Impact of Blood Cultures on the Changes of Treatment in Hospitalized Patients with Community-Acquired Pneumonia

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Abstract [1]: Background: Initial blood cultures (BCs) with severe community-acquired pneumonia (CAP) are warranted. However, other than severity, the specific contributing factors that affect the decision to change antimicrobial agents have not been evaluated previously.

Methods: Consecutive adults with CAP hospitalized between January 2008 and December 2010 were assessed retrospectively. We enrolled those who were over 18 years old with typical symptoms of pneumonia and with an infiltrate consistent with pneumonia, from which 2 sets of BCs were obtained. Those who had been immunocompromised, hospitalized, or prescribed antibiotics in the past 30 days were excluded. We retrospectively assessed the factors contributing to the change in antimicrobial agents as well as the frequency of these changes in the enrolled patients based on the initial BC results.

Results: In total, 793 patients with initial diagnosis of CAP were admitted; 399 met the inclusion criteria. Among them, 386 were made definitive diagnosis of CAP after admission (the remaining 13 were made alternative diagnosis [non-pneumonia illnesses]). BC results were positive in 17 (4.4%) out of 386 CAP patients, among whom antimicrobial therapy was changed based on the BC results in 8 (2.1%) (Pneumonia Severity Index [PSI] grade IV; 2, PSI grade V; 6). Alternative diagnosis after admission was contributing factors for changing antimicrobial agents based on the positive blood culture results.

Conclusions: The use of BCs should be limited to patients with very severe cases. It would be helpful to find alternative diagnosis and modify treatment.

Keywords: Blood cultures, community-acquired pneumonia, antimicrobial agents.

INTRODUCTION

Initial blood cultures (BCs) are recommended for patients with severe community-acquired pneumonia (CAP), especially in intensive care unit (ICU) admission, with cavitary infiltrate, leukopenia, active alcohol abuse, chronic severe liver disease, asplenia, positive pneumococcal urine antigen test, and pleural effusion [2]. The limited usefulness of initial BCs in patients with Pneumonia Severity Index (PSI) grade I-III has been reported in a previous study [3]. However, the specific contributing factors that affect the decision to change antimicrobial agents based on positive blood cultures have not been evaluated previously. In our hospital, one of the primary community hospitals in the Tokyo metropolitan area, 2 sets of BCs from almost all patients with CAP requiring admission are routinely obtained in the emergency department (ED) or outpatient department. The aims of this study were to investigate the frequency of antimicrobial agent changes based on the BC results after admission and to validate the necessity of BCs in severe CAP. Furthermore, we explored the clinical features of patients whose antimicrobial agents had been changed.

MATERIALS AND METHODS

Sample Selection

We retrospectively investigated patients admitted with CAP between January 1, 2008, and December 31, 2010. CAP was defined as the presence of symptoms of lower respiratory tract infection such as cough, sputum production, and dyspnea, along with infiltrate on the chest radiography or chest computed tomography images on admission.

To be included in this study, patients had to be 18 years or older and from whom 2 sets of BCs (2 cultures bottles [one aerobic and one anaerobic] drawn at two different times) had been obtained before starting antimicrobial agents on admission. We included patients from nursing facilities. By contrast, we excluded patients on immunosuppressant therapy (steroid therapy, chemotherapy for malignant diseases, disease-modifying anti-rheumatic drug therapy, anti-cytokine therapy), and with human immunodeficiency virus infection (HIV) as defined by the Centers for Disease Control and Prevention.
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Control and Prevention [4]. We also excluded patients with history of admission or antimicrobial agent use in the past 30 days.

Data Collection

Each patient’s medical record was obtained through electronic data collection. Most of the clinical variables were derived from the PSI of Fine et al. [5]. Additionally, we gathered information about the patients’ comorbidities, which were defined on the basis of documented histories from their admission summaries. We only considered the results of the initial 2 sets of BCs obtained on admission, and not the results of BCs obtained after admission.

