

## Original Article



# A Direct Rapid Phenotypic Antimicrobial Susceptibility Test Enables Early Selection of Optimal Antibiotics to Treat Bacteremia in COVID-19 Patients

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## ABSTRACT

**Background:** Co-infection with bacteria and severe acute respiratory syndrome coronavirus 2 may result in greater use of healthcare resources and a poor prognosis. Therefore, early selection and use of optimal antibiotics are essential. The direct rapid antimicrobial susceptibility test (dRAST) can detect antibiotic resistance within 6 h of a Gram smear result. This study aimed to assess the effectiveness of dRAST for improving early selection of appropriate antibiotics for coronavirus disease 2019 (COVID-19) patients with bacteremia.






**Materials and Methods:** This retrospective study included 96 blood culture-positive COVID-19 patients. Bacterial isolates and antimicrobial resistance profiles of each case were evaluated. Cases were divided into two groups based on whether they underwent conventional antibiotic susceptibility test (AST) or dRAST. The time to optimal targeted treatment for the two groups was investigated and compared. In addition, we examined the proportion of cases for which appropriate antibiotics were selected and broad spectrum antibiotics were administered at 72 h from blood sample collection.

**Results:** The mean time to optimal targeted antibiotic treatment was shorter for the dRAST group [55.7; standard deviation (SD), 28.7 *vs.* 92.3; SD, 51.1 h;  $P = 0.041$ ]. The proportion of cases receiving optimal targeted antibiotics 72 h after blood collection for culture was higher [6/10 (60.0%) *vs.* 10/25 (40.0%)] and the percentage receiving broad spectrum antibiotics at 72 h was lower [6/10 (60.0%) *vs.* 19/25 (76.0%)] in the dRAST group than in the conventional AST group. In terms of microbiology profile, the contamination rate was high (35.5%) and multidrug-resistant strains were common (63.2%) in COVID-19 patients with bacteremia.

**Conclusion:** Application of dRAST for selection of antibiotics to treat bacteremia in COVID-19 patients may enable earlier and optimal treatment. The high incidence of contamination and resistant organisms in blood cultures from COVID-19 patients suggest that dRAST may speed up appropriate targeted treatment.

**Keywords:** Rapid phenotypic antimicrobial susceptibility testing; SARS-CoV-2; Bacteremia; Antibiotic resistance

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**Conflict of Interest**

WBP and TSK serve as consultants for QuantaMatrix, Inc. WBP is associate editor of Infection and Chemotherapy, NJK is editorial board of Infection and Chemotherapy; however, he played no role in the selection of peer reviewers, or in the evaluation and decision process. The other authors have no competing interests to declare.

**Author Contributions**

Conceptualization: TSK, WBP. Data curation: DHP, TSK, WBP. Formal analysis: DHP, WBP. Investigation: DHP, WBP. Visualization: DHP, WBP. Writing – original draft: DHP. Writing – review & editing: EC, CKK, PGC, NJK, TSK, WBP, MDO.

**INTRODUCTION**

Coronavirus disease 2019 (COVID-19) is an ongoing pandemic that has, so far, resulted in a large number of positive cases and deaths worldwide [1]. Despite the rollout of several vaccines, many countries are still struggling with ongoing outbreaks. In the midst of the pandemic, medical staff have learned a lot about the disease, and treatments have changed continuously as more evidence emerges from extensive research [2, 3]. In particular, the role of antibiotics for the treatment of COVID-19 has continued to change, and the importance of antimicrobial stewardship is being increasingly emphasized [4].

COVID-19 patients are prone to bacterial co-infection and superinfection, which are related to a poor prognosis and a fatal outcome, similar to other respiratory viruses such as influenza [5-7]. According to previous studies, the overall proportion of secondary bacterial infections in COVID-19 patients was actually low [8], however they were more common in critically ill patients [9]. Therefore, it is important to diagnose and treat combined bacterial infections in severely ill patients with COVID-19. However, a major obstacle to identification of secondary bacterial infection in patients with severe COVID-19 is high levels of blood culture contamination [10-12]. Consequently, patients should be re-evaluated continuously using appropriate culture tests and to assess the probability of co-infection with bacteria [13].

