
Ertapenem 1gm Q24h	0.50	0.879	0.799	0.719	0.638
Doripenem 500mg Q8h	1	0.983	0.949	0.889	0.769

***Source: Ambrose and Bhavnani. CLSI Meeting Agenda Book June 2009**

Clinical Efficacy:

Infections due to KPC and metallo beta-lactamase producing *Enterobacteriaceae* have been associated with high rates of mortality making their straightforward detection by clinical laboratories and the accuracy of breakpoints critical. [13-17] Currently available clinical data support the efficacy of carbapenems for infections due to *Enterobacteriaceae* with MICs up to the current CLSI breakpoints. (Data presented to the CLSI *Enterobacteriaceae* working group 1/2010) Infections due to *Enterobacteriaceae* with MICs in excess of the current breakpoints may be effectively treated utilizing doses in excess of those listed above or by utilizing alternative infusion lengths. However the currently available clinical data to support the utilization of alternative dosing regimens and infusion times for the management of infections due to *Enterobacteriaceae* with MICs in excess of the June 2010 CLSI breakpoints were limited. At the January 2011 meeting clinical outcome and epidemiologic data were presented in a proposal to increase the susceptible ertpapenem breakpoint from 0.25 µg/mL (which was approved at the June 2010 meeting) to 0.5 µg/mL. (Data presented to the CLSI *Enterobacteriaceae* working group 1/2011) The clinical data were from a small single center case series of patients with ESBL infections due to organisms with ertapenem MICs of 0.5 or 1 µg/mL to ertapenem. There was no evidence of clinical failures at these MICs. These data as well as epidemiologic data suggesting that a fraction of ESBL producing *E. coli* without other mechanisms of resistance have MICs of 0.5, there was no decrease in the ability to detect KPC producing organisms at a breakpoint of 0.5, as well as a desire to harmonize with the EUCAST breakpoints resulted in a vote to increase of the ertapenem susceptible breakpoint from 0.25 to 0.5 µg/mL at the June 2011 CLSI meeting.

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