Definitive diagnosis of illnesses after admission was made based on the results of cultures and clinical evaluation by treating doctors. The presence of bacterial endocarditis was determined based on the DUKE criteria [6]. In patient characteristics, altered mental status is not a part of the definition of “cerebrovascular disease.” Specimens were considered contaminated if only bacteria from normal skin flora were detected and treating doctors evaluated the result as contamination.

A change in antimicrobial agent management was defined as any change in the antimicrobial agent itself, or the addition or termination of agents. The rationales for change were obtained from the documentation on the patient charts recorded by the treating doctors.

The choice of initial antimicrobial agents for CAP was mainly based on the Japanese Respiratory Society Guidelines for the Management of Community-Acquired Pneumonia in Adults (the second edition, 2005). In the guidelines, empiric use of penicillin derivatives with the beta-lactamase inhibitors, Piperacillin, and cephalosporins is recommended for inpatient settings without respiratory illnesses. In case of patients with respiratory diseases such as chronic obstructive pulmonary disease, use of carbapenem or fluoroquinolones is warranted. Furthermore, in suspicion of atypical pneumonia, adding tetracyclines, macrolides, or fluoroquinolones is also recommended.

Statistical Analysis

Statistical calculations were performed using InStat Statistical Software Package Version 3.01 (GraphPad Software Inc., CA). Variables are presented as mean ± standard deviation unless otherwise stated. We used $\chi^2$ analysis and the t-test for comparison between 2 groups. $P < 0.05$ was considered statistically significant.

RESULTS

Patients’ Characteristics

Of the 793 patients admitted with initial diagnosis of CAP, 394 were excluded (immunosuppressant use, 51; HIV infection, 4; admission 30 days prior, 141; antimicrobial agents use 30 days prior, 192; and BCs not performed, 6). The details are illustrated in Fig. (1). The remaining 399 patients (232 men and 167 women) had a mean age of 78.4 ± 14.6 years. In total, 97 patients (24%) had been admitted from nursing homes. Clinical variables as well as comorbid illnesses have also been summarized (Table 1). The Streptococcus pneumoniae Urine Antigen Test (BinaxNOW

![Fig. (1). Enrollment and outcomes. Abx: antibiotics; BC: blood culture; CAP: community-acquired pneumonia; HIV: human immunodeficiency virus.](image-url)
| Patients                                | n (%) or Mean ± SD |
|-----------------------------------------|--------------------|
| Age, years                              | 78.4 ± 14.6        |
| Male/Female                             | 229/170            |
| Nursing Home Resident                    | 97 (24.3)          |
| Sputum culture                          |                    |
| Geckler Classification 4 or 5 sputum    | 339 (85.0)         |
| S. pneumoniae Urine Antigen (+)         | 55 (13.8)          |
| Legionella Urine Antigen (+)            | 2 (0.5)            |
| pH < 7.35                               | 39 (9.8)           |
| Na < 130 mEq/L                          | 37 (9.3)           |
| Blood Urea Nitrogen > 30 mg/dL          | 86 (21.6)          |
| Hematocrit < 30%                        | 52 (13.0)          |
| Glucose > 250 mg/dL                     | 32 (8.0)           |
| White Blood Cell Count/μL (mean)        | 11667.1 ± 3333.4   |
| Pleural Effusion                        | 85 (21.3)          |
| Altered Mental Status                   | 156 (39.1)         |
| Respiratory rate ≥ 30/min               | 77 (19.3)          |
| Heart Rate ≥ 125/min                    | 42 (10.5)          |
| Systolic Blood Pressure < 90 mmHg      | 25 (6.3)           |
| Body Temperature < 35°C or ≥40°C        | 42 (10.5)          |
| PaO<sub>2</sub> < 60 mmHg or SpO<sub>2</sub> < 90% | 182 (45.6)        |
| Neoplasm                                | 28 (7.0)           |
| Liver Disease                           | 16 (4.0)           |
| Congestive Heart Failure                | 91 (22.8)          |
| Cerebrovascular Disease                 | 91 (22.8)          |
| Renal Disease                           | 25 (6.3)           |
| Intensive Care Unit admission           | 30 (7.5)           |
| PSI grade I                             | 7 (1.8)            |
| PSI grade II                            | 19 (4.8)           |
| PSI grade III                           | 54 (13.5)          |
| PSI grade IV                            | 126 (31.6)         |
| PSI grade V                             | 132 (33.1)         |
| Hospital Stay, days                     | 18.9 ± 21.1        |
| PSI grade I                             | 8.4 ± 2.2          |
| PSI grade II                            | 8.5 ± 7.7          |
| PSI grade III                           | 10.8 ± 6.6         |
| PSI grade IV                            | 19.0 ± 21.5        |
| PSI grade V                             | 25.8 ± 24.4        |
| Mortality Rate                          |                     |
| PSI grade I                             | 39/399 (9.8)       |
| PSI grade II                            | 0/7 (0.0)          |
| PSI grade III                           | 1/19 (5.3)         |
| PSI grade IV                            | 1/54 (1.9)         |
| PSI grade V                             | 10/126 (7.9)       |
| PSI grade V                             | 26/132 (19.7)      |
| Empiric antimicrobial agents            | ABPC/SBT 189, CTRX 103 |
|                                         | PIPC/TAZ 64, CLDM 37, MINO 26 CFPM 24, CPFX 22, AZM 12 |
|                                         | CTX 5, VCM 5, MEPIM 2, ABPC 1 |
|                                         | AZT 1, CAM 1, CEZ 1, CMZ 1 |
|                                         | LVFX 1, LBD 1, MNZ 1 |

