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Impact of the multiplex polymerase chain reaction in culture-positive samples on appropriate antibiotic use in patients with staphylococcal bacteremia☆

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ABSTRACT

Rapid identification of the microorganisms in patients with bacteremia may be useful in clinical practice. We evaluated the impact of the multiplex polymerase chain reaction (PCR) on appropriate antibiotic use for patients with gram-positive cocci cluster (GPCC) bacteremia. We divided the GPCC bacteremia cases into a pre-PCR group (2010–2011) and a post-PCR group (2012–2013). A total 664 cases were included in the pre-PCR group; and 570, in the post-PCR group. In methicillin-susceptible *Staphylococcus aureus* (MSSA) cases, optimal antibiotics were administered earlier in the post-PCR group (77.4 h *versus* 42.6 h, $P = 0.035$). Although the proportions of glycopeptide exposure did not differ (54.7% *versus* 56.7%, $P = 0.799$), the duration of exposure decreased (69.6 h *versus* 30.7 h, $P = 0.004$). In methicillin-resistant *S. aureus* cases, the time to optimal antibiotics administration did not differ (45.4 h *versus* 43.7 h, $P = 0.275$). Multiplex PCR test significantly improved the early initiation of optimal antibiotics in MSSA bacteremia and reduced the unnecessary glycopeptide exposure.

1. Introduction

Staphylococcus aureus bacteremia (SAB) is a major cause of serious infections in community as well as nosocomial settings. The burden of SAB is huge both in clinical (Song et al., 2013) and economic terms (Kim et al., 2014a). In spite of progress, a considerable proportion of SAB patients are treated with inappropriate empirical antibiotics due to the time between the onset of bacteremia and receipt of blood culture results (Khatib et al., 2006; Kim et al., 2004; Paul et al., 2010; Rodriguez-Bano et al., 2009; Shorr et al., 2008). Because delayed administration of optimal antibiotics is 1 of the key factors causing the high mortality of SAB (Khatib et al., 2006; Lodise et al., 2003; Paul et al., 2010; Rodriguez-Bano et al., 2009; Ruimy et al., 2008) and affecting the length of hospitalization and hospital costs (Shorr et al., 2008), methods for reducing the delay in obtaining the results of blood culture are needed.

Standard culture methods used to identify species and antibiotic susceptibility require 48–96 h from the moment of blood culture positivity, but some newer techniques reduce this interval (Blaschke et al., 2012; Buchan et al., 2013; Clerc et al., 2014; Grobner and Kempf, 2007; Liesenfeld et al., 2014; Lucignano et al., 2011; Paule et al., 2005; Wellinghausen et al., 2009). A few studies have evaluated the clinical impact of rapid diagnostic tests and have obtained favorable outcomes (Bauer et al., 2010; Nagel et al., 2014; Nicolsen et al., 2013; Perez et al., 2014). However, the relatively small sample sizes and/or absence of control groups limit the value of these studies.

In our institution, rapid identification of *S. aureus* and its methicillin susceptibility by multiplex polymerase chain reaction (PCR)—a culture-based rapid identification technique—has been performed since 2012. We selected *S. aureus* as a target microorganism for rapid diagnostics because nosocomial SAB imposes a tremendous burden and also because it is suitable for multiplex PCR; i.e., testing for only a few genes is enough to establish species and antimicrobial susceptibility. We had adopted multiplex PCR because the accuracy of diagnostic test was well evaluated (Blaschke et al., 2012; Buchan et al., 2013; Grobner and Kempf, 2007; Lucignano et al., 2011; Paule et al., 2005; Ruimy et al., 2008; Wang et al., 2013; Wellinghausen et al., 2009). However, we did not know whether this technique had been useful for antimicrobial stewardship program. Therefore, we decided to evaluate the impact of the multiplex PCR method for rapid identification of gram-positive

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cocci clusters (GPCC) in blood cultures on the appropriate use of antibiotics in our clinical setting.

2. Materials and methods

2.1. Study population

We retrospectively reviewed the medical records of patients whose blood culture grew GPCC from January 2010 to December 2013 in Seoul National University Bundang Hospital. Because multiplex PCR for identification of GPCC was introduced in February 2012, we divided the SAB cases into a pre-PCR group (from January 2010 to December 2011) and a post-PCR group (from February 2012 to December 2013). Exclusion criteria were 1) patients transferred to our hospital after identification of the pathogen in another hospital, 2) discordant results between the multiplex PCR and blood culture, 3) polymicrobial infections, and 4) patient death or discharge before blood culture results were reported.

2.2. PCR methods

The procedure for multiplex PCR was as follows. Blood cultures were set up in BacT/Alert 3D (bioMérieux, Durham, NC, USA) or BD BACTEC FX (BD Diagnostics, Sparks, MD, USA). If bacterial growth was detected and the Gram stain revealed GPCC, multiplex PCR was performed using the cultured specimen. The targets of the PCR were *mecA*, *femA* specific for *S. aureus*, *femA* specific for *Staphylococcus epidermidis*, *16S rRNA* for universal bacteria, and *16S rRNA* specific for staphylococci. The PCR test was performed in the afternoon on Monday through Friday and in the morning on Saturday using the bacterial colonies that identified as GPCC before 10 AM. If the Gram stain results were reported after 10 AM, the PCR test was performed the next day. On Sundays, PCR was not performed. The PCR results were recorded in an electronic medical record system without additional active notification or raising any alarm.

