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연속적인 임상 혈액 배양 양성 검체를 이용한 QMAC-dRAST의 성능 평가

Performance Evaluation of QMAC-dRAST Using Consecutive Positive Clinical Blood Culture Samples

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Background: Bacteremia is life-threatening to patients, with a case fatality rate of 30–40%. The QMAC-dRAST system (QuantaMatrix, Republic of Korea), which is based on time-lapse imaging technology, can generate antimicrobial susceptibility testing (AST) results earlier than conventional equipment. Here, we evaluated the performance of QMAC-dRAST for positive blood culture samples.
Methods: In total, 204 isolates were collected from positive blood cultures, with 104 Gram-positive cocci (GPC) and 100 Gram-negative rods (GNR), including *Staphylococcus* spp., *Enterococcus* spp., *Enterobacteriaceae*, *Pseudomonas aeruginosa*, and *Acinetobacter* spp. Before and after improvement of the AST algorithm, 67 GPC isolates and 72 GNR isolates were tested and their results were compared. In the final test, 37 GPC and 28 GNR were added, and the agreement rates between QMAC-dRAST and Vitek 2 were analyzed using 204 samples. To resolve discrepant AST results between two systems, broth microdilution tests were performed.
Results: In the first and second tests with 67 GPC and 72 GNR, the categorical agreement (CA) between QMAC-dRAST and Vitek 2 was increased from 92.7% and 96.2% to 94.3% and 96.5% by updating the AST algorithm, respectively. For all 204 samples, the agreement rates were 94.5% and 95.4% for CA; 4.8% and 0.6% for very major errors; 2.5% and 2.0% for major errors; and 2.1% and 3.0% for minor errors.
Conclusions: The QMAC-dRAST system has reliable performance and the advantage of faster AST reporting than conventional methods. This system will demonstrate more acceptable agreement rates with conventional AST systems in the future by improving AST algorithms.

Key Words: Antimicrobial susceptibility testing, Blood culture, Bacteremia

INTRODUCTION

Bacteremia is a major cause of morbidity and mortality in patients who receive inadequate antimicrobial treatment [1]. The case fatality rate for bacteremia is 30–40% [2]. In Korea, bacteremia caused by major antimicrobial-resistant pathogens, especially among patients hospitalized in intensive care units, has a high incidence [3, 4]. Furthermore, extended-spectrum β-lactamase-producing *Escherichia coli* and *Klebsiella pneumoniae*, vancomycin-resistant *Enterococcus faecium*, and imipenem-resistant *Acinetobacter baumannii* have been on the rise [5-7].

Rapid antimicrobial susceptibility testing (AST) results are important for the selection of suitable anti-bacterial treatments for bacteremia. The main problem with current AST methods is the long turnaround time (TAT). In most cases, conducting AST requires overnight incubation and usually requires 48–72 hours to complete, depending on the drug–organism combination [8].

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Conventional AST devices such as Vitek 2 (bioMérieux Inc., Marcy l'Etoile, France), MicroScan WalkAway (Beckman Coulter Inc., Carlsbad, CA, USA), and BD Phoenix (BD Diagnostic Systems, Sparks, MD, USA) are now widely used in clinical laboratories, but these systems take at least 8 to 20 hours to produce AST results, not including bacterial incubation and isolation time [9].

Here, we describe a direct & Rapid Antimicrobial Susceptibility Testing (dRAST) system called QMAC-dRAST (QuantaMatrix Inc., Seoul, Republic of Korea) which can shorten TAT to less than 30 hours. This system can process a wide dynamic range of inoculum sizes directly from positive blood culture bottles without measuring inoculum size and without a separation process [10]. QMAC-dRAST is based on a microfluidic system using plastic microchips consisting of micropatterned radial chambers containing an agarose matrix with patient blood samples and satellite wells containing freeze-dried antibiotics at different concentrations. Automatic time-lapse microscopic imaging technology of this system analyzes bacterial microcolony growth in 6 hours directly in the wells [10-13]. Several studies have evaluated the clinical performance of QMAC-dRAST [14-16]. However, previous studies did not show agreement rates classified by bacterial species between other AST systems and QMAC-dRAST. In this study, we evaluated QMAC-dRAST using positive blood culture samples and presented data classified by antimicrobial agents or bacterial species. Also, we checked for changes in AST results made by an updated interpretation algorithm of AST results (AST algorithm).