ABPC: ampicillin, AZM: azithromycin, AZT: aztreonam, CAM: clarithromycin, CEZ: cefazolin, CFPM: cefepime, CLDM: clindamycin, CMZ: cefmetazole, CPFX: ciprofloxacin, CTRX: ceftriaxone, CTX: cefotaxime, LVFX: levofloxacin, LBD: linezolid, MEPIM: meropenem, MINO: minocycline, MNZ: metronidazole, PIPC: piperacillin, PSI: Pneumonia Severity Index, SBT: sulbactam, S. pneumoniae: Streptococcus pneumoniae, TAZ: tazobactam, VCM: vancomycin.
Influence of Blood Cultures on the Changes in Antimicrobial Agents

The bacteria detected from the sputum cultures (Table 2) show that most common pathogen was *Streptococcus pneumoniae*, followed by *Haemophilus influenzae* and *Streptococcus agalactiae*.

Table 2. Bacteria Detected from the Sputum Cultures

| Bacteria from the Sputum Cultures | n = 122 |
|-----------------------------------|--------|
| *Streptococcus pneumoniae* (PRSP) | 36 (5) |
| *Haemophilus influenzae*           | 15     |
| *Streptococcus agalactiae*        | 15     |
| *Moraxella catarrhalis*           | 14     |
| *Klebsiella pneumonia*            | 13     |
| *Staphylococcus aureus* (MRSA)    | 13 (2) |
| *Escherichia coli* (penicillin resistant species) | 6 (1) |
| *Pseudomonas aeruginosa*          | 6      |
| *Aeromonas hydrophila*            | 1      |
| *Citrobacter freundii*            | 1      |
| *Klebsiella oxytoca*              | 1      |
| *Proteus mirabilis*               | 1      |

MRSA: methicillin resistant *Staphylococcus aureus*. PRSP: penicillin resistant *Streptococcus pneumoniae*.

Among patients who fulfilled the inclusion criteria (n=399), 386 were made definitive diagnosis of CAP after admission (the remaining 13 were made alternative diagnosis [non-pneumonia illnesses] based on the results of cultures and the evaluation by treating doctors after admission).

