Predictive factors of true bacteremia and the clinical utility of blood cultures as a prognostic tool in patients with community-onset pneumonia

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Abstract
Although blood cultures (BCs) are an important component of diagnostic practice for antibiotic management in patients with pneumonia, several studies have questioned whether they should be performed. The objective of this study was to evaluate the predictive factors of bacteremia and the role of BCs in patients with community-onset pneumonia (community-acquired pneumonia and healthcare-associated pneumonia).

This study was retrospectively conducted in patients with community-onset pneumonia who were hospitalized at Jeju National University Hospital between January 2012 and December 2014. A true bacteremia (TB) group and a contaminants or negative bacteremia (CNB) group were classified according to the bacterial growth on the BC media and were investigated for the clinical relevance of the BCs.

We enrolled 785 patients; the TB group and the CNB group contained 36 patients (4.5%) and 749 (95.4%) patients, respectively. Only 10 patients (1.2%) required a change in antibiotic therapy based on the BC results (3 patients with an escalation, 7 with a de-escalation). There was no significant difference between the community-acquired pneumonia and the healthcare-associated pneumonia groups with regard to the rate of antibiotic change due to the BC results (1.1% vs 1.4%, \(P = 0.751\)). Chronic liver disease (odds ratio [OR] 2.973, 95% confidence interval [CI] 1.304–6.370), and Pneumonia Severity Index (PSI) class V (OR 2.405, 95% CI 1.007–5.743) were independently associated with TB. In patients with PSI class V and a CURB-65 score of 4 to 5 points, the TB group tended to show a higher inhospital mortality rate than the CNB group (50.0% vs 29.4%; \(P = 0.060\), 60.0% vs 42.5%; \(P = 0.480\)). The areas under the curve for PSI score and CURB-65 score for predicting TB revealed an increased tendency compared with that of C-reactive protein (0.72, 95% CI 0.630–0.809; and 0.72, 95% CI 0.622–0.819 vs 0.629, 95% CI 0.522–0.735, respectively).

It seemed reasonable to selectively conduct BC in patients hospitalized with severe community-onset pneumonia based upon its low overall positive rate, its effects on antimicrobial modification, and the associations of TB with the severity indices of pneumonia.

Abbreviations: ARP = antibiotic-resistant pathogens, AUC = area under the curve, BC = blood culture, CAP = community-acquired pneumonia, CI = confidence interval, CNB = contaminants or negative bacteremia, CO = community onset, CRP = C-reactive protein, CURB-65 = confusion, urea, respiratory rate, blood pressure, age ≥65, HCAP = healthcare-associated pneumonia, MDR = multidrug-resistant, PSI = Pneumonia Severity Index, TB = true bacteremia.

Keywords: bacteremia, health care, microbiology, pneumonia

1. Introduction

Microbiological studies in the management of pneumonia include bacterial cultures of clinical specimens, such as sputum, pleural effusion, and blood. It has been widely debated as to when blood cultures (BCs) should be ordered in patients with pneumonia. In community-acquired pneumonia (CAP), the yield of BCs has been reported to be as low as 5% to 14%, whereas positive BC results have not been associated with better outcomes in some studies. False-positive results could even lead to prolonged hospital stays, higher costs, or the overuse of antimicrobial agents.

There is a distinction among the different guidelines in terms of performing BCs in patients with CAP. The American Thoracic Society (ATS)/Infectious Diseases Society of America (IDSA) in 2007 stated that BCs should be performed selectively. British Thoracic Society (BTS) guidelines also recommended that BCs should be ordered in patients with moderate or severe CAP, but can be omitted in CAP patients with lower severity and no comorbidity. On the contrary, the recent guidelines from the European Respiratory Society and the European Society of Clinical Microbiology and Infectious Diseases (ERS/ECCMID)
state that BCs should be performed in all patients admitted with CAP.[10]

In 2005, the ATS/IDSA introduced the concept of healthcare-associated pneumonia (HCAP) as a type of community-onset (CO) pneumonia.[11] HCAP comprises a proportion of 17.3% to 73.7% of CO pneumonia.[12–19] And, compared with CAP, HCAP is known to be associated with higher rates of multidrug-resistant (MDR) pathogens which require broad-spectrum antimicrobial therapy or modification of an initial therapy.[11,20]

However, studies about the clinical usefulness of BCs in patients with HCAP are very scarce.

Therefore, we aimed to examine the clinical usefulness of BCs in patients with CO pneumonia, including CAP and HCAP, and to investigate the predictive factors of bacteremia.