During the pandemic, the majority of COVID-19 patients received antibiotics empirically without evidence of bacterial infection [14]. Most of those patients even received broad spectrum antibiotics unnecessarily [15]. Increased prescription of antibiotics [16] increases the incidence of multidrug-resistant bacteria in critically ill COVID-19 patients, which is a serious medical concern [17, 18] Therefore, it is crucial to use appropriate antibiotics to treat COVID-19 patients based on best current evidence.

The time to diagnosis and treatment of bacteremia was often delayed during the COVID-19 pandemic [19]. Mortality rates in patients with septic shock increase with each hour of delay of administration of antibiotics [20]. Therefore, early diagnosis of bacterial infection and timely administration of appropriate antibiotics are essential. To detect bacteremia early, it is necessary to obtain blood culture results quickly [21]. However, it takes about 3 days to report the results of conventional antibiotic susceptibility tests (AST); this delay in identifying the culprit pathogen leads to unnecessary use of broad spectrum antibiotics.

A novel AST, called the direct rapid antibiotic susceptibility test (dRAST; QuantaMatrix, Inc., Seoul, Korea.), delivers antimicrobial susceptibility test results within 6 h after a Gram smear examination by analyzing changes in the morphology of a single bacterial cell under various antibiotic conditions [22]. dRAST can accelerate administration of optimal antibiotics and reduce use of broad spectrum antibiotics [23, 24]. However, clinical application of dRAST has not yet been established widely, especially during the COVID-19 pandemic. Herein, we assessed the effectiveness of dRAST for improving selection of appropriate antibiotics and the prognosis of COVID-19 patients with bacteremia.

