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Original article

Enhanced antimicrobial stewardship based on rapid phenotypic antimicrobial susceptibility testing for bacteraemia in patients with haematological malignancies: a randomized controlled trial☆

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ABSTRACT

Objectives: Recently, rapid phenotypic antimicrobial susceptibility testing (AST) based on microscopic imaging analysis has been developed. The aim of this study was to determine whether implementation of antimicrobial stewardship programmes (ASP) based on rapid phenotypic AST can increase the proportion of patients with haematological malignancies who receive optimal targeted antibiotics during early periods of bacteraemia.

Methods: This randomized controlled trial enrolled patients with haematological malignancies and at least one positive blood culture. Patients were randomly assigned 1:1 to conventional ($n = 60$) or rapid phenotypic ($n = 56$) AST. The primary outcome was the proportion of patients receiving optimal targeted antibiotics 72 hr after blood collection for culture.

Results: The percentage receiving optimal targeted antibiotics at 72 hr was significantly higher in the rapid phenotypic AST group (45/56, 80.4%) than in conventional AST group (34/60, 56.7%) (relative risk (RR) 1.42, 95% confidence interval (CI) 1.09–1.83). The percentage receiving unnecessary broad-spectrum antibiotics at 72 hr was significantly lower (7/26, 12.5% vs 18/60, 30.0%; RR 0.42, 95% CI 0.19–0.92) and the mean time to optimal targeted antibiotic treatment was significantly shorter (38.1, standard deviation (SD) 38.2 vs 72.8, SD 93.0 hr; $p < 0.001$) in the rapid phenotypic AST group. The mean time from blood collection to the AST result was significantly shorter in the rapid phenotypic AST group (48.3, SD 17.6 vs 83.1, SD 22.2 hr).

Discussion: ASP based on rapid phenotypic AST can rapidly optimize antibiotic treatment for bacteraemia in patients with haematological malignancy. Rapid phenotypic AST can improve antimicrobial stewardship in immunocompromised patients. **J.-H. Kim, Clin Microbiol Infect 2020;▪:1**

Introduction

Hospitalized patients with haematological malignancies are at high risk of bacteraemia and sepsis due to various severe immunocompromised conditions, including persistent neutropoenia [1]. Early effective antibiotic treatment is essential because immune deficiency can cause rapid progression of sepsis and mortality [2]. This has led to the initial administration of very broad-spectrum antibiotics, followed by switching to narrower spectrum antibiotics if resistant strains are not isolated

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[3]. This de-escalation strategy, however, may result in unnecessary exposure to broad-spectrum antibiotics of patients, resulting in further acquisition of multidrug-resistant organisms (MDROs) [4–7].

Conventional antimicrobial susceptibility testing (AST) takes about 3 days to produce results, and the presence of resistant organisms cannot be determined during early stages of bacteraemia [8]. Although antimicrobial stewardship programmes (ASPs) promote the use of optimal targeted antibiotics, management of bacteraemia using ASP in immunocompromised patients is complicated and challenging with conventional AST. More timely availability of susceptibility results could allow an application of early, effective ASP for optimal targeted antibiotics.

To overcome the limitations of conventional ASTs, several rapid AST methods, which can be classified into genotypic and phenotypic methods, have been developed. Rapid genotypic AST uses molecular methods such as the polymerase chain reaction for known resistant genes [9,10]. However, the interpretation of the results may be limited because resistance varies temporally or geographically and genetic resistance markers do not always correlate with phenotypic susceptibility [11,12]. More recently, rapid phenotypic AST methods have been developed [13,14]. To our knowledge, no randomized controlled study to date has evaluated the effects of ASP based on rapid phenotypic AST in immunocompromised patients, including those with haematological malignancies.

The primary objective of this study was to determine whether implementation of ASP based on rapid phenotypic AST can increase the proportion of patients with haematological malignancies who receive optimal targeted antibiotics during early periods of bacteraemia.

