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Interim analysis: Randomized controlled trial for the effect of rapid phenotypic antimicrobial susceptibility testing on antimicrobial stewardship in hematologic patients with positive blood culture

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Revised abstract

BACKGROUND

In patients with hematologic diseases, treatment- or disease-related neutropenia frequently develops, which can easily cause bacteremia. Timely appropriate antibiotic treatment is crucial for bacteremia, but, caution is also needed to prevent overuse of broad-spectrum antibiotics. Antimicrobial stewardship regarding optimal targeted antibiotics in this high risk group is difficult and complicated. We investigated whether implementation of antimicrobial stewardship using rapid phenotypic antimicrobial susceptibility test (AST) could increase the proportion of patients with hematologic disease who received optimal targeted antibiotics in early period of bacteremia.

METHODS

We have been performing a randomized, controlled, assessor blind, single center trial for patients with hematologic diseases at the Seoul National University Hospital (ClinicalTrials.gov, registration number NCT03611257). Patients with confirmed positive blood culture were randomly assigned at a 1:1 ratio into two groups. Patients in the control group were managed according to antimicrobial stewardship with standard AST. In the intervention group, antimicrobial stewardship using rapid phenotypic AST (QMAC-dRAST) was applied. The primary outcome was the proportion of patients receiving optimal targeted antibiotics 72 hours after blood collection for culture. The secondary outcomes included the proportion of patients receiving optimal targeted antibiotics 48 hours after blood collection for culture. In the present interim analysis, primary and secondary outcome were assessed in the intention-to-treat analysis.

RESULTS

Between Sep 1, 2018, and June 10, 2019, 86 patients with confirmed positive blood cultures were randomly assigned to the control group (n=44) or intervention group (n=42). Mean time from collecting blood culture to reporting AST result was significantly shorter in the intervention group (49.9 hours) than in the control group (81.2 hours) ($P < 0.001$). The proportion of patients receiving optimal targeted antibiotics 72 hours after blood culture collection was in 26 of 44 (59.1%) patients in the control group, in 33 of 42 (78.6%) patients in the intervention group (odds ratio 2.53; 95% CI, 0.98-6.57; $P = 0.055$). The proportion of patients receiving optimal targeted antibiotics at 48 hours was 52.3% (23 of 44 patients) in the control group and 73.8% (31 of 42 patients) in the intervention group (odds ratio 2.57; 95% CI, 1.04-6.37; p=0.041).

CONCLUSION

The antimicrobial stewardship using rapid phenotypic AST may be more useful than that with standard AST for inducing optimal targeted antibiotic use in early period of bacteremia in patients with hematologic diseases.

Introduction

- Treatment- or disease-related neutropenia frequently develops in patients with hematologic diseases, which are commonly related with bacteremia.
- Timely appropriate antibiotic treatment is crucial for bacteremia treatment. However, empirical treatments might fail in the era of increasing prevalence of multidrug resistant organisms (MDROs).
- Caution is also needed at decision of broad-spectrum antibiotics administration in uncomplicated clinical situation, because of possible additional acquisition of MDROs by exposure to broad-spectrum antibiotics.
- Antimicrobial stewardship regarding optimal targeted antibiotics in this high risk patient group is difficult and complicated.
- To our knowledge, there is no randomized controlled study showing whether rapid phenotypic AST can help antibiotic stewardship in selecting appropriate antibiotics in patients with hematologic diseases.

We conducted this randomized, controlled trial to investigate whether implementation of rapid phenotypic AST in clinical practice could increase the proportion of patients with hematologic disease who received optimal targeted antibiotics in early period of bacteremia.

Methods

Study subject

- The prospective randomization controlled study was performed in Seoul National University of Hospital in South Korea, and has been conducted since Sep. 2018.
- Patients who (1) were aged ≥ 16 years and (2) were expected to be admitted for more than 2 days for treatment of hematologic disease, and (3) had positive blood culture during hospitalization were eligible for this study.

Randomization

- Eligible patients were randomly assigned in a 1:1 ratio either to the control group (standard AST method), or to the intervention group (rapid phenotypic AST; QMAC-dRAST) using computerized block (n=8) randomization.

Procedure

- The control group: Standard ID and AST using Vitek2 or Microscan were done, but MALDI-TOF results were informed if requested.
- The intervention group: Results of MALDI-TOF and QMAC-dRAST were transferred automatically to ID specialists by phone text message.
- The both group: ID specialists did antimicrobial stewardship based on the results of the standard or rapid phenotypic AST for each group, respectively.