2.3. Definitions

Sampling time was defined as the time that a blood sample was drawn for blood culture. Time to blood culture positivity was defined as the time between sampling and reporting of the results of Gram staining. Time to PCR report was defined as the time between sampling and reporting of the PCR results. Time to blood culture report was defined as the time interval between sampling time to the time of report of culture and antimicrobial susceptibility result. Optimal antibiotics were defined as first-generation cephalosporin or nafcillin in methicillin-susceptible *S. aureus* (MSSA) bacteremia and glycopeptide in methicillin-resistant *S. aureus* (MRSA) bacteremia.

Because the aim of our study was to compare how early the unnecessary antibiotics was discontinued in patients with blood culture contamination, only cases of contamination were included among the cases of coagulase-negative staphylococci (CoNS) bacteremia. Contaminants were defined as 1 of the following criteria: 1) only 1 set of blood culture of 2 or more sets was positive for CoNS; 2) 2 or more blood cultures were positive for CoNS but their antibiograms were discordant; in other cases, contamination was decided by 2 separate infectious disease physicians working independently.

2.4. Data variables

The following data were collected: demographic data such as age and sex; sampling time; time of reporting of Gram stain, PCR, and culture results; and time of administration and discontinuation of antibiotics.

2.5. Statistical analysis

In each group, we compared the times to blood culture positivity and times to report of blood culture results in the pre-PCR and post-PCR subgroups. Because times to PCR report were not available in the pre-PCR group, times to PCR report cannot be compared between the pre-PCR and post-PCR groups.

In cases of *S. aureus* bacteremia, we compared the times to optimal antibiotics in the pre-PCR and post-PCR groups. In cases of MSSA bacteremia and CoNS contamination, the frequency and duration of unnecessary glycopeptide use were evaluated in the 2 groups.

Pearson's chi-square tests were used to compare dichotomous data. Student's *t* tests were used to compare differences between continuous variables, and Mann–Whitney *U* tests to compare nonparametric cases. A 2-tailed *P* value of <0.05 was consider statistically significant. SPSS Software Version 18.0 (SPSS, Chicago, IL, USA) was used for statistical analyses.

2.6. Study approval

This study was approved by the Institutional Review Board of Seoul National University Bundang Hospital.

3. Results

3.1. Baseline characteristics

There were a total of 1805 patients with GPCC bacteremia during the study period. Among them, 571 cases were excluded for the following reasons: death or transfer out before report of blood culture results ($n = 488$), polymicrobial infection ($n = 40$), and previous culture result influencing the choice of empirical antibiotics ($n = 31$). After exclusion, 1234 cases were included in the final analysis, and among them, 664 were in the pre-PCR group and 570 were in the post-PCR group (Fig. 1). There were no differences of baseline characteristics between the 2 groups. Of 191 cases of MRSA bacteremia, 94 and 97 were in the pre-PCR and post-PCR groups, respectively. Eighty-six MSSA bacteremias were included in the pre-PCR group, and 67 were in the post-PCR group. Among 890 cases of CoNS, 484 were in the pre-PCR group, and 406 were in the post-PCR group. One hundred twenty-one cases of CoNS bacteremia were regarded as true bacteremia, while 426 (88.0%) cases in the pre-PCR group and 343 (84.4%) cases in the post-PCR group were considered to be due to contamination.

3.2. Time to identification

Time to blood culture positivity did not differ between the pre-PCR and post-PCR groups in either MRSA or MSSA bacteremia. The time to blood culture result report in MRSA bacteremia was significantly higher in the pre-PCR group than the post-PCR group (90.4 h *versus* 75.2 h, $P < 0.001$), but in MSSA bacteremia, it was similar in the 2 groups (Table 1). The interval between sampling and identification of microorganisms and their methicillin susceptibility was lower by about 2 calendar days in the post-PCR groups, i.e., 90.4 h *versus* 49.0 h in the MRSA group and 92.1 h *versus* 47.1 h in the MSSA group.

3.3. Impact on optimal antibiotic use and glycopeptide exposure

Optimal antibiotics were initiated later in the pre-PCR period than the post-PCR period in our MSSA cases (77.4 h *versus* 42.6 h, $P = 0.035$). However, in the MRSA bacteremia cases, the intervals between sampling and initiation of optimal antibiotics were similar (45.4 h *versus* 43.7 h, $P = 0.275$) (Table 2).

In the MSSA bacteremia cases, the frequency of use of empirical glycopeptide was similar in the 2 groups, but the duration of glycopeptide exposure was lower in the post-PCR group (69.6 h *versus* 30.7 h, $P = 0.004$) (Table 2).

The frequency of empirical glycopeptide use in cases of CoNS contamination was lower than in the SAB cases (29.5% *versus* 77.0%, $P < 0.001$), but the frequency was similar in the pre-PCR and post-PCR patients. The duration of glycopeptide exposure was shorter in the