Materials and methods

Study design and inclusion criteria

We performed a prospective, randomized, controlled, single-centre trial from September 2018 to September 2019 at Seoul National University Hospital, a 1779-bed, tertiary hospital in Seoul, Republic of Korea (ClinicalTrials.gov, registration number NCT03611257). The study protocol was approved by the Institutional Review Board (number 1806-173-955) of Seoul National University Hospital, and written informed consent was obtained from all patients before study participation. A data and safety monitoring board consisting of two unblinded independent infectious diseases (ID) physicians reviewed the safety for study participants and the validity of the trial data every 6 months throughout the study. Prespecified interim analyses were also planned every 6 months during the study. The predefined stopping trial rule was a primary outcome significantly inferior in the intervention group.

Patients aged $\geq$16 years expected to be admitted for more than 2 days for treatment of haematological malignancies, their complications or undergoing haematopoietic stem cell transplantation were screened. Those with at least one confirmed positive blood culture were eligible for this study. After detection of positive signal, Gram stain of positive blood cultures was routinely performed from 9 am to 6 pm. When Gram stain results were confirmed and reported, study investigators approached the patient. Patients were excluded if they were expected to be discharged from the hospital within 2 days of randomization, died or transitioned to hospice care within 24 hr of bacteraemia onset, had fungaemia without evidence of bacteraemia or declined to provide written consent.

Randomization and blinding

Eligible patients were randomly assigned 1:1 to ASP based on conventional AST (control group) or rapid phenotypic AST (intervention group), using a block randomization method with computerized generation of random numbers and a block size of eight. Randomization was performed by independent microbiology laboratory personnel blinded to medical information about individual patients. Because of the nature of the study intervention, blindness was applied until the results of rapid phenotypic AST were reported.

Procedure

Patients in the control group were processed routinely by the staff of the microbiology laboratory. Following positive blood culture, aliquots of samples were subjected directly to matrix-assisted laser desorption/ionization time-of-flight (MALDI-TOF) mass spectrometry (Biotyper and Sepsityper kits; Bruker Daltonik GmbH, Bremen, Germany), performed from Monday to Friday during the day, if requested by the primary medical team [15,16]. As current standard methods for pathogen identification and AST, the MicroScan (Beckman Coulter, Inc., Atlanta, GA) for Gram-positive bacteria and the VITEK2 system (bioMérieux, Inc.) for Gram-negative bacteria were automatically used for colonies isolated on the same day including weekend. Based on the results of Gram staining, pathogen identification and/or AST, appropriate antibiotics were recommended by accredited ID physicians.

Patients in the intervention group were evaluated by rapid phenotypic AST in addition to standard methods. Rapid phenotypic AST was performed using the QMAC-dRAST (QuantaMatrix, Inc., Seoul, Republic of Korea), a method based on microscopic imaging analysis with microfluidic chip technology (Fig. 1) [14]. Coupled with MALDI-TOF, this testing can determine minimal inhibitory concentration and antimicrobial susceptibility ~6 hr after Gram staining. Minimal inhibitory concentration results were interpreted according to the Clinical and Laboratory Standards Institute M100-S28, 2018 [17]. QMAC-dRAST was performed twice daily (10 am and 5 pm) from Monday through Friday and once daily (10 am) on weekends and holidays. The QMAC-dRAST machine automatically conveyed the AST results to ID physicians by text message. The ID physicians contacted the primary medical team and recommended antibiotics based on these results.

Outcomes

The primary outcome was the proportion of patients receiving optimal targeted antibiotics 72 hr after blood sample collection for culture. The prespecified secondary outcomes included (a) the proportion receiving optimal targeted antibiotics at 48 hr, (b) the proportions receiving unnecessary broad-spectrum antibiotics at 48 hr and 72 hr, (c) the proportions receiving ineffective antibiotics at 48 hr and 72 hr, (d) time to optimal targeted treatment (hours), (e) time to defervescence (days), (f) amount of major broad-spectrum antibiotics (glycopeptide, carbapenem) used within 1 week of randomization, (g) the proportion with positive blood culture 48 hr after a first positive blood culture, (h) the proportion infected with *Clostridioides difficile* based on stool testing and/or MDROs based on testing of any clinical specimen collected within 30 days of randomization and (i) bacteraemia-related mortality within 30 days of randomization.