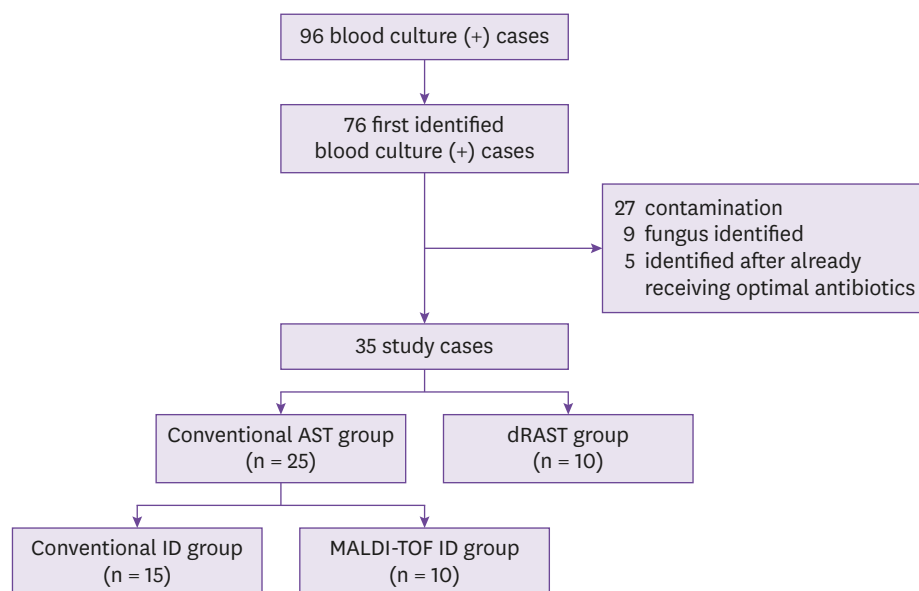
## MATERIALS AND METHODS

### 1. Study design

This was a cross-sectional retrospective study conducted at Seoul National University Hospital (Seoul, Korea), a tertiary hospital with 1,779 beds including 48 nationally designated negative pressure isolation units. Data from all blood culture-positive cases of COVID-19 hospitalized from June 1, 2020 to September 30, 2021 were collected, and 96 blood culture-positive cases were identified among total 1,984 blood culture samples collected during the study period. Of these, 20 cases in which the same bacteria were identified in follow-up blood cultures were excluded (Fig. 1), leaving 76 cases in which bacteria were first identified. Cases with fungemia were excluded because dRAST does not provide information about antifungal resistance. Next, cases considered to be contamination were excluded. Finally, cases that had already received antibiotics appropriate for the identified bacteria at the time of blood collection for culture were excluded. Thus, 35 cases were identified and divided into two groups based on whether they underwent conventional AST or dRAST. The conventional AST group was further subdivided into two groups on the basis of whether they underwent conventional identification (ID) or matrix-assisted laser desorption/ionization time-of-flight (MALDI-TOF) mass spectrometry. There was one case that underwent MALDI-TOF but its identification result was unreliable assigned to conventional ID group.

### 2. Procedures

When a positive blood culture result was notified, medical staff treating COVID-19 patients could request a dRAST with MALDI-TOF or MALDI-TOF only, based on individual judgment. They evaluated the need for obtaining results earlier on basis of clinical factors such as patients' severity. If requested by the primary medical team, blood culture samples were subjected to MALDI-TOF mass spectrometry (Biotyper and Sepsityper kits; Bruker Daltonik GmbH, Bremen, Germany) [25]. Then if ordered, rapid phenotypic AST was performed using the QMAC-dRAST (QuantaMatrix, Inc., Korea), a method based on microscopic



**Figure 1.** Diagram of the study design.

AST, antibiotic susceptibility test; dRAST, direct rapid antibiotic susceptibility test; ID, identification; MALDI-TOF, matrix-assisted laser desorption/ionization time-of-flight.

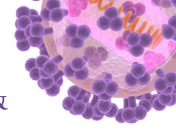


image analysis with microfluidic chip technology [22]. Along with MALDI-TOF, dRAST can determine minimal inhibitory concentrations (MIC) and antimicrobial susceptibility within 6 h after Gram staining. MIC results were interpreted according to the Clinical and Laboratory Standards Institute M100-Ed30, 2020 [26]. Conventional AST used the MicroScan (Beckman Coulter, Inc., Atlanta, GA, USA) for Gram-positive bacteria and the VITEK2 system (bioMérieux, Inc., Durham, NC, USA) for Gram-negative bacteria.

### 3. Outcomes

The effectiveness of dRAST was evaluated by comparing the dRAST and conventional AST groups with respect to the following outcomes: time from blood collection to reporting of AST results; time to optimal targeted antibiotic treatment; proportions of cases receiving optimal targeted antibiotics at 48 and 72 h post blood collection; proportions of cases receiving broad spectrum antibiotics at 72 h post blood collection; amount of major broad spectrum antibiotics (glycopeptide, carbapenem) used within 1 week from blood collection; time to defervescence; and proportion of cases with persistent bacteremia at follow up culture conducted 48 h after a first positive blood culture. In addition, subgroup analysis of the same outcomes comparing conventional ID and MALDI-TOF ID groups was conducted to investigate whether rapid identification rather than rapid AST improves clinical outcomes.

In addition, basic characteristics such as age, sex, Gram stain profile, multidrug resistance of the identified microorganisms, and intensive care unit (ICU) admission of cases in the dRAST and conventional AST groups were evaluated. Bacterial isolates and the antimicrobial resistance profile of all 76 cases with bacteremia were also investigated.