The Rate of Bacteremia and Frequency of Antimicrobial Agent Change

The bacteria detected from the BCs (Table 3) show that most common pathogen was *Staphylococcus epidermidis*, which is commonly considered the causative bacteria of contamination. *Streptococcus pneumoniae* was second most common bacterium detected from the BCs, followed by *Escherichia coli*. Fig. (1) demonstrates that the number of pneumonia causing positive BCs was 17 (4.4%) out of 386 patients, whereas other etiologies (alternative diagnosis) yielded positive BCs in 10 patients (bacteremia from unknown origin: 6, urinary tract infection: 3, infectious endocarditis: 1). 12 patients were evaluated as contamination by treating doctors even though the results were positive.

Table 3. Bacteria Detected from the Blood Cultures

| Bacteria from Blood Cultures | n = 43 |
|-----------------------------|--------|
| *Staphylococcus epidermidis* | 10     |
| *Streptococcus pneumonia* (PRSP) | 9 (1) |
| *Escherichia coli* (Penicillin resistant species) | 4 (0) |
| *Klebsiella pneumoniae*     | 3      |
| *Staphylococcus aureus* (MRSA) | 3 (0) |
| *Streptococcus milleri*     | 2      |
| *Streptococcus agalactiae*  | 1      |
| *Streptococcus salivarius*  | 1      |
| *Streptococcus simulans*    | 1      |
| *Streptococcus sanguis*     | 1      |
| *Streptococcus viridans*    | 1      |
| *Clostridium species*       | 1      |
| *Fusobacterium*             | 1      |
| *Lactobacillus*             | 1      |
| *Bacteroides*               | 1      |
| *Glucose non-fermentative bacilli* | 1 |
| *Klebsiella oxytoca*        | 1      |
| *Pseudomonas aeruginosa*    | 1      |

MRSA: methicillin resistant *Staphylococcus aureus*. PRSP: penicillin resistant *Streptococcus pneumoniae*.

Among the 17 patients with positive BCs in CAP diagnosis, 8 (Pneumonia Severity Index [PSI] grade IV; 2, PSI grade V; 6) changed antimicrobial agents based on the positive BC results (Figs. 1, 2). Therefore, 2.1% out of 386 patients with definitive CAP diagnosis (0%, 0%, 0%, 1.6%, and 4.8% out of PSI grade I patients (7), grade II patients (19), grade III patients (53), grade IV patients (122), and grade V patients (124), respectively) changed antimicrobial agents based on the positive blood culture results (Fig. 2).
Specifically, 5 patients changed the antimicrobial agent itself, 2 added new agents, and 1 terminated therapy based on the BC results (Fig. 1).

The specific diagnoses, bacteria and antibiotics in the patients who changed therapy based on positive blood culture results are shown in Table 4 (the rationale [comments] for changing antimicrobial agents was based on admission summaries for each patient). By contrast, no one changed therapy based on negative BC results.

We compared the clinical variables of the patients who changed antimicrobial agents based on the positive BC results (n = 17) with the patients who did not (n = 10) (Table 5). The former group had significantly higher frequency of alternative diagnosis after admission. Also the former group had better mortality than the latter group. However, we could not show a significant difference of severity (PSI score) between two groups. The specific empiric antimicrobial agents in both groups are also demonstrated in Table 5.

Table 4. The Specific Diagnoses, Bacteria and Drugs in Patients who Changed Antimicrobial Therapy