Three independent ID physicians who were unaware of the group assignments determined classification of the antibiotic treatments for each patient by consensus: optimal targeted antibiotic, unnecessary broad-spectrum antibiotic and ineffective

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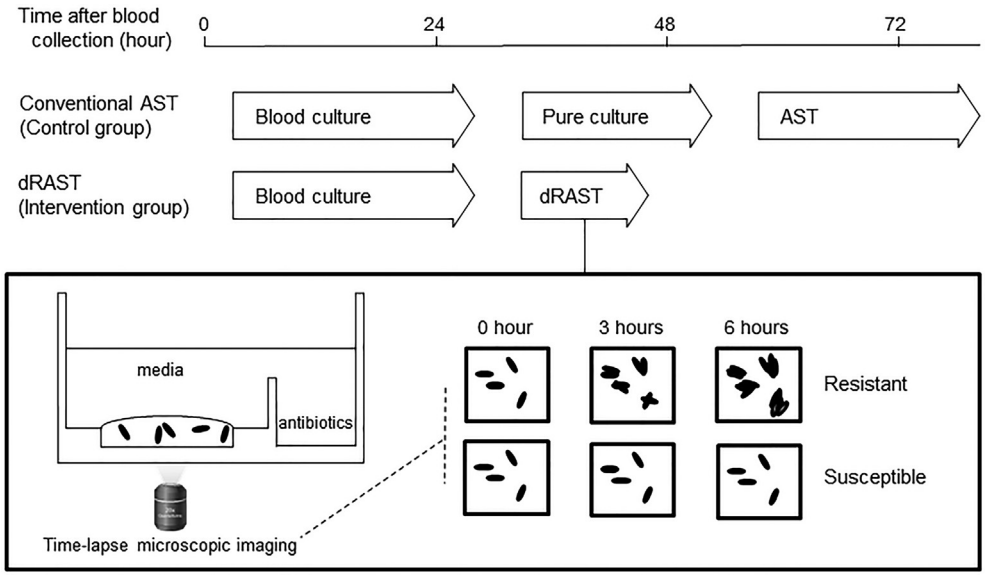

Fig. 1. Process of blood culture in the control and intervention groups. Timeline was adjusted based on actual practice in this study. AST, antimicrobial susceptibility test; dRAST, direct rapid antimicrobial susceptibility testing.

antibiotic treatment, as previously described [18,19]. If the isolate was from only one of the blood culture bottles and suspected to be a contaminant, it was considered optimal not to use an antibiotic against this contaminant.

MDROs include methicillin-resistant *Staphylococcus aureus*, vancomycin-resistant *Enterococcus* species, and other bacteria resistant to at least one agent in at least three antimicrobial categories [20]. Common skin flora, such as coagulase negative staphylococci, *Bacillus* species, *Enterococcus* species and viridans streptococci were considered likely contaminants when isolated from only one blood culture bottle and when the patient did not present clinical features [21].

Susceptibility errors of QMAC-dRAST were determined in reference to the broth microdilution test (BMD), a reference standard method recommended by Clinical and Laboratory Standards Institute [22]. Very major error, defined as false susceptibility according to BMD, could result in ineffective antibiotic treatment. Major error, defined as false resistance, could result in unnecessary treatment with broad-spectrum antibiotics. Minor error, defined as intermediate susceptibility according to QMAC-dRAST and susceptibility or resistance, or vice versa, could result either in unnecessary treatment with broad-spectrum antibiotics or treatment with ineffective antibiotics.

Statistical analysis

A previous simulation study showed that the proportions of patients who could receive optimal targeted antibiotics after the results of Gram stain/MALDI TOF and QMAC-dRAST became available were about 71% and 97%, respectively [18]. Assuming that 60% of patients in the control group and 85% of those in the intervention group would receive optimal targeted antibiotics, respectively, based on the compliance of the primary medical team with antibiotic de-escalation, 116 patients would be needed to achieve 80% power with a one-sided alpha error of 0.05, allowing for 15% dropout.

Primary and secondary outcomes were assessed in the intention-to-treat (ITT) population, which included all randomized patients who met inclusion and exclusion criteria, and in the per protocol population, which included all patients in the ITT population excepting those in whom MALDI-TOF analysis failed to identify the pathogen or those infected with QMAC-dRAST off-panel strains (*Streptococcus* species and Gram-positive bacilli). Baseline comparison of categorical variables between the two groups was performed using Pearson's chi-square test or Fisher's exact test. Baseline comparison of continuous variables was done using Student's t test. Unadjusted relative risk (RR) and 95% confidence intervals (CI) for the primary and secondary outcomes were determined. Major broad-spectrum antibiotics (glycopeptide, carbapenem) use was compared in the intervention and control groups as days of therapy (DOT) per 1000 patient-days [23,24]. Time-to-event data were evaluated by the Kaplan–Meier method and compared using the log-rank test. All tests of significance were two-sided except for the comparison of the primary outcome, which was one-sided. All statistical analyses were performed using STATA, version 15.0 (StataCorp LP, College Station, TX), and $p < 0.05$ was considered statistically significant.