Optimal antibiotics, defined as the most effective antibiotics with the narrowest spectrum, are determined based on antibiotic resistance profile. In this study, multidrug-resistant strains were defined as methicillin-resistant *Staphylococcus aureus*, vancomycin-resistant *Enterococcus* species, and other bacteria resistant to at least one agent in at least three antimicrobial categories [27]. If normal skin flora, including coagulase-negative staphylococci, were identified from only one blood culture bottle, then the case was considered to be contamination [28]. Also, if there was negative conversion in a follow-up blood culture without administration of antibiotics, or if there were no signs of infection, then the case was regarded as contamination.

### 4. Statistical analysis

Counting data were expressed as the number and percentage, and measurement data were expressed as the mean  $\pm$  standard deviation (SD). Comparisons between two groups were performed using two independent-sample *t*-tests and the chi-square test. Data that were nonparametrically distributed were expressed as the median and interquartile range and analyzed using the Mann-Whitney *U*-test and the chi-square test (between-group comparisons). All statistical analyses were conducted using SPSS version 26.0 (SPSS, Inc., Chicago, IL, USA).

### 5. Ethics

This study was approved by the Institutional Review Board of Seoul National University Hospital (IRB No. H-2111-033-1269). The requirement for informed consent was waived by the IRB.

**Table 1.** Baseline characteristics of the study population

| Characteristics        | Conventional AST (n = 25) | dRAST (n = 10)     | P-value |
|------------------------|---------------------------|--------------------|---------|
| Age                    | 73.0 [63.0 - 77.0]        | 73.0 [66.0 - 80.0] | 0.351   |
| Sex                    |                           |                    | 0.123   |
| Male                   | 18 (72.0)                 | 4 (40.0)           |         |
| Female                 | 7 (28.0)                  | 6 (60.0)           |         |
| Organisms              |                           |                    | 0.077   |
| Gram-positive bacteria | 18 (72.0)                 | 4 (40.0)           |         |
| Gram-negative bacteria | 7 (28.0)                  | 6 (60.0)           |         |
| MDRO                   | 19 (76.0)                 | 4 (40.0)           | 0.106   |
| Gram-positive bacteria | 13 (52.0)                 | 1 (10.0)           |         |
| Gram-negative bacteria | 6 (24.0)                  | 3 (30.0)           |         |
| ICU admission          | 19 (76.0)                 | 8 (80.0)           | 0.799   |

Data are presented as the number (%) or median [interquartile range].

P-value was calculated using the Mann-Whitney U-test (continuous variables) or Chi-square test (categorical variables).

AST, antibiotic susceptibility test; dRAST, direct rapid antibiotic susceptibility test; MDRO, multidrug-resistant organisms; ICU, intensive care unit.

## RESULTS

### 1. Baseline characteristics

Of the 35 cases selected, 25 underwent conventional AST and ten underwent dRAST. There were no significant differences between the groups in terms of age, sex, Gram stain profile, multidrug resistance, or ICU admission. (**Table 1**). In the conventional AST group, and in contrast to the dRAST group, Gram-positive bacteria were more common than Gram-negative bacteria; however, the difference was not significant. Also, there was no difference in the proportion of multidrug-resistant bacteria between the two groups.

### 2. Effectiveness of dRAST

The mean time from blood sample collection to optimal targeted antibiotic treatment was shorter for the dRAST group ( $55.7 \pm 28.7$  h) than for the conventional AST group ( $92.3 \pm 51.1$  h;  $P = 0.041$ ). Also, the proportion of cases receiving optimal targeted antibiotics at 72 h after blood collection for culture was higher in the dRAST group than in the AST group [6/10 (60.0%) vs. 10/25 (40.0%), respectively], although the difference was not statistically significant ( $P = 0.454$ ). However, the percentage of cases receiving appropriate antibiotics at 48 h was the same for dRAST (2/10, 20.0%) and conventional AST (5/25, 20.0%) groups.