2. Methods

2.1. Study population and design

This retrospective observational study was performed at Jeju National University Hospital (a 600-bed, university-affiliated hospital in Jeju, South Korea). Adult patients (≥18 years) who were hospitalized due to CAP or HCAP from January 2012 through December 2014 were investigated. We reviewed their medical records and collected data. According to the US Centers for Disease Control and Prevention Criteria, the BC results were classified as positive, contaminated, or negative.[21] Based upon clinical relevance, we divided the participants into 2 groups: a true bacteremia (TB) group and a contaminants/negative bacteremia (CNB) group. Since contaminants do not generally have effects on patients’ clinical outcomes, we decided to combine contaminants group with negative bacteremia group along with referring to previous studies.[22–24] We basically conducted statistical analysis based on 2 groups: TB group versus CNB group.

Clinical manifestations, underlying diseases, severity of the pneumonia, and the clinical outcomes were compared between the 2 groups. The study protocol was approved by the Ethical Review Committee of Jeju National University Hospital (approval number: 2015–11–011).

2.2. Definition

Pneumonia was defined as the presence of a new infiltrate on chest radiography and at least 1 of the following: fever (≥38.0°C) or hypothermia (<35.0°C); new-onset cough; pleuritic chest pain; dyspnea; or altered breath sounds on auscultation. HCAP was defined according to ATS/IDSA guidelines.[11] CAP was defined as a diagnosis of pneumonia in patients who did not meet any of the criteria for HCAP. The patients whose pneumonia developed after being hospitalized for >72 hours or who were readmitted due to pneumonia within 10 days of leaving the hospital or being transferred from other hospitals after a hospitalization lasting longer than >48 hours were excluded.

Changes in antibiotic regimens were classified as escalation, de-escalation, or no change after drug susceptibility tests (DSTs) were complete. When a new therapy was initiated to cover a broader spectrum of pathogens according to the results of the DSTs, it was regarded as an escalation of antimicrobial therapy.

On the contrary, when the spectrum of an initial antimicrobial therapy became narrower, it was defined as a de-escalation.

Patients were determined to have TB if BCs performed within 36 hours of presentation to the hospital isolated organisms that were not defined as a contaminant.[8] According to previous reports, although many microorganisms (eg, Enterococcus species, non-pneumococcal Streptococci) do not cause pneumonia, we decided to include patients in our study who had TB due to these organisms.[10] BC results that grew coagulase-negative staphylococci, Corynebacterium species, Clostridium species, Micrococcus species, Propionibacterium species, and Bacillus species were defined as contaminated.[18]

2.3. Statistical analyses

The data are presented as median (interquartile range) for continuous variables and as number (%) for categorical variables. Continuous variables were compared using the Mann–Whitney U test, and categorical variables were compared using the Pearson chi-square test, and the Fisher exact test was used when any cell contained less than 5. Multivariate logistic regression analyses were performed to identify independent prognostic factors associated with bacteremia, as measured by the estimated odds ratio (OR) with 95% confidence interval (CI).

The discriminatory power of each factor for bacteremia was assessed by calculating the area under each receiver-operating characteristic (ROC) curve. The estimated area under the ROC curve (AUC) values were compared using the Hanley-McNeil test.[25] The cut-off point that showed the highest Youden index was considered the optimal cut-off value.[26] All tests were 2-sided, and P values <0.05 were considered statistically significant. All analyses were performed using the Statistical Package for the Social Sciences (SPSS) network version 18.0 (SPSS; Chicago, IL).

3. Results

3.1. Study population, bacteremia, and modification of antimicrobial regimens

We identified 920 patients who were admitted with CO pneumonia. As BCs were not performed in 135 of these patients, we analyzed the remaining 785 patients. Bacteremia was detected in 75 patients (9.5%). The culture results of 39 of these patients (5.2%) were found to be contaminated, whereas those from 36 (4.8%) were proven to contain pathogens (TB).

Since 6 (0.7%) patients died before the results of the BCs were available, they were excluded from the analysis of the effectiveness of antimicrobial therapy. Of the remaining 30 patients with bacteremia, antibiotic regimens were modified in 13 (1.6%). On the basis of the BC results, 3 (0.3%) experienced escalation of antibiotic regimen, and 7 (0.8%) required de-escalation. All patients with an escalation received vancomycin as an additional agent. The rates of regimen changes based on the BC results in patients with CAP and HCAP were 1.1% (6/504) and 1.4% (4/281), respectively (P = 0.751; Fig. 1).

3.2. Clinical characteristics

There were 36 patients (4.5%) in the TB group and 749 (95.4%) in the CNB group. Table 1 shows the clinical characteristics and outcomes of both groups. The number of patients with HCAP and the distribution of categories of HCAP were similar between the 2 groups. Among several comorbidities, only chronic liver disease was frequently more reported in the TB group (16.6% vs 5.4%; P = 0.016).