Results

Patients

Of the 266 patients screened for eligibility during the trial period, 116 with confirmed positive blood cultures were selected and randomized, 60 to the control group and 56 to the intervention group (ITT population, Fig 2). After excluding two patients in the intervention group in whom pathogen could not be identified by MALDI-TOF analysis, and 25 patients with QMAC-dRAST off-panel strains (13 in the control group and 12 in the intervention group), 89 patients were included in the per protocol population.

The baseline characteristics of the two groups were generally balanced (Table 1). Mean time from blood sample collection to reporting AST results was significantly shorter in the intervention (48.3, standard deviation (SD) 17.6 hr) than in the control (83.1, SD 22.2 hr) group ($p < 0.001$, Table 1). MALDI-TOF analysis identified the organism in positive blood cultures from 75 of 77 (97.4%) patients, including 21 of 21 (100%) in the control group and 54 of 56 (96.4%) in the intervention group. The most frequently identified

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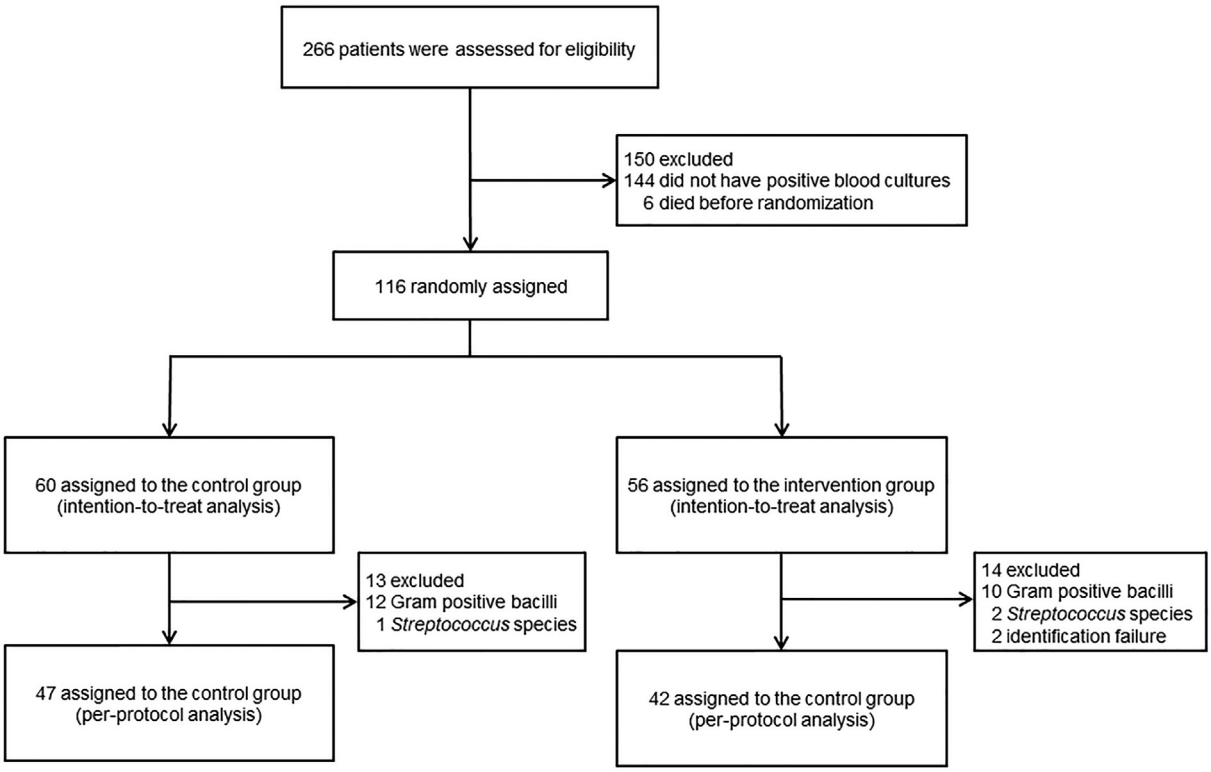

Fig. 2. Study profile.

organism was *Escherichia coli* (21.6%), followed by *Enterococcus* spp. (19.8%) and coagulase-negative staphylococci (12.9%) (Table S1).

