Effect of applying the new Clinical and Laboratory Standards Institute ticarcillin-clavulanate, piperacillin, piperacillin-tazobactam and imipenem susceptibility breakpoints for *Pseudomonas aeruginosa* in Hong Kong

Pak-Leung Ho*, Kin-Hung Chow, Herman Tse, Vincent C. C. Cheng

Department of Microbiology and Carol Yu Centre for Infection, The University of Hong Kong, Queen Mary hospital, Hong Kong

Correspondence to

Pak-Leung Ho, MD, FRCPath

Department of Microbiology and Carol Yu Centre for Infection, The University of Hong Kong, Queen Mary hospital, Pokfulam Road, Pokfulam, Hong Kong SAR, CHINA.

Tel.: +852-2255 4897; fax: +852-2255 1241.

E-mail address: plho@hkucc.hku.hk

Word count = 568 (excluding references)

Sir,

The CLSI recently published new interpretive criteria for the anti-pseudomonal penicillins and carbapenems for susceptibility testing of *Pseudomonas aeruginosa* [1]. The susceptible breakpoints for piperacillin and piperacillin-tazobactam were lowered from ≥18 mm (piperacillin component, MIC ≤64 μg/ml) to ≥21 mm (MIC ≤16 μg/ml); that for ticarcillin-clavulanate and imipenem were lowered from ≥15 mm (ticarcillin component, ≤64 μg/ml) to ≥24 mm (≤16 μg/ml) and from ≥16 mm (≤4 μg/ml) to ≥19 mm (≤2 μg/ml), respectively [1,2]. Here, the computerized database from January 2009 to December 2011 in a clinical microbiology laboratory for *P. aeruginosa* was used to assess how implementation of the new interpretive criteria would have affected the susceptibility categorization. In the laboratory, the CLSI's disk diffusion method was used routinely for susceptibility testing of bacteria [3].

The results for 11540 *P. aeruginosa* isolates were analysed. Inhibition zone distributions showed that the new susceptibility breakpoints for ticarcillin-clavulanate were close to and larger than the modal value for the bacterial collection. On the other hand, the new susceptibility breakpoints for piperacillin, piperacillin-tazobactam and imipenem remained much smaller than the modal inhibition zone values. The mean (± standard deviation) and mode inhibition zone diameters were as follows: piperacillin, 25.9 (± 5.6) and 28 mm; piperacillin-tazobactam, 26.4 (± 6.6) and 30 mm; ticarcillin-clavulanate, 20.8 (± 5.4) and 22 mm; and imipenem, 25.0 (± 5.5) and 25 mm. Therefore, implementation of the new interpretive criteria (Table 1) would drastically reduce the susceptibility rate for ticarcillin-clavulanate (-49.4%). The changes in the susceptibility rates for the other three agents were modest: piperacillin (-3.5%), piperacilin-tazobactam (-2.8%) and imipenem (-1.8%). To assess the effect of the new interpretive criteria on isolates from different sources, we further analysed the results according four specimen groups (blood, urine, respiratory and other

specimens). At the old interpretive criteria, 83.2-84.1% of the isolates were susceptible to ticarcillin-clavulanate. When the results were interpreted by the new interpretive criteria, the ticarcillin-clavulanate susceptibility rates declined to 26.5-38.0%. The reduction in ticarcillin-clavulanate susceptibility rate was most pronounced for isolates from blood specimens (-56.6%), followed by urine (-55.9%), other specimens (-51.2%) and urine (-45.2%).

We submit that the new CLSI breakpoints for ticarcillin-clavulanate are debatable for several reasons. Firstly, for ticarcillin-clavulanate, the same disc content and virtually the same methodology was recommended by the CLSI and European Committee on Antimicrobial Susceptibility Testing (EUCAST) for testing *P. aeruginosa* [1,4]. According to the EUCAST, the inhibition zone diameter deems to be equivalent to the interpretive breakpoint ≤16 μg/ml (ticarcillin component) is ≥17 mm. At the breakpoint of ≥17 mm, 78.3% of the *P. aeruginosa* in this study would be classified as ticarcillin-clavulanate susceptible. Since the disc contents recommended for testing piperacillin and piperacillin-tazobactam by the CLSI and EUCAST are different, our inhibition zone distributions could not be interpreted by the EUCAST breakpoints. Secondly, it has been argued that susceptibility breakpoints should not be set to cut into the wild type inhibition zone (or MIC) distribution. Otherwise, large number of isolates would be interpreted as resistant and many isolates would shift between different interpretation categories when tested by different laboratories or upon retesting by the same laboratory. In our locality, ticarcillin-clavulanate has been widely used for treatment of various types of *P. aeruginosa* infections and clinical failures are uncommon [5]. Implementation of the new CLSI interpretive criteria would mean that very few *P. aeruginosa* isolates would then remain ticarcillin-clavulanate susceptible and clinicians would be led to prescribe other more expensive anti-pseudomonal antimicrobial agents.