The TB group exhibited worse clinical parameters. Of the laboratory findings, initial median C-reactive protein (CRP) and procalcitonin levels were higher in the TB group (16.7 vs 11.1 mg/dL; P = 0.010, and 7.8 vs 0.2 mg/dL; <0.0001). The median
confusion, urea, respiratory rate, blood pressure, age ≥65 (CURB-65) scores and PSI scores as severity indices of pneumonia were higher in the TB group (3 vs 1; \( P < 0.001 \), and 134 vs 102; \( P < 0.001 \)). The TB group showed a higher inhospital mortality rate (30.5% vs 10.6%; \( P = 0.001 \)).

3.3. Distribution of microorganisms

Table 2 shows the distribution of microorganisms isolated from the BCs. In the TB group, *Staphylococcus aureus* and *Escherichia coli* were most common, followed by *Streptococcus pneumoniae* and *Klebsiella pneumoniae*. *Staphylococcus epidermidis* was the most frequently isolated microorganism among the blood contaminants.

3.4. Risk factors of true bacteremia and its clinical implications

True bacteremia was more frequently observed in patients who belonged to PSI class V compared with classes I to IV (9.5% vs 2.8%; \( P < 0.001 \); Fig. 2A). Additionally, CURB-65 scores of 4 to 5 had a significantly higher TB rate of 20.0% (10/50) compared with a rate of 3.5% (26/735) for CURB-65 scores from 0 to 3 (\( P < 0.001 \); Fig. 2A).

The multivariate analysis for the risk factors of TB showed that 2 pneumonia severity scoring systems were independently associated with TB: a CURB-65 score of 4 to 5 points (OR 3.484, 95% CI 1.304–9.307) and PSI class V (OR 2.405, 95% CI 1.007–5.743). Chronic liver disease was also a significant risk factor of TB (OR 2.973, 95% CI 1.099–8.037). Age, tube feeding, HCAP, body temperature, and CRP were not associated with TB (Fig. 3).

In patients with PSI class V and CURB-65 score of 4 to 5, the TB group exhibited a higher inhospital mortality rate than the CNB group (50.0% vs 29.4%; \( P = 0.06 \), 60.0% vs 42.5%; \( P = 0.48 \); Fig. 2B).

3.5. Discriminatory power of the severity index for pneumonia associated with TB

Figure 4 shows the ROC curves for TB of each severity scoring system. Both the PSI and the CURB-65 scores had a high discriminatory power to predict TB. The AUC of the PSI score was 0.720 (95% CI 0.630–0.809), whereas that of the CURB-65 score was 0.720 (95% CI 0.622–0.819). These results were higher than those of the CRP (AUC 0.629, 95% CI 0.522–0.735), although the 3 did not statistically differ. The highest Youden index was shown at cut-off points of 116.5 (sensitivity 75.0%, specificity 62.0%) for the PSI and 2.5 (sensitivity 61.1%, specificity 79.7%) for the CURB-65 score.

4. Discussion

The ERS/ECCMID guidelines for CAP recommend that BCs should be conducted in all patients hospitalized with CAP. In contrast, the ATS/IDSA and BTS guidelines impose a limit on conducting BCs in patients with CAP. As a result, physicians could be confused about ordering BCs when they take care of
patients with CAP. Additionally, the concept of HCAP intensifies this confusion. Therefore, it is important to verify whether BCs have value as a tool to improve treatment outcomes, suppress resistance, and decrease medical costs in CO pneumonia. It would also valuable to identify which patients with CO-pneumonia would obtain the most benefit from BCs.

In our study, we calculated the TB rate for all patients hospitalized with CO-pneumonia; it was no more than 4.5%. Previous studies have included mostly patients with CAP and have reported that the incidence of the TB ranges from 3.7% to 16.0%.[3,22,24,33] Low overall TB rates indicate that it might not be necessary to perform BC in all hospitalized patients, which contrasts with the recent ERS/ECCMID guidelines. However, TB rates in patients with a high severity of illness such as PSI class V or CURB-65 scores of 4 to 5 points were 9.3% and 20.0%, respectively. This might indicate that the role of BCs increases as the severity of pneumonia increases.

In addition, we found that chronic liver disease was also 1 of the independent factors for predicting TB in patients with CO-pneumonia. Change in the immune system, including depression of the activity of the reticuloendothelial system and neutrophil leukocyte dysfunction, is likely to contribute to TB in these patients.[14] As a result, it could be reasonable to perform BCs selectively in a proportion of patients with CO-pneumonia.

Although previous studies have tried to construct a more useful tool to predict bacteremia using clinical variables in patients hospitalized with CAP, these prediction model seems to be not easy to perform in clinical practice.[8,31,32] Our results for predicting TB may be helpful for clinicians in practice.