Primary outcome

The proportion of patients receiving optimal targeted antibiotics 72 hr after blood collection for culture was significantly higher in the intervention (45/56, 80.4%) than in the control (34/60, 56.7%) group (RR 1.42, 95% CI 1.09–1.83; p 0.004; Table 2). Seven patients (7/56, 12.5%) in the intervention group were exposed to unnecessary broad-spectrum antibiotics, six because their primary medical teams did not adhere to the ASP regarding early de-escalation, and one due to exposure to unnecessary carbapenem because of a major error with QMAC-dRAST in regard to piperacillin/tazobactam susceptibility of *Pseudomonas aeruginosa*. Four patients (4/56, 7.1%) in the intervention group were treated with ineffective antibiotics, three because the time to blood culture positivity was >72 hr, with all three found to be infected with vancomycin-resistant *E. faecium*. The fourth patient, infected with *P. aeruginosa* bacteraemia, was assessed as receiving ineffective antibiotic treatment (piperacillin/tazobactam, intermediate susceptibility in QMAC-dRAST), which finally revealed piperacillin/tazobactam resistance in standard AST and BMD test.

Secondary outcomes

The proportion of ITT patients receiving optimal targeted antibiotics 48 hr after blood sample collection for culture tended to be higher in the intervention than in the control group (37/56, 66.1% vs 29/60, 48.3%; RR 1.36, 95% CI 0.99–1.88; p 0.057; Table 2). In per protocol analysis, similar result was shown (29/42, 69.1% vs 23/47, 48.9%; RR 1.42, 95% CI 0.99–2.01; p 0.058; Table S2).

The proportion of patients receiving unnecessary broad-spectrum antibiotics 72 hr after blood collection for culture was significantly lower in the intervention than in the control group (7/56, 12.5% vs 18/60, 30.0%; RR 0.42, 95% CI 0.19–0.92; p 0.031; Table 2), although a significant difference was not observed 48 hr after blood collection.

The proportions of patients receiving ineffective antibiotics 48 and 72 hr after blood collection, the proportions of positive blood cultures 48 hr after initial blood culture and the proportions infected with *C. difficile* or MDROs 30 days after enrolment tended to be lower in the intervention group than in the control group, which were not statistically significant. The 30-day bacteraemia-related mortality rate did not differ between the two groups. Per protocol analysis yielded similar results (Table S2).

Mean time from blood sample collection to optimal targeted antibiotic therapy was significantly shorter in the intervention than in the control group (38.2, SD 38.2 vs 72.8, SD 93.0 hr; $p < 0.001$). After excluding time before the first report of positivity, a factor unrelated to the effect of the intervention, this difference between two groups remained significant (20.4 vs 51.3 hr; $p < 0.001$; Fig 3), although mean time to defervescence did not differ significantly (5.7 vs 6.1 days; p 0.766; Fig. S1). Within 7 days of blood sample collection, glycopeptide administration was significantly greater in the control than in the intervention group (421.4 vs 234.7 DOT/1000 patient-days; p 0.015), although carbapenem administration did not differ significantly in the two groups (454.8 vs 359.7 DOT/

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Table 1
Baseline characteristics of the study population