| Gender | Age | PSI | Bacteria from BCs | Origins | Abx | Comments |
|--------|-----|-----|-------------------|---------|-----|----------|
| 1      | M   | 95  | V                 | Unknown | ABPC/ABPC/SBT⇒VCM+ABPC/SBT | Added VCM for Staphylococcus infection |
| 2      | F   | 82  | V                 |          | PIPC/TAZ⇒ABPC+CTRX | De-escalation for Streptococcus infection |
| 3      | F   | 85  | III               | UTI     | ABPC/SBT⇒LVFX | Switched Abx for E. coli infection |
| 4      | F   | 76  | V                 |          | CTRX⇒ABPC/SBT+CPFX | Switched Abx for Streptococcus infection |
| 5      | M   | 75  | IV                | Pneumonia | CTRX⇒ABPC+CTRX | Added ABPC for S. pneumoniae infection |
| 6      | M   | 81  | V                 | Pneumonia | ABPC/SBT⇒CTRX | Switched to CTRX for GNR infection |
| 7      | M   | 71  | V                 |          | ABPC/SBT⇒RFP+VCM | Switched Abx for S. epidermis infection |
| 8      | M   | 78  | V                 |          | ABPC/SBT⇒PIPC/TAZ | Switched Abx for GNR infection |
| 9      | M   | 65  | V                 | Pneumonia | ABPC+CPFX+CTRX⇒VCM⇒CTRX+CPFX | De-escalation |
| 10     | M   | 67  | V                 | Pneumonia | CTRX×CPFX⇒CPDX | De-escalation |
| 11     | M   | 87  | IV                | UTI     | ABPC/SBT+MINO⇒CPFX+CLDM | Switched Abx for GNR infection and UTI |
| 12     | F   | 87  | V                 | Pneumonia | CPFX+CLDM⇒CTRX+CLDM | De-escalation |
| 13     | M   | 86  | IV                | Pneumonia | CPFX⇒CTRX | De-escalation |
| 14     | F   | 88  | V                 | UTI     | ABPC/SBT⇒LVFX | Switched Abx for GNR infection |
| 15     | M   | 87  | V                 | Lactobacillus | CTRX+CLDM⇒MEPM | Switched Abx based on sensitivity test |
| 16     | F   | 93  | V                 | E. coli Clostridium K. pneumoniae Bacteroides | Unknown | ABPC/SBT⇒ABPC/SBT+CTRX | Added CTRX for GNR infection |
| 17     | M   | 43  | V                 | S. aureus | CTRX+AZM⇒CEZ | De-escalation |

ABPC: ampicillin, Abx: antibiotics, AZM: azithromycin, CEZ: ce fazolin, CLDM: clindamycin, CPDX: Cefpodoxime, CPFX: ciprofloxacin, CTRX: ceftriaxone, CTX: cefotaxime, F: female, GPC: gram positive coccus, GNR: gram negative rods, LVFX: levofloxacin, M: male, MEPM: meropenem, MINO: minocycline, MSSA: methicillin sensitive Staphylococcus aureus, PIPC: piperacillin, RFP: rifampicin, SBT: sulbactam, TAZ: tazobactam, UTI: urinary tract infection, VCM: vancomycin
DISCUSSION

In previous studies, initial BCs for pneumonia were positive for pathogens in 7-16% of hospitalized patients [3,7,8]. As the sensitivity of sputum cultures and gram-stained sputum examinations is limited, obtaining BCs especially for pneumococcal pneumonia is warranted currently [9]. By contrast, the arguments against obtaining BCs are that the positivity is relatively low, and the rate of false-positive cultures is high. Contaminations might prolong hospital stays due to the use of vancomycin [10].

We have demonstrated that the frequency of changing antimicrobial therapy increased as the severity of pneumonia (PSI grade) increased (Fig. 2). In particular, very severe cases (PSI grade V) needed to change therapy much more frequently based on the BC results than patients with other PSI grades. Contrary to the previous study in which the frequency of antimicrobial agents change was quite high