The proportion of cases receiving broad spectrum antibiotics 72 h after blood collection was lower in the dRAST group than in the AST group [6/10 (60.0%) vs. 19/25 (76.0%), respectively;  $P = 0.421$ ]; again, the difference was not significant. There was no difference between the groups regarding the number of days of broad spectrum antibiotics administration within 7 days of blood sample collection (4.70 for dRAST vs. 4.72 days for AST;  $P = 0.985$ ).

Regarding prognosis, time to defervescence was significantly shorter for the dRAST group ( $1.10 \pm 1.20$  days) than for the conventional AST group ( $3.04 \pm 3.08$  days;  $P = 0.011$ ). However, the proportion of cases with persistent bacteremia was higher in the dRAST group than in the AST group [4/10 (40.0%) vs. 6/25 (24.0%), respectively].

The mean time from blood collection to the AST result was significantly shorter for the dRAST group than in the AST group ( $62.5 \pm 21.6$  vs.  $102.3 \pm 28.8$  h, respectively;  $P = 0.421$ ) (**Table 2**).

**Table 2.** Outcomes of conventional AST versus dRAST for COVID-19 patients with bacteremia

| Outcomes  | Conventional AST (n = 25) | dRAST (n = 10) | P-value             |
|---|---------------------------|----------------|---------------------|
| Time to report AST (h)                            | 102.25 ± 28.82            | 62.48 ± 21.62  | <0.001 <sup>a</sup> |
| Time to optimal targeted antibiotic treatment (h) | 92.30 ± 51.13             | 55.71 ± 28.66  | 0.041 <sup>a</sup>  |
| Optimal targeted antibiotics                      |                           |                |                     |
| 48 h  | 5 (20.0)                  | 2 (20.0)       | >0.999              |
| 72 h  | 10 (40.0)                 | 6 (60.0)       | 0.454               |
| Broad spectrum antibiotics                        |                           |                |                     |
| 72 h  | 19 (76.0)                 | 6 (60.0)       | 0.421               |
| in 7 days (days)                                  | 4.72 ± 2.17               | 4.70 ± 3.02    | 0.985               |
| Time to defervescence (days)                      | 3.04 ± 3.08               | 1.10 ± 1.20    | 0.011 <sup>a</sup>  |
| Persistent bacteremia                             | 6 (24.0)                  | 4 (40.0)       | 0.421               |

Data are presented as the number (%) or as the mean ± standard deviation.

P-value was calculated using the Student's *t*-test (continuous variables) or Chi-square test (categorical variables).

<sup>a</sup>Statistically significant.

AST, antibiotic susceptibility test; dRAST, direct rapid antibiotic susceptibility test.

**Table 3.** Subgroup analysis of outcomes of conventional ID versus MALDI-TOF for COVID-19 patients with bacteremia

| Outcomes  | Conventional ID (n = 15) | MALDI-TOF (n = 10) | P-value            |
|---|--------------------------|--------------------|--------------------|
| Time to report AST (h)                            | 105.3 ± 34.5             | 97.6 ± 18.0        | 0.522              |
| Time to optimal targeted antibiotic treatment (h) | 108.7 ± 58.6             | 67.7 ± 22.7        | 0.024 <sup>a</sup> |
| Optimal targeted antibiotics                      |                          |                    |                    |
| 48 h  | 2 (13.3)                 | 3 (30.0)           | 0.358              |
| 72 h  | 4 (26.7)                 | 6 (60.0)           | 0.122              |
| Broad spectrum antibiotics                        |                          |                    |                    |
| 72 h  | 10 (66.7)                | 9 (90.0)           | 0.345              |
| in 7 days (days)                                  | 5.0 [3.0 – 7.0]          | 4.5 [4.0 – 7.0]    | 0.955              |
| Time to defervescence (days)                      | 1.0 [0.0 – 4.5]          | 3.0 [0.0 – 6.0]    | 0.572              |
| Persistent bacteremia                             | 3 (20.0)                 | 3 (30.0)           | 0.653              |

Data are presented as the number (%) or as the mean ± standard deviation or median [interquartile range].