MATERIALS AND METHODS

1. Specimen collection

Specimens were collected from October 2017 to March 2018 from positive blood culture samples of patients at Severance Hospital, Yonsei University College of Medicine, Seoul, South Korea. This study was approved by the Severance Hospital Institutional Review Board, Seoul, Korea (IRB No.1-2017-0079). The total number of isolates was 204, with 104 Gram-positive cocci (GPC) and 100 Gram-negative rods (GNR), including *Staphylococcus* spp., *Enterococcus* spp., *Enterobacteriaceae*, *Pseudomonas aeruginosa*, and *Acinetobacter* spp. Polymicrobial blood culture samples were excluded from this study. All isolates were identified using the Vitek 2 and matrix-assisted laser desorption/ionization time-of-flight mass spectrometry identification system (Bruker Daltonics Inc., Billerica, MA, USA). These isolates, which had been inoculated in Mueller Hinton broth containing 15% glycerol and stored at -70℃, were cultured in blood agar.

2. Bacteria spiking protocol

For AST using the QMAC-dRAST method, each bacterial colony from blood agar plates was mixed with 1.0 mL of 0.9% saline in a glass tube. Then, a 0.5 McFarland Standard suspension of the tested bacteria was made (approximately 1.5×10^8 CFU/mL). Serial dilution was performed, resulting in a final bacterial concentration of approximately 1.0×10^3 CFU/mL, and 1.0 mL of the final diluted sample was inoculated into a Bact/Alert FA blood culture bottle containing 5.0 mL of sheep blood. A sample from the bottle was taken after the Bact/Alert 3D system (bioMérieux Inc., Marcy l' Etoile, France) detected it as positive and was then tested directly in the QMAC-dRAST system. After the first test with 67 GPC and 72 GNR, the AST algorithm was updated. We reexamined 67 GPC and 72 GNR using the new AST algorithm in the second test. Then, an additional 37 GPC and 28 GNR were tested in the final test.

3. Performance evaluation of the QMAC-dRAST system

We compared the results of QMAC-dRAST with those of Vitek 2. For discrepant AST results between QMAC-dRAST and Vitek 2, broth microdilution (BMD) tests were additionally conducted to resolve discrepancies. Different types of antibiotics were tested for each of the bacteria according to the QMAC-dRAST product panel. The Vitek 2 ASTs were conducted according to the manufacturer's guidelines and BMD tests were performed based on the Clinical and Laboratory Standards Institute (CLSI) guidelines [17].

4. Quality control

For quality control, three GPC strains (*S. aureus* ATCC 29213, *Enterococcus faecalis* ATCC 29212, *E. faecalis* ATCC 51299) and three GNR strains (*Escherichia coli* ATCC 25922, *P. aeruginosa* ATCC 27853, *K. pneumoniae* ATCC 700603) were used for the QMAC-dRAST system and BMD tests. For the Vitek 2 system, three GPC strains (*S. aureus* ATCC 29213, *E. faecalis* ATCC 29212, *E. faecalis* ATCC 51299) and two GNR strains (*E. coli* ATCC 25922 and *P. aeruginosa* ATCC 27853) were used.

5. Data analyses

The isolates were categorized into resistant (R), susceptible (S),

or intermediate (I) groups based on the AST results of Vitek 2 according to the manufacturer's instructions. The concordance of results between QMAC-dRAST and Vitek 2 was determined using categorical agreement (CA, i.e., agreement of results between the test method and the comparator) and essential agreement (EA, i.e., agreement within ±1 two-fold dilution of the test method under evaluation with the comparator minimum inhibitory concentration determination). Discrepant results for the detection of antimicrobial susceptibility were classified as very major errors (VME, i.e., susceptible by the test method vs. resistant by the comparator), major errors (ME, i.e., resistant by the test method vs. susceptible by the comparator), and minor errors (mE, i.e., intermediate by the test method vs. resistant or susceptible by the comparator or *vice versa*) [18]. Data are presented as numbers with percentages for categorical variables.