	Control group ($n = 60$)	Intervention group ($n = 56$)
Age, median (IQR)	57 (43–63)	56 (41–64)
Male sex	30 (50.0)	30 (53.6)
Charlson Comorbidity Index, median (IQR)	2 (2–7)	2 (2–3)
Haematological disease		
Acute leukaemia	38 (63.3)	39 (69.6)
Myeloid	31 (51.7)	26 (46.4)
Lymphoblastic	7 (11.6)	10 (17.9)
Mixed type	0	3 (5.3)
Lymphoma	10 (16.7)	11 (19.6)
Myelodysplastic syndrome	6 (10.0)	2 (3.6)
Multiple myeloma	4 (6.7)	2 (3.6)
Other disease[a]	2 (3.3)	2 (3.6)
Haematological treatment		
Chemotherapy	41 (68.3)	36 (64.3)
Allogeneic HSCT	10 (16.7)	9 (16.1)
Autologous HSCT	3 (5.0)	5 (8.9)
Other[b]	6 (10.0)	6 (10.7)
Neutropoenia (ANC/mm^3)		
<100	47 (78.3)	39 (69.6)
<500	52 (86.7)	41 (73.2)
Days hospitalized before randomization, median (IQR)	19 (14–27)	18 (14–27)
Time to culture positivity (hours), mean ± SD	26.4 ± 16.8	28.0 ± 16.5
Time to AST report (hours), mean ± SD	83.1 ± 22.2	48.3 ± 17.6
Organisms		
Gram-positive bacteria	32 (53.3)	30 (53.6)
Gram-negative bacteria	24 (40.0)	25 (44.6)
Polymicrobial infection	4 (6.7)	1 (1.8)
MDRO	32 (53.3)	25 (44.6)
Gram-positive bacteria	19 (31.7)	17 (30.3)
Gram-negative bacteria	9 (15.0)	8 (14.3)
Polymicrobial infection	4 (6.6)	0
Likely contaminant	7 (11.7)	11 (19.6)
Pitt bacteraemia score, mean ± SD	1.0 ± 1.3	0.9 ± 1.1
Requiring vasopressor	9 (15.0)	7 (12.5)
ICU admission	1 (1.7)	3 (5.4)

Data are presented as *n* (%), unless otherwise specified. There were no significant differences between two groups with the exception of time to AST reports ($p < 0.001$). IQR, interquartile range; ANC, absolute neutrophil count; AST, antimicrobial susceptibility test; HSCT, haematopoietic stem cell transplantation; ICU, intensive care unit; MDRO, multidrug-resistant organism. SD, standard deviation.

[a] Including one patient each with aplastic anaemia and chronic myeloid leukaemia in the control group and one patient each with chronic myeloid leukaemia and mixed germ cell tumour in the intervention group.

[b] Including general supportive care ($n = 3$), immunosuppressive therapy for graft-versus-host disease ($n = 2$), and infection control ($n = 1$) in the control group, and general supportive care ($n = 2$), immunosuppressive therapy for graft-versus-host disease ($n = 2$), and infection control ($n = 2$) in the intervention group.

1000 patient-days; p 0.406). Per protocol analysis yielded similar results (data not shown).

Discussion

This prospective trial showed that implementation of ASP based on rapid phenotypic AST significantly increased the proportion of patients with haematological malignancies who received optimal targeted antibiotic treatment during the early period of bacteraemia. This intervention may be effective as early as ~48 hr after blood collection for culture, the average time from blood collection to the rapid phenotypic AST report. Unnecessary broad-spectrum antibiotics were administered less frequently and consumption of broad-spectrum antibiotics such as glycopeptides was reduced in the intervention group.

Regarding our primary outcome, the reduction of unnecessary broad-spectrum antibiotic administration contributed significantly to the high proportion of optimal targeted antibiotic treatment in the intervention group. Broad-spectrum antibiotics may be overused after 72 hr in patients with haematological malignancies because of concerns that ineffective treatment of bacteraemia could leave these patients at risk for severe, potentially life-threatening complications. Clinicians may have been reluctant to follow ASP recommendations of antibiotic de-escalation, if ASPs driven by ID physicians were provided without AST results. Furthermore, many clinicians prefer measures such as antibiotic escalation or add-on recommendations to restrictive recommendations [25]. Our study findings suggest that timely intervention with rapid phenotypic AST helps the primary medical team to make earlier decisions for de-escalation. This intervention might contribute to reduce antibiotic selection pressure in this high-risk population, although a significant decrease in further colonization by MDROs was not shown in our study.

Nevertheless, in our study, about 10% of patients remained on unnecessary broad-spectrum antibiotic treatment in the intervention group. The level of an ASP as active messenger and educator of results may determine the impact of rapid phenotypic AST on appropriateness of antibiotic treatment. Previous studies suggest that the introduction of rapid diagnostic testing alone without ASP does not provide the same benefit as with ASP [26,27]. More effective communication strategies between the ASP team and the primary medical team are essential to maximize utility of rapid microbiological tests.

