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Guideline

Consensus Statement on the Adherence to Clinical and Laboratory Standards Institute (CLSI) Antimicrobial Susceptibility Testing Guidelines (CLSI-2010 and CLSI-2010-update) for *Enterobacteriaceae* in Clinical Microbiology Laboratories in Taiwan

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A consensus meeting was organized under the auspices of the Infectious Diseases Society of Taiwan, the Taiwan Society of Microbiology, the Taiwan Society of Laboratory Medicine, and the Taiwan Society of Clinical Pathology and Laboratory Medicine. The meeting, which was held on September 16, 2010, aimed to develop a consensus statement on the adherence to two recently-released Informational Supplements to the Clinical and Laboratory Standards Institute (CLSI) Antimicrobial Susceptibility Guidelines (CLSI-2010 and CLSI-June 2010-update) for *Enterobacteriaceae* in clinical microbiology laboratories of Taiwanese hospitals.[1–3]

These two 2010 CLSI Informational Supplements include new (revised) interpretive criteria for several cephalosporins (cefazolin, cefotaxime, ceftriaxone, ceftizoxime), aztreonam, and carbapenems (ertapenem, imipenem, meropenem, and doripenem) for *Enterobacteriaceae* isolates using the disk diffusion method (Table 1) and minimum inhibitory

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concentrations (MIC) susceptibility testing (Tables 2 and 3).[1–3] These revised interpretive criteria were approved by the CLSI committee members after evaluation of the pharmacokinetic-pharmacodynamic properties of these agents, the distribution of MIC, and, unfortunately, limited data on clinical outcome.

For cephalosporins, the current CLSI Informational Supplements note that when using the new interpretive criteria, routine testing for extended-spectrum β-lactamases (ESBL) is no longer necessary before reporting results (e.g. it is no longer necessary to edit results for cephalosporins, aztreonam, or penicillins from susceptible to resistant).[1–2]

Table 1. Interpretive zone diameter breakpoints for disk diffusion susceptibility testing for several cephalosporins, aztreonam, and carbapenems established in January 2009 and January 2010 by the Clinical and Laboratory Standards Institute[a]

Antimicrobial agent	CLSI document	Interpretive zone diameter breakpoints (mm)		
		Susceptible	Intermediate	Resistant
Cefotaxime or ceftriaxone	M100-S20 (2010)	≥26	23–25	≤22
		≥23	20–22	≤19
	M100-S19 (2009)	≥21	14–20	≤13
Ceftazidime	M100-S20 (2010)	≥21	18–20	≤17
	M100-S19 (2009)	≥18	15–17	≤14
Ceftizoxime	M100-S20 (2010)	≥25	22–24	≤21
	M100-S19 (2009)	≥20	15–19	≤14
Aztreonam	M100-S20 (2010)	≥21	18–20	≤17
	M100-S19 (2009)	≥22	16–21	≤15
Doripenem	M100-S20-U (2010-June)	≥23	20–22	≤19
Ertapenem	M100-S20-U (2010-June)	≥23	20–22	≤19
	M100-S20 (2010)	≥19	16–18	≤15
Imipenem/Meropenem	M100-S20-U (2010-June)	≥23	20–22	≤19
	M100-S20 (2010)	≥16	14–15	≤13

[a]Information from references 1 and 2. CLSI=Clinical and Laboratory Standards Institute.

Table 2. Minimum inhibitory concentration interpretive breakpoints for several cephalosporins and aztreonam established in January 2009 and January 2010 by the Clinical and Laboratory Standards Institute and the minimum inhibitory concentration ranges tested in two commercial automated instruments[a]

Agent	MIC interpretive breakpoints (μg/mL)						MIC range[b]	
	CLSI 2009 (M100-S19)			CLSI 2010 (M100-S20)				
	Susceptible	Intermediate	Resistant	Susceptible	Intermediate	Resistant	Vitek II	Phoenix
Cefazolin	≤8	16	≥32	≤1	2	≥4	4–64[b]	4–16[b]
Cefotaxime	≤8	16–32	≥64	≤1	2	≥4	1–64	1–32
Ceftriaxone	≤8	16–32	≥64	≤1	2	≥4	1–64	4–32[b]
Ceftizoxime	≤8	16–32	≥64	≤1	2	≥4	1–64	–
Ceftazidime	≤8	16	≥32	≤4	8	≥16	1–64	0.5–16
Cefepime								
Aztreonam	≤8	16	≥32	≤4	8	≥16	1–64	2–16