RESULTS

1. Evaluation of QMAC-dRAST algorithm improvement

In the first test, 67 GPC and 72 GNR were tested and the agreement rates between QMAC-dRAST and Vitek 2 results were analyzed. Discrepant results were found in certain AST cases. Therefore, we updated the AST algorithm. In the second test, ASTs of 67 GPC and 72 GNR were performed again by QMAC-dRAST after AST algorithm improvement. We compared AST results between QMAC-dRAST and Vitek 2 before and after AST algorithm optimization. As a result of the AST algorithm update, tetracycline susceptibility test results for 9 isolates of *Staphylococcus* spp. (4 *S. epidermidis*, 1 *S. haemolyticus*, 2 *S. hominis*, 1 *S. warneri*, and 1 coagulase-negative *staphylococcus* [CoNS]) were corrected. A ME occurred in oxacillin AST results for *S. capitis* and three MEs in

Table 1. Comparison of agreement and discrepancy rates between QMAC-dRAST and Vitek 2* before and after AST algorithm improvement

Bacteria	Before improvement					After improvement				
	No. of AST results	CA (%)	VME (%)	ME (%)	mE (%)	No. of AST results	CA (%)	VME (%)	ME (%)	mE (%)
GPC	618	92.7	6.5	2.7	2.9	618	94.3	5.1	2.4	2.1
GNR	962	96.2	1.2	1.6	2.4	965†	96.5	1.2	1.2	2.4

*To resolve discordant results between QMAC-dRAST and Vitek 2, broth microdilution tests were performed as a reference method.; †Colistin AST results of *Pseudomonas aeruginosa* were added.
Abbreviations: AST, antimicrobial susceptibility testing; CA, categorical agreement; VME, very major error; ME, major error; mE, minor error; GPC, gram-positive cocci; GNR, gram-negative rods.

Table 2. Agreement and discrepancy rates between QMAC-dRAST and Vitek 2* after AST algorithm optimization

Bacterial species	No. of isolates†	No. of AST results	CA (%)	VME (%)	ME (%)	mE (%)
GPC						
Enterococcus faecalis	9 (4)	36	94.4	0.0	3.0	2.8
Enterococcus faecium	22 (11)	88	96.6	1.7	0.0	2.3
Enterococcus spp.	2 (2)	8	100.0	0.0	0.0	0.0
Staphylococcus aureus	23 (2)	253	93.7	12.7	3.0	1.2
Coagulase-negative staphylococci (CoNS)	48 (48)	528	94.5	3.8	2.4	2.5
Total	104 (67)	913	94.5	4.8	2.5	2.1
GNR						
Escherichia coli	33 (33)	462	97.8	1.5	0.6	1.3
Klebsiella pneumoniae	23 (23)	322	99.1	0.0	0.4	0.6
Proteus spp.	6 (2)	84	92.9	0.0	0.0	7.1
Serratia marcescens	4 (2)	56	85.7	0.0	8.3	8.9
Other *Enterobacteriaceae*	9 (3)	140	96.4	0.0	0.0	3.6
Pseudomonas aeruginosa	13 (3)	127	84.3	0.0	9.4	8.7
Acinetobacter baumannii complex	9 (4)	111	94.6	0.0	4.5	2.7
Burkholderia cepacian	3 (2)	12	83.3	0.0	8.3	8.3
Total	100 (72)	1,314	95.4	0.6	2.0	3.0

*For discrepant results between QMAC-dRAST and Vitek 2, broth microdilution test results were used to resolve discrepancies.; †The number of isolates tested in the first test (before the AST algorithm update) are shown in parentheses.
Abbreviations: AST, antimicrobial susceptibility testing; CA, categorical agreement; VME, very major error; ME, major error; mE, minor error; GPC, gram-positive cocci; GNR, gram-negative rods.

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the results for imipenem (1 *Enterobacter cloacae*, 1 *E. coli*, 1 *K. pneumoniae*) were also corrected. For GPC, AST algorithm improvement increased CA from 92.7% to 94.3%, and decreased VME from 6.5% to 5.1% and ME from 2.7% to 2.4%; for GNR, it increased CA from 96.2% to 96.5%, had no effect on VME (1.2%), and decreased ME from 1.6% to 1.2% (Table 1).

2. Performance evaluation of QMAC-dRAST for all samples

In the final test, an additional 37 GPC and 28 GNR were included, so that 104 GPC and 100 GNR were tested after AST algorithm improvement. A total of 913 AST results for QMAC-dRAST with GPC and 1,314 results with GNR were compared with Vitek 2 results. For GPC, the agreement rates were 94.5% for CA, 4.8% for VME, 2.5% for ME, and 2.1% for mE. For GNR, the agreement rates were 95.4% for CA, 0.6% for VME, 2.0% for ME, and 3.0% for mE. Most VMEs in GPC were detected for *S. aureus* and CoNS (Table 2). In vancomycin susceptibility tests, among 17 GPC isolates determined to be resistant, only one (5.9%) *E. faecium* isolate showed a false susceptible result by QMAC-dRAST (Table 3). GNR samples yielded VMEs only in *E. coli* but produced relatively many MEs in some