We found that antibiotic prescription based on QMAC-dRAST was generally safe and significantly reduced time from blood culture collection to AST compared with current standard methods. Discrepancies in antibiotic prescription, which occurred due to differences between QMAC-dRAST and current standard methods results, were few, although there was a need for improving

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Table 2
Comparison of primary and secondary outcomes in the control and intervention groups

	Control group	Intervention group	Relative risk (95% CI)	p
Primary outcome				
Optimal targeted antibiotics (72 hr)				
Intention-to-treat analysis	34/60 (56.7)	45/56 (80.4)	1.42 (1.09–1.83)	0.004
Per protocol analysis	27/47 (57.5)	34/42 (81.0)	1.40 (1.06–1.86)	0.010
Secondary outcome[a]				
Optimal targeted antibiotics (48 hr)	29 (48.3)	37 (66.1)	1.36 (0.99–1.88)	0.057
Unnecessary broad-spectrum antibiotics (48 hr)	19 (31.7)	12 (21.4)	0.68 (0.36–1.26)	0.220
Unnecessary broad-spectrum antibiotics (72 hr)	18 (30.0)	7 (12.5)	0.42 (0.19–0.92)	0.031
Ineffective antibiotics (48 hr)	12 (20.0)	7 (12.5)	0.63 (0.26–1.47)	0.283
Ineffective antibiotics (72 hr)	8 (13.3)	4 (7.1)	0.53 (0.17–1.68)	0.285
Persistent bacteraemia[b]	10 (16.7)	6 (10.7)	0.64 (0.25–1.65)	0.359
Acquisition of *C. difficile* or multidrug-resistant organisms within 30 days after enrolment[c]	11 (18.3)	7 (12.5)	0.68 (0.28–1.64)	0.391
30-day bacteraemia-related mortality	3 (5.0)	3 (5.4)	1.07 (0.23–5.10)	0.931

CI, confidence interval.
[a] Based on intention-to-treat analysis.
[b] Defined as positive blood culture 48 hr after initial positive blood culture.
[c] Including vancomycin-resistant *Enterococcus faecium* ($n = 7$), *C. difficile* ($n = 2$), MRSA ($n = 1$), and carbapenem-resistant *Enterobacteriaceae* ($n = 1$) in the control group, and vancomycin-resistant *Enterococcus faecium* ($n = 4$), *C. difficile* ($n = 1$), multidrug-resistant *Acinetobacter baumannii* ($n = 1$), and extended spectrum β-lactamase-producing *Enterobacteriaceae* ($n = 1$) in the intervention group.

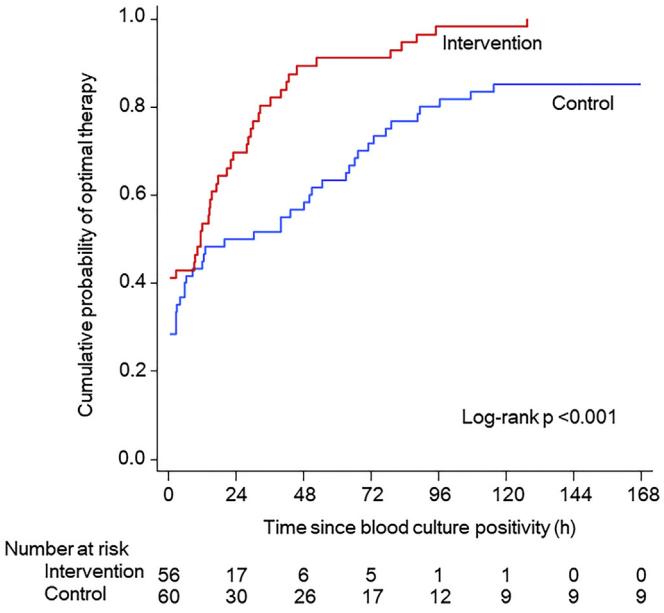

Fig. 3. Kaplan–Meier estimates of the time from blood culture positivity to optimal targeted antibiotic therapy.

performance of the test regarding non-fermenters such as *P. aeruginosa*. While our previous simulation study reported that QMAC-dRAST reduced the time to AST by about 50 hr [19], our time saving were smaller, with 35 hr for time to AST report. Compared with the current standard method which was performed as a standardized automated system whenever the pure culture step was completed, QMAC-dRAST was performed only twice on working days and once at weekends and holidays. This might partly explain the time saving-difference between studies.