[a]Information from references 1 and 2; [b]the MIC ranges are not able to detect susceptible or intermediate isolates when using new CLSI-2010 interpretive MIC breakpoints (M100-S20). MIC=minimum inhibitory concentration; CLSI=Clinical and Laboratory Standards Institute.

Table 3. Minimum inhibitory concentration interpretive breakpoints for carbapenems established in January 2010 and June 2010 by the Clinical and Laboratory Standards Institute and the minimum inhibitory concentration ranges tested in two commercial automated instruments[a]

Agent	MIC interpretive breakpoints (μg/mL)						MIC range (μg/mL)	
	CLSI 2010 (M100-S20)			CLSI 2010-Update (M100-S20-U)				
	Susceptible	Intermediate	Resistant	Susceptible	Intermediate	Resistant	Vitek II	Phoenix
Ertapenem	≤2	4	≥8	≤0.25	0.5	≥1	0.5–8[b]	0.5–4[b]
Imipenem	≤4	8	≥16	≤1	2	≥4	0.25–16	1–8
Meropenem	≤4	8	≥16	≤1	2	≥4	0.25–16	1–8
Doripenem	–	–	–	≤1	2	≥4	0.12–8	–

[a]Information from references 4 and 5; [b]the MIC ranges are not able to detect susceptible or intermediate isolates when using the new CLSI-2010 June interpretive MIC breakpoints (M100-S20-U). MIC=minimum inhibitory concentration; CLSI=Clinical and Laboratory Standards Institute.

ESBL testing may still be useful for epidemiological or infection control purposes, and should still be performed until the new interpretive criteria are implemented.[1–2] These informational supplements did not change the interpretive criteria for cefepime and cefuroxime (parenteral).[1–2] They also emphasize that interpretive criteria for drugs with limited availability in many countries (i.e. moxalactam, cefonicid, cefamandole, and cefoperazone) were not evaluated.[2] If considering use of these drugs in treating patients with infections due to *Escherichia coli, Klebsiella,* or *Proteus* spp. isolates, ESBL testing should be performed. If the isolates exhibited an ESBL-producing phenotype, the results for moxalactam, cefonicid, cefamandole, and cefoperazone should be considered as resistant.[2]

The rationale for setting new interpretive breakpoints for carbapenems is the presence of carbapenamases in *Enterobacteriaceae* that are largely responsible for MICs and zone diameters in the new intermediate and resistant ranges.[3] Implementation of the new breakpoints can obviate the need for screening or confirmatory testing for *Klebsiella pneumoniae* carbapenamases (KPC) by the modified Hodge test (MHT).[3] Once laboratories implement these new interpretive criteria, MHT does not need to be performed other than for epidemiology and infection control purposes.[3]

The consensus meeting agreed that there is no need to apply the revised interpretive criteria for cephalosporins and carbapenems to define susceptibility categories for

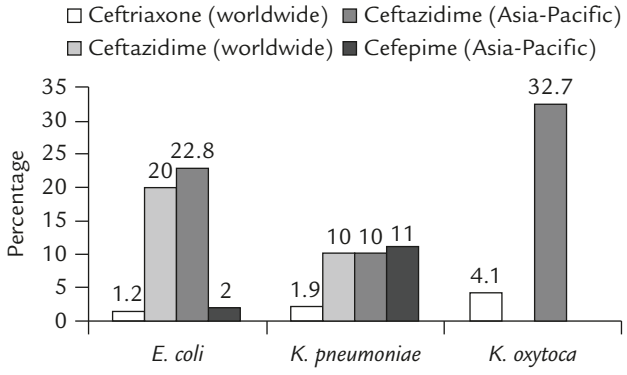

Figure. Susceptibility rates to ceftriaxone, ceftazidime and cefepime for extended-spectrum β-lactamase-producing *Escherichia coli, Klebsiella pneumoniae* and *K. oxytoca* isolates retrieved from SMART (Study for Monitoring Antimicrobial Resistance Trends) data from the Asia-Pacific region (2008) and worldwide (2007–9). The data were analyzed based on the new 2010 CLSI MIC interpretive breakpoints for *Enterobacteriaceae* (M00-S20). Adapted from reference 3.

