Effect of direct rapid antibiotic susceptibility testing (dRAST) on treatment for bacteremia in patients with hematologic diseases: interim analysis of randomized controlled trial

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Disclosure

- I have been a consultant for QuantaMatrix Inc., which is developing and commercializing the QMAC-dRAST technology.
Bacteremia
- common cause of morbidity and mortality because it can progress to severe sepsis and septic shock
- Early administration of appropriate antibiotics is critical to increase the survival rate in patients with bacteremia

Rapid antimicrobial susceptibility test (AST)
- can decrease mortality rates and healthcare costs by helping choose appropriate antibiotics in the early period of bacteremia
- may help antimicrobial stewardship by reducing use of unnecessary broad-spectrum empirical antibiotics

Background

J Clin Microbial 1999;37:1415-8
J Clin Microbial 1994;32:1757-62

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dRAST (direct Rapid Antimicrobial Susceptibility Testing, QuantaMatrix Inc.)

- 6 hours rapid phenotypic AST directly from positive blood cultures
- using MAC (Microfluidic Agarose Channel) chip and a time-lapse imaging
Clinical usefulness of dRAST

- A retrospective simulation study (Jun. – Dec. 2015)
- The antibiotics based on dRAST were the same as those indicated by broth microdilution test
  - for 94% (49/52) with Gram-positive bacteremia
  - for 99% (66/67) with Gram-negative bacteremia
- Optimal treatment could have been given with dRAST results
  - for 56% (19/34) receiving ineffective and suboptimal treatment
- De-escalation could have been possible based on dRAST results
  - for 82% (27/33) receiving unnecessary broad-spectrum antibiotics
For bacteremia in patients with hematologic diseases

- Early administration of appropriate antibiotics is more important because **severe, prolonged neutropenia is common**
- Physicians prefer broad-spectrum antibiotics due to concerning rapid progression to severe sepsis
- Therefore, **antimicrobial stewardship is not easy** in hematologic patients with bacteremia

There is no randomized controlled study showing rapid phenotypic AST can help select appropriate antibiotics or perform antibiotic stewardship in hematologic patients

**Lancet Oncol 2014;15(13):e606-19**
The purpose of this study

- to investigate whether use of rapid phenotypic AST can increase the proportion of patients with hematologic disease who receive optimal antibiotics in early period of bacteremia.
Methods
Methods

- **Design**
  - Prospective, randomized, controlled, assessor blinded, single center trial (ClinicalTrials.gov, number NCT03611257)

- **Period:** September 2018 – ongoing

- **Place:** Seoul National University Hospital (1,800-bed), Seoul, South Korea

- **Subjects**
  - **Inclusion criteria**
    - Patients (>15 YO) were expected to be admitted for more than 2 days for treatment of hematologic disease
    - Positive blood culture
  - **Exclusion criteria**
    - were expected to discharge the hospital within 2 days of enrollment
    - died or transitioned to hospice care within 24 hours of bacteremia onset
    - had a fungemia without evidence of bacteremia
    - refused to provide written consent
Methods

- **Randomization**
  - 1:1 ratio, block randomization (block size = 8) by computerized generation of random number
  - Done by an independent personnel who did not know patients’ medical information

- **Blindness**
  - Information about group allocation was blinded to assessors who evaluated appropriateness of antibiotics
  - Not blinded to clinicians responsible for patient care

- **Intervention**
  - **dRAST group**
    - Results of direct MALDI-TOF and dRAST were automatically transferred to clinicians including ID specialists by phone text message
  - **Control group**
    - Results of direct MALDI-TOF were revealed to clinicians, if they requested.
Methods

**Outcome**

- **Primary outcome**
  - the proportion of patients receiving optimal targeted antibiotics 72 hours after blood collection for blood culture.

- **Secondary outcome**
  - the proportion of patients receiving optimal targeted antibiotics 48 hours after blood collection for blood culture
  - the proportion of patients receiving ineffective antibiotics 48 and 72 hours after blood collection
  - time to administration of optimal targeted antibiotics
  - incidence of persistent bacteremia
  - acquisition of *Clostridium difficile* or MDR organisms within 30 days after enrollment
  - 30-day mortality rate related with bacteremia
Definitions

- Optimal targeted antibiotics
  - The organisms were susceptible,
  - the most effective and narrowest spectrum treatment, considering neutropenia
  - For example, piperacillin/tazobactam was considered as optimal targeted antibiotics against non-ESBL producing *E. coli*

- Ineffective antibiotics
  - The organisms were not susceptible
Methods

- **Statistics**
  - Sample size
    - Control group: 0.6 vs intervention group: 0.85
    - 1 sided test, alpha error 0.05, beta error 0.2, drop rate 15%
    - Target sample size: a total of 116 patients (58 patients for each group)
  - Statistical methods
    - Pearson’s chi-square test or Fisher’s exact test for categorical variables
    - Student’s t-test for continuous variables

- **Ethics**
  - SNUH IRB approved this study (IRB #: 1806-173-955)
  - Written informed consent was obtained from all patients before participation
Results
Results

- Study flow

Assessed for eligibility (n=148)

Excluded (exclusion criteria or not meeting inclusion criteria)

Randomization (n=53)

dRAST group (n=27)