Primary outcome

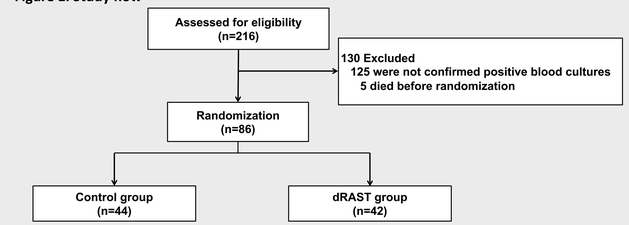
- The proportion of patients receiving optimal targeted antibiotics 72 hours after blood collection for culture

Secondary outcomes

- The proportion of patients receiving optimal targeted antibiotics 48 hours after blood collection for culture
- The proportion of patients receiving ineffective antibiotics 48 and 72 hours after blood culture collection
- The proportion of patients receiving unnecessary broad-spectrum antibiotics 48 and 72 hours after blood culture collection

Results

Figure 1. Study flow



- Between Sep 1, 2018, and June 10, 2019, 216 patients were screened for eligibility. Of them, 86 patients with confirmed positive blood cultures were randomly assigned into **control group (n=44) or intervention group (n=42)**.

Table 1. Baseline characteristics of study population at randomization

	Control group (n=44)	Intervention group (n=42)	P-value
Age, median (range)	56 (17-85)	57 (18-83)	0.883
Sex, male, n (%)	24 (54.6)	22 (52.4)	0.841
Charlson comorbidity score, median (range)	2 (2-9)	2 (2-8)	0.292
Underlying hematologic disease			0.855
Acute myeloid leukemia, n (%)	26 (59.1)	21 (50.0)	
Acute lymphoid leukemia, n (%)	5 (11.4)	6 (14.3)	
Lymphoma, n (%)	5 (11.4)	7 (16.7)	
Other, n (%)	8 (18.1)	8 (19.0)	
Hospitalization day before randomization (day), mean ± SD (range)	20±16 (0-94)	27±27 (0-142)	0.148
Time to culture positivity (hour), mean ± SD (range)	26.3±14.4 (10.7-75.6)	30.3±18.0 (9.6-76.9)	0.267
Time to AST report (hour), mean ± SD (range)	81.2±21.5 (53.3-141.5)	49.9±18.2 (24.9-98.0)	< 0.001
Pathogen			0.415
Gram negative bacteria	18 (40.9)	19 (45.2)	
Gram positive bacteria	24 (54.6)	23 (54.7)	
Polymicrobial infection	2 (4.5)	0	
MDR pathogen, n (%)	23 (52.3)	22 (52.4)	0.992
Likely contaminant, n (%)	5 (11.4)	10 (23.8)	0.128
Profound neutropenia, n (%)	37 (88.1)	33 (80.5)	0.340
Septic shock, n (%)	8 (18.2)	8 (19.1)	0.918
ICU admission, n (%)	1 (2.3)	3 (7.1)	0.284

- Generally, the two groups were balanced with regard to baseline characteristics
- Mean time from blood culture collection to AST result reporting was significantly shorter **in the intervention group (49.9 hours) than in the control group (81.2 hours) ($P < 0.001$)**.

Table 2. Comparison of primary and secondary outcome between the groups

Outcomes	Control group	Intervention group	Odds ratio	95% CI (P-value)
Patients receiving optimal targeted antibiotics (72 hours)	26/44 (59.1)	33/42 (78.6)	2.53	0.98-6.57 (0.055)
Patients receiving optimal targeted antibiotics (48 hours)	23/44 (52.3)	31/42 (73.8)	2.57	1.04-6.37 (0.041)
Patients receiving ineffective antibiotics (48 hours)	8/44 (18.2)	3/42 (7.1)	0.35	0.09-1.41 (0.138)
Patients receiving ineffective antibiotics (72 hours)	4/44 (9.1)	3/42 (7.1)	0.77	0.16-3.66 (0.742)
Patients receiving unnecessary broad spectrum antibiotics (48 hours)	13/44 (29.6)	8/42 (19.1)	0.56	0.21-1.53 (0.260)
Patients receiving unnecessary broad spectrum antibiotics (72 hours)	14/44 (31.8)	6/42 (14.3)	0.36	0.12-1.04 (0.060)

- Proportion of patients receiving optimal targeted antibiotics 72 hours after blood collection for culture was in **59.1% (26 of 44 patients) in the control group, and in 78.6% (33 of 42 patients) in the intervention group (odds ratio 2.53; 95% CI, 0.98-6.57; $P = 0.055$)**.
- Of patients who did not meet primary outcome in the intervention group, six patients were received unnecessary broad spectrum antibiotics and three were received ineffective antibiotics.
- In three cases with ineffective antibiotics 72 hours after blood collection in the intervention group, the time to positivity of blood culture was > 72 hours.
- The main reason for administration of unnecessary broad spectrum antibiotics in the intervention group was poor compliance of the clinicians to recommendation of de-escalation from ID specialists.
- The proportion of patients receiving optimal targeted antibiotics 48 hours after blood collection for culture was in **52.3% (23 of 44 patients) in the control group, and 73.8% (31 of 42 patients) in the intervention group (odds ratio 2.57; 95% CI, 1.04-6.37; p=0.041)**.

Conclusion

- Rapid phenotypical AST may be useful for antimicrobial stewardship by increasing proportion of patients receiving optimal targeted antibiotics early in hematologic patients with bacteremia.