Acknowledgements

The work was supported by research grants from the Research Fund for the Control of Infectious Diseases (RFCID) of the Food and Health Bureau of the Hong Kong SAR Government.

Competing interesting: None to declare.

Ethical approval: Not required.

87 **Table 1.** Comparison of the susceptibility rates for 11540 *P. aeruginosa* to selected antimicrobial agents using the M100-S21 and M100-S22

88 CLSI interpretive criteria

Organism and agent	% Susceptible		% Intermediate		% Resistant		Difference in % susceptible[b]
	CLSI-2011[a]	CLSI-2012[a]	CLSI-2011	CLSI-2012	CLSI-2011	CLSI-2012	
Piperacillin	92.7	89.2	-	5.7	7.3	5.1	-3.5
Piperacillin-tazobactam	93.9	91.1	-	4.4	6.1	4.4	-2.8
Ticarcillin-clavulanate	83.5	34.1	-	19.8	16.5	46.1	-49.4
Imipenem	91.3	89.5	1.1	8.7	7.6	1.7	-1.8

89 [a]According to the interpretive criteria published by the CLSI in January 2011 (M100-S21) [2] and January 2012 (M11-S22) for *P. aeruginosa*.

90 The 2011/**2012 CLSI breakpoints**, i.e. inhibition zone diameters (equivalent MIC), were as follows: piperacillin (with or without tazobactam),

91 susceptible ≥18 mm (≤64 μg/ml)**/≥21 mm (≤16 μg/ml)**; intermediate, none/**15-20 mm (32-64 μg/ml)**; and resistant, ≤17 mm (≥128 μg/ml)/**≤14**

92 **mm (≥128 μg/ml)**; ticarcillin (with or without clavulanate), susceptible, ≥15 mm (≤64 μg/ml)/**≥24 mm (≤16 μg/ml)**; intermediate, none/**16-23**

93 **mm (32-64 μg/ml)**; and resistant, ≤14 mm (≥128 μg/ml)/**≤15 mm (≥128 μg/ml)**; and imipenem, susceptible, ≥16 mm (4 μg/ml)/**≥19 mm (≤2**

94 **μg/ml)**; intermediate, 14-15 mm (8 μg/ml)/**16-18 mm (4 μg/ml)**; resistant, ≤13 mm (≥16 μg/ml)/**≤15 mm (≥8 μg/ml)**.

95 [b]*P* value <0.001 for all comparisons (CLSI 2011 versus 2012).

References

(1) Clinical and Laboratory Standards Institute. Performance standards for antimicrobial susceptibility testing: twenty-two informational supplement. [M100-S22]. 2011. Wayne, Pa, Clinical and Laboratory Standards Institute.

(2) Clinical and Laboratory Standards Institute. Performance standards for antimicrobial susceptibility testing: twenty-first informational supplement. [M100-S21]. 2011. Wayne, Pa, Clinical and Laboratory Standards Institute.

(3) Ho PL, Lai EL, Chow KH, Cheng VC. Effect of applying the new CLSI imipenem susceptibility breakpoints for *Enterobacteriaceae* in Hong Kong. J Antimicrob Chemother 2011; 66:2671-3.

(4) European Committee on Antimicrobial Susceptibility Testing. Breakpoint tables for interpretation of MICs and zone diameters, v2.0. Basel, Switzerland: EUCAST. 2012. http://www.eucast.org/clinical.breakpoints/ [accessed 12 May 2012].

(5) Cheng VC, To KK, Li IW, Tang BS, Chan JF, Kwan S et al. Antimicrobial stewardship program directed at broad-spectrum intravenous antibiotics prescription in a tertiary hospital. Eur J Clin Microbiol Infect Dis 2009; 28:1447-56.