Normally, 1 of the indications for BCs is to determine whether antibiotic therapy should be altered based upon the results. However, several studies have reported that BCs rarely affect antibiotic therapy for patients with pneumonia.[27,28,35] On the whole, in our study, only 1.2% (10 of 785 patients) had their antibiotic regimen modified according to the BC results. A systematic review has revealed that TB rates were 0% to 14% among cases of CAP, which resulted in antibiotic narrowing in 0% to 3% of cases and broadening in 0% to 1%.[34] These results suggest that it would not be beneficial to routinely conduct BCs in all patients with CAP.

Pneumonia Severity Index and CURB-65 have been accepted as useful tools to help clinicians predict mortality in patients with
Our study showed that in patients with PSI class V or CURB-65 scores of 4 to 5 points, the relative risk of mortality due to CO-pneumonia was about 1.5 to 2 times higher in the TB group compared with the CNB group (Fig. 4). At the same time, a positive correlation of PSI class or CURB-65 score with positive BCs was demonstrated (Figs. 2 and 3). These results suggest that BCs could be a useful prognostic tool for predicting mortality in patients with high-severity indices of pneumonia.

A few studies have assessed the need for BCs in HCAP. A recent systematic review of 15 studies with a total of 3898 patients admitted with CAP reported the microorganisms in patients with positive BCs. *S pneumoniae* was the most common pathogens, followed by *S aureus* and *E coli*. Several previous studies have reported very low isolation rate of antibiotic-resistant pathogens (ARPs). In contrast, a recent prospective, observational study revealed a relatively high rate of ARP bacteremia in CAP (30/2892 patients; 1.0%). In our study, HCAP was not a predictive factor of TB, and the rates of change in antibiotic therapy did not differ between CAP and HCAP. Therefore, we suggest that performing BCs on a routine basis in HCAP is not likely to be valuable. However, its usefulness needs to be evaluated through further well-designed studies.

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| Microorganisms                              | Number of patients with microorganisms isolated from blood |
|--------------------------------------------|------------------------------------------------------------|
| **True Pathogens**                          |                                                           |
| *Streptococcus pneumonia*                   | 6 (8.0%)                                                   |
| Other *Streptococcus* species               | 2 (2.6%)                                                   |
| *Staphylococcus aureus*                     | 10 (13.3%)                                                 |
| Methicillin-sensitive *S aureus*            | 5 (6.6%)                                                   |
| Methicillin-resistant *S aureus*            | 5 (6.6%)                                                   |
| Escherichia coli                            | 10 (13.3%)                                                 |
| Klebsiella pneumoniae                       | 5 (6.6%)                                                   |
| *Enterococcus* species                      | 1 (1.3%)                                                   |
| *Pseudomonas aeruginosa*                    | 1 (1.3%)                                                   |
| Other                                       | 1 (1.3%)                                                   |
| **Contaminants**                            |                                                           |
| Coagulase-negative *staphylococci*         | 30 (42.0%)                                                 |
| *Staphylococcus* epidermidis                | 15 (20.0%)                                                 |
| *Staphylococcus hominis*                    | 14 (18.6%)                                                 |
| *Staphylococcus* capsul                    | 4 (5.3%)                                                   |
| Other coagulase-negative *staphylococci*   | 3 (4.0%)                                                   |
| *Clostridium perfringens*                   | 1 (1.3%)                                                   |
| *Corynebacterium* species                   | 1 (1.3%)                                                   |
| Other                                       | 1 (1.3%)                                                   |

Data are presented as number (%).

Table 2

| Microorganisms                              | Number of patients with microorganisms isolated from blood |
|--------------------------------------------|------------------------------------------------------------|
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| Methicillin-resistant *S aureus*            | 5 (6.6%)                                                   |
| Escherichia coli                            | 10 (13.3%)                                                 |
| Klebsiella pneumoniae                       | 5 (6.6%)                                                   |
| *Enterococcus* species                      | 1 (1.3%)                                                   |
| *Pseudomonas aeruginosa*                    | 1 (1.3%)                                                   |
| Other                                       | 1 (1.3%)                                                   |
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| *Corynebacterium* species                   | 1 (1.3%)                                                   |
| Other                                       | 1 (1.3%)                                                   |

Data are presented as number (%).

Figure 2. Relationship between severity of pneumonia and true bacteremia. A, Bacteremia rates according to PSI class and CURB-65 score. B, In-hospital mortality rates of true bacteremia in PSI class V and CURB-65 score of 4 to 5 points. CNB = contaminants or negative bacteremia, CURB-65 = confusion, urea, respiratory rate, blood pressure, age ≥65, PSI = Pneumonia Severity Index, TB = true bacteremia.

Figure 3. Logistic regression analysis for risk factors associated with true bacteremia in patients admitted with community-onset pneumonia. CURB-65 = confusion, urea, respiratory rate, blood pressure, age ≥65, HCAP = healthcare-associated pneumonia, PSI = Pneumonia Severity Index.
perform BCs selectively in CO patients with a higher severity of pneumonia.

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