Table 3. Agreement and discrepancy rates classified by antibiotics between QMAC-dRAST and Vitek 2*

Bacterial species and antimicrobial agents	No. of AST results	EA (%)	CA (%)	VME (%)	ME (%)	mE (%)
GPC						
Ampicillin	33	100.0	100.0	0.0	0.0	0.0
Ciprofloxacin	71	94.4	91.5	5.4	5.9	2.8
Clindamycin	71	95.8	93.0	5.9	0.0	5.6
Erythromycin	71	91.5	88.7	11.8	0.0	5.6
Gentamicin	71	100.0	94.4	0.0	0.0	5.6
Linezolid	104	99.0	99.0	0.0	1.0	0.0
Oxacillin	71	98.6	97.2	2.0	4.5	0.0
Penicillin	104	94.2	93.3	3.4	26.7	0.0
Rifampin	71	98.6	98.6	11.1	0.0	0.0
Tetracycline	71	94.4	94.4	13.6	2.0	0.0
Cotrimoxazole	71	95.8	91.5	4.0	10.9	0.0
Vancomycin	104	95.2	94.2	5.9	0.0	4.8
Total	913	96.3	94.5	4.8	2.5	2.1
GNR						
Amikacin	98	100.0	100.0	0.0	0.0	0.0
Amoxicillin/Clavulanate	76	100.0	97.4	0.0	0.0	2.6
Ampicillin	76	100.0	98.7	0.0	0.0	1.3
Ampicillin/Sulbactam	9	88.9	88.9	0.0	16.7	0.0
Aztreonam	89	97.8	98.9	0.0	1.5	0.0
Cefazolin	76	100.0	92.1	0.0	0.0	7.9
Cefepime	98	94.9	91.8	0.0	2.9	6.1
Cefotaxime	85	96.5	95.3	0.0	3.7	2.4
Ceftazidime	101	93.1	91.1	4.2	5.3	4.0
Ciprofloxacin	98	99.0	95.9	0.0	1.5	3.1
Colistin	17	100.0	82.4	0.0	17.6	0.0
Ertapenem	76	98.7	98.7	0.0	0.0	1.3
Gentamicin	98	100.0	99.0	0.0	0.0	1.0
Imipenem	98	95.9	91.8	0.0	1.3	7.1
Meropenem	22	95.5	95.5	0.0	6.7	0.0
Minocycline	11	100.0	100.0	0.0	0.0	0.0
Piperacillin/Tazobactam	98	94.9	91.8	7.7	1.3	6.1
Cotrimoxazole	88	100.0	97.7	0.0	3.3	0.0
Total	1314	97.7	95.4	0.6	2.0	3.0

*For discordant results between QMAC-dRAST and Vitek 2, broth microdilution tests were performed to resolve such discrepancies.
Abbreviations: AST, antimicrobial susceptibility testing; CA, categorical agreement; VME, very major error; ME, major error; mE, minor error; GPC, gram-positive cocci; GNR, gram-negative rods.

species (Table 2). In GPC, VMEs were found for most of the tested antibiotics except for ampicillin, gentamicin, and linezolid; most MEs were discovered for penicillin and cotrimoxazole. However, in GNR, only ceftazidime and piperacillin/tazobactam produced VMEs, but most antibiotics yielded MEs (Table 3).

DISCUSSION

Presently, four devices are capable of automated AST: Vitek 2, MicroScan WalkAway, BD Phoenix, and Sensititre ARIS 2X (TREK Diagnostic Systems Inc., Westlake, OH, USA). The first three systems generate results within 3.5–16 hours, whereas Sensititre ARIS 2X takes more time on average to report the final results [19]. However, those three faster methods require standardized microbial inoculation and also have the disadvantage of not being able to conduct AST directly with positive blood culture bottles. Samples should be cultured for 24–48 hours or longer before inoculation into the AST system [19-21].

However, QMAC-dRAST reports AST results only by observing changes in bacterial cell shape using microscopic imaging without the need for incubation [10, 12, 13]. Thus, TAT can be reduced by about 24 to 48 hours, reducing the empirical treatment period, which is especially important for major antibiotic-resistant pathogens such as carbapenem-resistant *Enterobacteriaceae*, vancomycin-resistant *enterococci*, and methicillin-resistant *S. aureus* [22-25]. Empirical treatment is often unsuitable for antimicrobial-resistant bacteremia, and the quick delivery of results helps clinicians reduce empirical anti-bacterial drug administration and respond to antimicrobial resistance.