P-value was calculated using the Student's *t*-test or Mann-Whitney *U*-test (continuous variables) and Chi-square test (categorical variables).

<sup>a</sup>Statistically significant.

ID, identification; MALDI-TOF, matrix-assisted laser desorption/ionization time-of-flight; COVID-19, coronavirus disease 2019.

### 3. Subgroup analysis: MALDI-TOF

Of the 25 cases that underwent conventional AST, 10 underwent MALDI-TOF and fifteen underwent conventional ID. Subgroup analysis of outcomes revealed that the mean time to optimal targeted antibiotic treatment was shorter for the MALDI-TOF group (67.7 ± 22.7 h) than for the conventional ID group (108.7 ± 58.6 h; *P* = 0.024). By contrast, there were no significant differences in other variables (**Table 3**). There was no difference between the two groups with respect to mean time from blood collection to the AST result (97.6 ± 18.0 for MALDI-TOF *vs.* 105.3 ± 34.5 h for conventional ID; *P* = 0.522).

### 4. Epidemiology of bacteremia in COVID-19 patients

Among the 76 cases in which bacteria were first identified, Gram-positive bacteria were isolated in 53 cases, Gram-negative bacteria were detected in 14 cases, and fungus was detected in nine cases (**Table 4**). Coagulase-negative *Staphylococcus*, which was considered to be a contaminant, was most common among the Gram-positive isolates, followed by *Enterococcus* species. The proportion of bacterial isolates which are considered as contamination was as high as 56.6% (30/53) from Gram-positive bacteremia cases. Of the Gram-negative bacterial isolates, *Acinetobacter baumannii* was the most common. The rate of contamination in cases of Gram-negative bacteremia was lower (2/14, 14.3%) than that in cases of Gram-positive bacteremia; however, the rate of multidrug resistance was 71.4% (10/14). Overall, the data show that multidrug-resistant strains were common in COVID-19 patients with bacteremia (48/76, 63.2%).



**Table 4.** Identification of bacteremia in COVID-19 patients

| Organisms                                | Total No. | Contamination No. |
|--|-----------|-------------------|
| Gram-positive bacteremia                 | <b>53</b> | <b>30</b>         |
| <i>Enterococcus</i> spp.                 | 14        | 2                 |
| Vancomycin resistance                    | 10        | 2                 |
| <i>Staphylococcus aureus</i>             | 4         | 1                 |
| Methicillin resistance                   | 1         | 0                 |
| Coagulase-negative <i>Staphylococcus</i> | 30        | 24                |
| Methicillin resistance                   | 27        | 22                |
| <i>Streptococcus</i> spp.                | 1         | 0                 |
| Gram-positive rod                        | 4         | 3                 |
| Gram-negative bacteremia                 | <b>14</b> | <b>2</b>          |
| <i>Escherichia coli</i>                  | 4         | 0                 |
| ESBL production                          | 2         | 0                 |
| <i>Pseudomonas aeruginosa</i>            | 1         | 0                 |
| Carbapenem resistance                    | 1         | 0                 |
| <i>Acinetobacter baumannii</i>           | 7         | 1                 |
| Carbapenem resistance                    | 7         | 1                 |
| <i>Stenophomonas maltophilia</i>         | 1         | 0                 |
| <i>Veillonella parvula</i>               | 1         | 1                 |
| Fungemia                                 | <b>9</b>  | <b>0</b>          |
| <i>Candida</i> spp.                      | 8         | 0                 |
| <i>Cryptococcus neoformans</i>           | 1         | 0                 |

COVID-19, coronavirus disease 2019; ESBL, extended spectrum beta-lactamase.