| Table 5. Comparison Between Patients who Changed Antimicrobial Agents and Patients who Did Not Based on the Positive Blood Culture Results |
|-----------------------------|-----------------------------|-----------------------------|-----------------------------|
|                             | Patients with Changed Antimicrobial Agents (n = 17) | Patients with Unchanged Antimicrobial Agents (n=10) | P-Value                 |
| Age, years                  | 79.18 ± 12.6                | 74.8 ± 25.0                 | 0.616                     |
| Male/Female                 | 11/6                        | 3/7                         | 0.081                     |
| Pleural Effusion            | 7/17 (41.2)                 | 5/10 (50.0)                 | 0.67                      |
| Altered Mental Status       | 7/17 (41.2)                 | 5/10 (50.0)                 | 0.67                      |
| Respiratory Rate ≥ 30/min   | 7/17 (41.2)                 | 3/10 (30.0)                 | 0.561                     |
| Systolic Blood Pressure < 90 mmHg | 5/17 (29.4)     | 3/10 (30.0)                 | 0.974                     |
| Body Temperature < 35°C or ≥40°C | 1/17 (5.9)           | 1/10 (10.0)                  | 0.693                     |
| Heart Rate ≥ 125/min        | 3/17 (17.6)                 | 3/10 (30.0)                 | 0.456                     |
| pH < 7.35                   | 4/17 (23.5)                 | 4/10 (40.0)                 | 0.365                     |
| PaO2 < 60 mmHg or SpO2 < 90% | 11/17 (64.7)                | 8/10 (80.0)                 | 0.401                     |
| Glucose > 250 mg/dL         | 2/17 (11.8)                 | 1/10 (10.0)                 | 0.888                     |
| Na < 130 mEq/L              | 4/17 (23.5)                 | 1/10 (10.0)                 | 0.382                     |
| Hematocrit < 30%            | 2/17 (11.8)                 | 3/10 (30.0)                 | 0.239                     |
| Blood Urea Nitrogen > 30 mg/dL | 10/17 (58.8)            | 4/10 (40.0)                 | 0.345                     |
| Neoplasm                    | 2/17 (11.8)                 | 2/10 (20.0)                 | 0.561                     |
| Liver Disease               | 3/17 (17.6)                 | 1/10 (10.0)                 | 0.589                     |
| Congestive Heart Failure    | 4/17 (23.5)                 | 1/10 (10.0)                 | 0.382                     |
| Cerebrovascular Disease     | 5/17 (29.4)                 | 0/10 (0.0)                  | 0.057                     |
| Renal Disease               | 1/17 (5.9)                  | 0/10 (0.0)                  | 0.434                     |
| Intensive Care Unit admission | 5/17 (29.4)               | 3/10 (30.0)                 | 0.974                     |
| Nursing Home Resident       | 2/17 (11.8)                 | 3/10 (30.0)                 | 0.384                     |
| White Blood Cell Count/μL   | 9935.3 ± 6152.8             | 9360 ± 6960.4               | 0.831                     |
| Hospital Stay, days         | 28.2 ± 18.9                 | 7.1 ± 9.18                  | <0.001                    |
| PSI grade I- IV/V           | 4/13                        | 3/7                         | 0.71                      |
| Mortality Rate              | 2/17 (11.8)                 | 5/10 (50.0)                 | 0.029                     |
| Alternative diagnosis       | 9/17 (52.9)                 | 1/10 (10.0)                 | 0.026                     |
| Empiric antimicrobial agents| ABPC/SBT 8, CTRX 5, CPFX 3, CLDM 2, ABPC 1, AZM 1, CEZ 1, CFPM 1, CTX 1, MINO 1, PIPC/TAZ 1, VCM 1 | ABPC/SBT 4, CLDM 3, CPFX 3, CTRX 2, PIPC/TAZ 2, MINO 1, VCM 1 |  |

ABPC: ampicillin, AZM: azithromycin, CEZ: cefazolin, CFPM: cefepime, CLDM: clindamycin, CPFX: ciprofloxacin, CTRX: ceftriaxone, CTX: cefotaxime, MINO: minocycline, PIPC: piperacillin, PSI: Pneumonia Severity Index, SBT: sulbactam, TAZ: tazobactam, VCM: vancomycin
CONFLICT OF INTEREST

The authors confirm that this article content has no conflict of interest.

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CONCLUSIONS

Among CAP patients from whom BCs were obtained, antimicrobial agents were changed in 2.1% based on the BC results. In particular, the use of BCs should be limited to patients with very severe cases (PSI grade V) in hospital settings. Further, many patients are not adequately diagnosed at the ER. Therefore, BC should be drawn as the probability of changing antibiotics is higher in other diseases like urosepsis or infectious endocarditis.

ABBREVIATIONS

CAP = Community-acquired pneumonia
BCs = Blood cultures
PSI = Pneumonia Severity Index
ED = Emergency department

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