In this study, an older QMAC-dRAST system (software v.1.0.13) was updated to resolve discrepancies. In the new QMAC-dRAST system (software v.1.0.14), the AST algorithm was updated for the following antimicrobial agent-bacterial species combinations: tetracycline-*Staphylococcus* spp., trimethoprim/sulfamethoxazole-*Staphylococcus* spp., and imipenem-GNR.

In the case of GPC, the overall performance of QMAC-dRAST met the criteria for AST in the Food and Drug Administration (FDA) guidelines (e.g. CA ≥90%, VME ≤1.5%, ME ≤3%) [18], except for VME (Table 2). Most VMEs were detected in *S. aureus* and CoNS. Therefore, it is necessary to improve the performance of QMAC-dRAST for *staphylococci*. In a previous study, Huh et al. evaluated the performance of QMAC-dRAST for *staphylococci* [15]. However, since agreement rates for *staphylococci* were presented together with *enterococci* in that study, a direct comparison with our study was not possible.

The overall performance of QMAC-dRAST with GNR met the FDA guidelines described above. Although we detected a small number of VMEs in *E. coli*, there was no VME for commonly used antimicrobial agents such as β-lactam/β-lactamase inhibitor, broad-spectrum cephalosporins, and carbapenem, except for ceftazidime and piperacillin/tazobactam in the case of GNR (Tables 2, 3).

Our study had certain limitations. First, BMD tests were performed only for samples that showed discrepancies between QMAC-dRAST and Vitek 2. In further studies, comparing all tests with BMD as a reference method will be desirable. Second, clinically rare bacterial strains were not included in this study. Therefore, the results of this study may not be applied to some other bacterial strains. More bacterial strains may be required to validate our results. However, the main strength of our study is that we presented the results classified by bacterial species.

In conclusion, the QMAC-dRAST automated system was comparable to Vitek 2 and had the advantage of reporting AST results more rapidly. The concordance of this system with conventional devices is likely to be further improved in the future by updating AST algorithms.

요 약

배경: 균혈증은 치사율이 30-40%에 이르며 환자에게 치명적일 수 있다. 타임 랩스 촬영 기술을 기반으로 한 QMAC-dRAST 시스템(QuantaMatrix, Republic of Korea)은 기존 장비보다 신속하게 항균제 감수성 검사(antimicrobial susceptibility testing, AST) 결과를 보고할 수 있다. 본 연구에서는 양성 임상 혈액 배양 검체에 대한 QMAC-dRAST의 성능을 평가하였다.

방법: 총 204개의 균주가 양성 혈액 배양에서 수집되었고 그 중 104개가 그람양성균, 100개가 그람음성균으로, *Staphylococcus* spp., *Enterococcus* spp., *Enterobacteriaceae*, *Pseudomonas aeruginosa*, 그리고 *Acinetobacter* spp.가 포함되었다. AST 결과 해석 알고리즘(AST 알고리즘) 개선 전후로 67개의 그람양성균과 72개의 그람음성균을 검사하였고 그 결과를 비교하였다. 최종 검사에서는 37개의 그람양성균과 28개의 그람음성균이 추가되었고, 최종적으로 204개의 균주를 이용하여 QMAC-dRAST와 Vitek 2 사이의 일치율을 분석하였다. QMAC-dRAST와 Vitek 2 사이의 불일치 AST 결과를 해결하기 위해, 미량액체배지희석법을 시행하였다.

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결과: 그람양성균 67개와 그람음성균 72개를 이용한 1, 2차 시험에서 AST 알고리즘을 개선한 결과, QMAC-dRAST와 Vitek 2의 categorical agreement가 각각 92.7%, 96.2%에서 94.3%, 96.5%로 증가하였다. 204개의 모든 균주 대상으로는 각각 94.5%, 95.4%의 categorical agreement와, 4.8%, 0.6%의 very major error와, 2.5%, 2.0%의 major error가 관찰되었으며, minor error는 2.1%, 3.0%로 나타났다.

결론: QMAC-dRAST 시스템은 신뢰할 만한 성능과 기존 방법보다 빨리 AST 결과를 보고할 수 있는 장점을 가지고 있다. 이 시스템은 향후 AST 알고리즘을 추가적으로 개선하여 기존 AST 시스템과 더욱 높은 일치율을 보여줄 것이다.

Conflicts of Interest

None declared.

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