The introduction of rapid phenotypic AST did not reduce bacteraemia-related mortality rates. Similar to our findings, a quasi-experimental study using rapid phenotypic AST reported no difference in mortality [28]. By contrast, a meta-analysis reported that the combination of ASP and rapid molecular diagnostic testing reduce mortality risk [29]. Besides the fact that this study was not designed to investigate the impact of rapid phenotypic AST on mortality, several factors might explain these differences among studies. First, medical conditions and underlying diseases can affect mortality. In the present study, uncontrolled haematological malignancy and bacteraemia could have contributed to mortality. Second, the rate of infection with carbapenem-resistant organisms was low in this study. The probability of treatment with appropriate antibiotics during the early period of bacteraemia may be lower in patients infected with antibiotic-resistant than with antibiotic-susceptible organisms [18].

The present study has a few limitations. First, it was a single-centre trial, which may reduce the applicability of study findings to other settings. Second, subjects and investigators could not be blinded to group allocation after rapid AST results became available. However, the rapid increase in the proportion of control patients receiving optimal targeted antibiotic treatment at around 83 hr after blood collection (the average turnaround time of conventional AST) suggests that ASP was as effective in the control group as in the intervention group. Finally, testing systems vary in capacity, and other factors such as the impact of other rapid phenotypic AST systems or rapid genotypic method on patients with haematological malignancy could not be determined. For example, the Accelerate Pheno™ system, as a rapid phenotypic AST, has the advantage that identification test can be performed simultaneously on one device, but allows for a single susceptibility test run per instrument [28]. QMAC-dRAST allows for multiple susceptibility tests run per instrument, but QMAC-dRAST does not have a pathogen identification function, so it must be used in conjunction with another modality such as MALDI-TOF [14]. For EUCAST rapid AST, since the area of technical uncertainty of approximately 2–5 mm is included in the interpretation criteria, even if tests are conducted for various antimicrobials, the reportable number of antimicrobials can be very small and currently the method is validated for only seven strains (*E. coli*, *K. pneumoniae*, *P. aeruginosa*, *S. aureus*, *E. faecalis*, *E. faecium* and *S. pneumoniae*) [30]. Rapid genotypic methods, such as Verigene and BioFire, could allow shorter total turnaround times than rapid phenotypic method, at the same time maintaining reliable performance. However, the interpretation of genotypic method results may be difficult by the complexity of resistance mechanisms, and the absence of resistance genes might not always ensure safe antibiotic de-escalation decision making with different local epidemiology [31,32].

In conclusion, ASP based on rapid phenotypic AST can optimize antibiotic treatment of bacteraemia more rapidly in patients with haematological malignancy. These findings suggest that rapid

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phenotypic AST can improve antimicrobial stewardship in immunocompromised patients.

Author contributions

W.B.P. conceptualized and participated in the design of the study. The datasets used and/or analysed during this study are available from W.B.P (wbpark1@snu.ac.kr). on reasonable request. T.S.K. conceptualized the design of the microbiological analyses and contributed to the study design. J.H.K. contributed to study design; performed the data analysis; planned the statistical analysis; drafted the initial manuscript; and revised subsequent drafts. I.K. contributed to the study design for haematological malignancies; reviewed results of data analysis; and reviewed and revised the manuscript. C.K.K., K.I.J., S.H.Y., J.Y.C., J.J., Y.J.K., D.Y.K., H.B.J., D.Y.K., Y.K., D.Y.S., J.H., N.J.K., S.S.Y. and M.d.O. participated in data collection and interpretation. All authors read and approved the final manuscript for submission.

Transparency declaration

W.B.P. and T.S.K. serve as consultants for QuantaMatrix, Inc. None of the other authors has any competing interests. This work was supported by the Korean Health Technology R&D Project, Ministry of Health & Welfare, Republic of Korea (Grants No. HI13C-1468), Seoul National University Hospital Research Fund (Grants No. 03-2018-0370) and QuantaMatrix Inc.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.cmi.2020.03.038.

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