Enterobacteriaceae for several reasons. First, the new ceftazidime (≤4 μg/mL) and the unchanged cefepime (≤8 μg/mL) susceptible breakpoints failed to identify many ESBL-producing *E. coli, K. pneumoniae,* and *K. oxytoca* (Figure).[4–5] Indications for the clinical use of cefepime or third-generation cephalosporins for the treatment of infections caused by ESBL-producing *E. coli* and *K. pneumoniae* isolates with lower MICs (≤8 μg/mL for cefepime and ≤4 μg/mL for ceftazidime) remain unclear.[2] Similarly, the clinical efficacy of carbapenems for the treatment of infections caused by isolates for which the carbapenem MIC or

disk diffusion test results are within the new intermediate range remains uncertain due to the lack of controlled clinical studies.[3] In Taiwan, ertapenem is widely used for the treatment of infections due to ESBL-producing and multidrug-resistant *Enterobacteriaceae*. Interestingly, an additional 12% of ESBL-producing *K. pneumoniae* isolates were not susceptible to ertapenem (90–78%) and an additional 27% of *Enterobacter cloacae* isolates were not susceptible to ertapenem (96–69%) when the new MIC interpretive breakpoints for carbapenems were applied compared with the old criteria [unpublished data from Study for Monitoring Antimicrobial Resistance Trends (SMART)-2009]. The majority of clinical microbiology laboratories in Taiwan routinely perform screening and confirmatory testing for *Enterobacteriaceae* isolates. Clinicians in Taiwan are familiar with the need for routine reporting of ESBL isolates and all are well trained to prescribe an appropriate and recommended agent (a carbapenem) for the treatment of patients with these infections. Furthermore, some agents, including moxalactam, flomoxef and cefoperazone, are still available in the formulary in many Taiwanese hospitals and are routinely included in susceptibility testing in clinical microbiology laboratories. Although very few laboratories in Taiwanese hospitals routinely perform MHT to screen for KPCs, there are no reports till now to document the presence any KPCs in *Enterobacteriaceae* isolates in Taiwan. Finally, several laboratories in Taiwan use automated instruments, including Vitek II (bioMérieux Vitek, Marcy l'Etoile, France) or Phoenix (Becton Dickinson, Sparks, MD, USA), for susceptibility testing of *Enterobacteriaceae* isolates. The MIC ranges of some antimicrobial agents tested in the antibiotic panels of these instruments (cefazolin and ertapenem in Phoenix and Vitek II; ceftriaxone in Phoenix) are not able to detect susceptible or intermediate isolates when using the new interpretive breakpoints (Tables 2 and 3).[1–3]

The consensus meeting concluded that owing to some subgroups of ESBL-producing isolates that remained susceptible to ceftazidime and cefepime defined by the CLSI 2010 breakpoints, confirmation testing of ESBL phenotypes may still be helpful in monitoring evolving epidemiology and to assist in early implementation of appropriate infection control measures. This situation is especially important in countries (e.g. Taiwan) with a high burden of infections caused by ESBL-producing *Enterobacteriaceae*. The decreased susceptibility to ertapenem of some *Enterobacteriaceae* isolates using the new criteria is alarming, particularly for ESBL-producing *K. pneumoniae* and *E. cloacae*. There is an urgent need to establish the local microbiological and clinical outcome data to support the necessity of implementing these new criteria in Taiwanese clinical microbiology laboratories and in clinical practice to ensure appropriate antimicrobial therapy in the management of infections due to *Enterobacteriaceae*.

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