Bacteremia episodes (n=38)

Control group (n=26)

Bacteremia episodes (n=35)
Results

Baseline characteristics of subjects and bacteremia episodes

<table>
<thead>
<tr>
<th>Subjects</th>
<th>dRAST (n=27)</th>
<th>Control (N=26)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, median (range)</td>
<td>55 (23-83)</td>
<td>56 (17-85)</td>
<td>0.605</td>
</tr>
<tr>
<td>Sex, Male</td>
<td>13 (48)</td>
<td>18 (69)</td>
<td>0.809</td>
</tr>
<tr>
<td>Underlying hematologic disease</td>
<td></td>
<td></td>
<td>0.617</td>
</tr>
<tr>
<td>AML</td>
<td>14 (52)</td>
<td>18 (69)</td>
<td></td>
</tr>
<tr>
<td>ALL</td>
<td>4 (15)</td>
<td>3 (12)</td>
<td></td>
</tr>
<tr>
<td>Lymphoma</td>
<td>5 (19)</td>
<td>3 (12)</td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>4 (15)</td>
<td>2 (8)</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Bacteremia episode</th>
<th>dRAST (n=38)</th>
<th>Control (n=35)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neutropenia, n (%)</td>
<td>34 (90)</td>
<td>32 (91)</td>
<td>0.777</td>
</tr>
<tr>
<td>Charlson comorbidity score, median (range)</td>
<td>0 (0-6)</td>
<td>0 (0-7)</td>
<td>0.508</td>
</tr>
<tr>
<td>Septic shock</td>
<td>7 (18)</td>
<td>8 (23)</td>
<td>0.639</td>
</tr>
<tr>
<td>ICU admission</td>
<td>4 (11)</td>
<td>3 (9)</td>
<td>0.777</td>
</tr>
</tbody>
</table>
## Results

### Baseline characteristics of pathogens and clinician’s compliance

<table>
<thead>
<tr>
<th>Variables</th>
<th>dRAST (38 episodes)</th>
<th>Control (35 episodes)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pathogen</td>
<td></td>
<td></td>
<td>0.203</td>
</tr>
<tr>
<td>Gram positive bacteria</td>
<td>21 (55)</td>
<td>22 (63)</td>
<td></td>
</tr>
<tr>
<td>Gram negative bacteria</td>
<td>17 (45)</td>
<td>11 (31)</td>
<td></td>
</tr>
<tr>
<td>Polymicrobial infection</td>
<td>0</td>
<td>2 (5.7)</td>
<td></td>
</tr>
<tr>
<td>MDR pathogen, n (%)</td>
<td>19 (50)</td>
<td>23 (66)</td>
<td>0.175</td>
</tr>
<tr>
<td>Time (hrs) to AST reporting, mean ± SD (range)</td>
<td>51 ± 19 (0-137)</td>
<td>83 ± 20 (0-144)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Compliance to antimicrobial stewardship</td>
<td>30 (79.0)</td>
<td>31 (88.6)</td>
<td>0.268</td>
</tr>
</tbody>
</table>
Results

- Proportion of patients receiving optimal targeted antibiotics

\[ P = 0.023 \]

\[ P = 0.156 \]
Results

- Proportion of patients receiving ineffective antibiotics

![Chart showing percentage of ineffective antibiotics for dRAST and Control groups at 48HR and 72HR.]

- **48HR**
  - dRAST: 3%
  - Control: 20%
  - *P* = 0.043

- **72HR**
  - dRAST: 3%
  - Control: 14%
  - *P* = 0.136
### Secondary outcomes

<table>
<thead>
<tr>
<th>Variables</th>
<th>dRAST (38 episodes)</th>
<th>Control (35 episodes)</th>
<th>$P$-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time (hrs) to optimal targeted antibiotics administration, mean ± SD (range)</td>
<td>40 ± 41 (0-137)</td>
<td>57 ± 37 (0-144.2)</td>
<td>0.079</td>
</tr>
<tr>
<td>Incidence of persistent bacteremia</td>
<td>4 (10.5)</td>
<td>7 (20.0)</td>
<td>0.223</td>
</tr>
<tr>
<td>Acquisition of <em>C. difficile</em> or MDR bacteria within 30 days</td>
<td>4 (11.4)</td>
<td>8 (24.2)</td>
<td>0.313</td>
</tr>
<tr>
<td>30-day mortality rate related with bacteremia</td>
<td>2 (5.3)</td>
<td>5 (14.3)</td>
<td>0.217</td>
</tr>
</tbody>
</table>
Limitation

- Interim analysis with limited number of subjects
  - Final analysis is expected to show more confirmative data

- The study subjects with hematologic diseases
  - Most subjects had severe neutropenia and grave course of bacteremia
  - may hamper generalization of this study results to patients with other diseases

- Automatic text message of dRAST results
  - This maximized intervention may not be acceptable in every hospital setting
Conclusions

- Introduction of rapid phenotypic AST (dRAST) may reduce administration of ineffective antibiotics in early period of bacteremia in patients with hematologic diseases.

- dRAST may be useful for antimicrobial stewardship by increasing proportion of patients receiving optimal targeted antibiotics early in hematologic patients with bacteremia.
Thank you for listening