## DISCUSSION

This study showed that dRAST helps to expedite selection and use of optimal antibiotics to treat COVID-19 patients with bacteremia. We found that dRAST reduced the time to reporting of the results of antibiotic susceptibility tests markedly when compared with conventional AST. The time to administration of optimal targeted antibiotics was remarkably shorter, and the proportion of cases receiving optimal targeted antibiotics used at 72 h after blood collection was higher, for the dRAST group. The time to reporting of results was approximately 40 h shorter than that for conventional AST; dRAST results were reported at an average of 62.5 h post-blood collection. This explains the difference in the proportion of cases receiving optimal antibiotics at 72 h but not at 48 h. In addition, in terms of prognosis, prompt administration of appropriate antibiotics after dRAST showed the benefit of earlier defervescence.

As MALDI-TOF was performed to identify bacteria prior to reporting AST, medical staff were able to predict and administer optimal antibiotics further swiftly. However, as shown in previous studies [29], MALDI-TOF alone was inadequate for resistant organisms. Conducting MALDI-TOF with dRAST is essential for selection of appropriate antibiotics to treat bacterial infections in COVID-19 patients with multidrug resistance. In addition, dRAST with MALDI-TOF further expedites the use of optimal antibiotics (55.7 ± 28.7 h) over MALDI-TOF alone (67.7 ± 22.7 h). Thus, MALDI-TOF with dRAST can speed up selection of proper antibiotics.

The proportion of broad spectrum antibiotics used at 72 h was lower for the dRAST group than for the AST group, although the difference was not statistically significant. Meanwhile, the use of broad spectrum antibiotics over the course of a week was similar for both groups. This is different from the results of previous studies [23], which may be due to the smaller sample size and the higher proportion of multidrug-resistant strains in both groups in this study. This suggests the need for further studies to evaluate the utility of dRAST for reducing use of broad spectrum antibiotics use during a pandemic. Additionally, the proportion

of cases with a positive blood culture 48 h after the initial blood culture was higher in the dRAST group. Further studies should investigate the reason why bacteremia persists despite appropriate antibiotic administration to COVID-19 patients.

In the present study, contamination of blood cultures was common as in previous studies [10-12]. Also, resistant organisms, such as methicillin-resistant coagulase-negative staphylococci and imipenem-resistant *Acinetobacter baumannii*, were identified frequently. High incidence of contamination may be due to procedural difficulties such as blood sampling in isolated wards. This reinforces the importance of antimicrobial stewardship for patients with COVID-19. Multidrug-resistant organisms can be transmitted to other susceptible patients and have the capability to trigger outbreaks in isolation wards [30]. Hence, surveillance of multidrug-resistant organisms and avoidance of unnecessary broad spectrum antibiotics are essential. Fortunately, the dRAST system in ICU setting has been covered since November 2021 by the national medical insurance in Korea. The high incidence of contamination and the presence of resistant organisms in blood cultures from COVID-19 patients mean that dRAST may help antimicrobial stewardship by speeding up differentiation of contaminants and multidrug-resistant bacterial infection.

This study has a few limitations. First, the sample size was small. This is because the frequency of true bacterial infection among patients hospitalized with COVID-19 was relatively low. We could collect 10 cases underwent dRAST during 16 month of the study period. Nonetheless, we could confirm that dRAST accelerated the use of appropriate antibiotics significantly, in spite of the small number of cases. Further research with additional cases is needed to investigate whether we could not find statistical significances due to small sample size. Second, the study was retrospective. However, to the best of our knowledge, this study is the first to report the effectiveness of rapid phenotypic AST for patients with COVID-19, and the results are consistent with those of a randomized controlled study [21]. Finally, the long-term prognostic impact of dRAST was not investigated. Further research is warranted to determine whether application of dRAST improves the long-term prognosis of patients.

In conclusion, application of dRAST for COVID-19 patients with bacteremia may enable earlier selection and use of optimal antibiotics. Considering that contamination and antibiotic resistant bacteria are common in severely ill patients with COVID-19, dRAST may be more helpful during the continuing COVID-19 pandemic.

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