外部精度管理調査における薬剤感受性試験の許容範囲からの逸脱頻度と正確度の統計学的評価に向けた試み

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Statistical Approach to Evaluate the Occurrence of Out-of Acceptable Ranges and Accuracy for Antimicrobial Susceptibility Tests in Inter-Laboratory Quality Control Program

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To evaluate the occurrence of out-of acceptable ranges and accuracy of antimicrobial susceptibility tests, we applied a new statistical tool to the Inter-Laboratory Quality Control Program established by the Kyushu Quality Control Research Group.

First, we defined acceptable ranges of minimum inhibitory concentration(MIC) for broth microdilution tests and inhibitory zone diameter for disk diffusion tests on the basis of Clinical and Laboratory Standards Institute(CLSI) M100-S21. In the analysis, more than two out-of acceptable range results in the 20 tests were considered as not allowable according to the CLSI document. Of the 90 participating laboratories, 46 (51%) experienced one or more occurrences of out-of acceptable range results. Then, a binomial test was applied to each participating laboratory. The results indicated that the occurrences of out-of acceptable range results in the 11 laboratories were significantly higher when compared to the CLSI recommendation (allowable rate ≤ 0.05). The standard deviation indices(SDI) were calculated by using reported results, mean and standard deviation values for the respective antimicrobial agents tested. In the evaluation of accuracy, mean value from each laboratory was statistically compared with zero using a Student's *t*-test. The results revealed that 5 of the 11 above laboratories reported erroneous test results that systematically drifted to the side of resistance.

In conclusion, our statistical approach has enabled us to detect significantly higher occurrences and source of interpretive errors in antimicrobial susceptibility tests; therefore, this approach can provide us with additional information that can improve the accuracy of the test results in clinical microbiology laboratories.

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Table 1 Acceptable MIC ranges and inhibitory zone diameters for quality control and category interpretation criteria defined by the Clinical and Laboratory Standards Institute (CLSI) M100-S21[2)]

Sample	Antimicrobial agent	Lower limits for MIC	Upper limits for MIC	Category interpretation for MIC		
				Susceptible	Intermediate	Resistant
I	Ampicillin	0.5	2	＜0.25		＞0.5
	Erythromycin	0.25	1	≤0.5	1～4	≥ 8
	Linezolid	1	4	≤ 4		≥ 8
	Minocycline	0.06	0.5	≤ 4	8	≥ 16
	Levofloxacin	0.06	0.5	≦ 1	2	≧ 4
II	Ampicillin	0.5	2	≤ 8		≥ 16
	Erythromycin	1	4	≤ 0.5	1～4	≥ 8
	Linezolid	1	4	≤ 2	4	≥ 8
	Minocycline	1	4	≦ 4	8	≧ 16
	Levofloxacin	0.25	2	≤ 2	4	≥ 8
		Maximum limits for disk diffusion	Minimum limits for disk diffusion	Category interpretation for disk diffusion		
				Susceptible	Intermediate	Resistant
III	Ampicillin	35	27	≥ 29		≤ 28
	Erythromycin	30	22	≧ 23	14～22	≦ 13
	Linezolid	32	25	≧ 21		≦ 20
	Minocycline	30	25	≧ 19	15～18	≦ 14
	Levofloxacin	30	25	≧ 19	16～18	≤ 15

Samples I, II and III were *Staphylococcus aureus* ATCC 29213, *Enterococcus faecalis* ATCC 29212 and *S. aureus* ATCC 25923, respectively
Numerical values indicate MICs (μg/ml) for samples I and II, and those for sample III are inhibitory zone diameters (mm).
Refer to reference (2).

Table 2 Classification of laboratories that reported one or more test result(s) out-of acceptable ranges

Test method	Group	Unacceptable, drift to susceptible	Acceptable	Unacceptable, drift to resistant	Not determined	No. of laboratories classified	Binominal test for unacceptable result(s)
Microdilution	A	2[a]	6[a]		2[a]	1	0.0572
	B		6	1[a]	2	1	0.3017
	C		6	1	3	3	0.3017
	D		5	1	3	2	0.2649
	E		5	1	4	7	0.2649
	F		4	1	3	2	0.2262
	G		4	1	5	2	0.2262
	H		3	1	4	2	0.1855
	I		3	1	6	4	0.1855
	J		2	1	2	1	0.1426
	K		2	1	4	2	0.1426
	L		2	1	7	2	0.1426
	M		8	2		1	0.0861
	N		6	2	2	1	0.0572
	O		5	2	3	1	***0.0444***[b]
	P		1	2	7	1	***0.0073***[b]
	Q		4	3	3	1	***0.0038***[b]
	R			1	4	1	0.0500
	S	1	5	1	3	1	***0.0444***[b]
	T	1		1	3	1	***0.0025***[b]
Disk diffusion	A			1		1	0.0500
	B		2	3		1	***0.0012***[b]
	C		3	2		2	***0.0226***[b]
	D		3	1		1	0.1855
	E		4	1		1	0.2262
	F	1	1	3		1	***0.00003***[b]
	G	1		2		1	***0.0001***[b]
	H	1	1	2		1	***0.0005***[b]

[a]Numerical values indicate number of occurrence
[b]Significantly high occurrence when compared to the CLSI allowable ratio (one out of 20).

Table 3 Characterization of laboratories that reported one or more test result(s) out-of acceptable ranges

Test method	Laboratory	Mean	Standard deviation	Degree of freedom	Mean of cumulative interpretations	Source of error[a]
Microdilution	O	2.24	1.78	6	***0.0214***	systematically drifted to resistant
	P	4.57	1.85	2	0.0728	
	Q	2.05	1.73	6	***0.0268***	systematically drifted to resistant
	S	-0.47	2.74	6	0.6914	
	T	1.96	5.88	1	0.7952	
Disk diffusion	B	-2.27	0.73	4	***0.0034***	systematically drifted to resistant
	C1	-2.29	1.17	4	***0.0170***	systematically drifted to resistant
	C2	-1.88	0.85	4	***0.0114***	systematically drifted to resistant
	F	-1.42	2.25	4	0.2752	
	G	-2.19	4.68	2	0.5761	
	H	-1.25	3.82	3	0.6106	

[a]Statistically significant ($p<0.05$) for mean by Student's *t*-test .

Table 4 Statistical analysis for Laboratory Q which experienced systematically drifted errors to resistant

Sample	Antimicrobial agent	Reported MIC value (μg/ml)	log_2-value of MIC	Mean for acceptable ranges	Standard deviation for acceptable ranges	Standard deviation index
I	Ampicillin	4	2	0	0.51	3.92
	Erythromycin	2	1	-1	0.51	3.92
	Linezolid	4	2	1	0.51	1.96
II	Ampicillin	4	2	0	0.51	3.92
	Erythromycin	2	1	1	0.51	0
	Linezolid	2	1	1	0.51	0
	Levofloxacin	1	0	-0.5	0.77	0.65