Increasing Incidence of Listeriosis and Infection-associated Clinical Outcomes

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Background: Listeriosis caused by Listeria monocytogenes has a high case-fatality rate (CFR) of approximately 20% to 30%. An increasing incidence of listeriosis has been reported in many countries recently. We investigated the annual incidence, clinical characteristics, and outcomes of listeriosis at three different hospitals in Korea and evaluated the effects of appropriate empiric antimicrobial treatments on patient outcomes.

Methods: We retrospectively collected the data of all culture-positive cases of human listeriosis from three hospitals of different sizes in Korea during 2006–2016 and calculated the annual number of cases and incidence per 100,000 admissions.

Results: A total of 58 patients with L. monocytogenes were included in this study. The incidence of listeriosis was significantly higher in 2013–2016 than in 2006–2012 (RR 3.1; 95% CI 1.79–5.36; P<0.001), mainly because of an increase in patients over 60 years of age (RR 3.69; 95% CI 1.70–8.02; P<0.001). Multivariate analysis showed that healthcare-associated infection (adjusted OR, 12.15; 95% CI, 2.56–86.01; P=0.004) and empirical treatment with first-line antimicrobial agents (adjusted OR, 0.08; 95% CI, 0.00–0.63; P=0.044) were associated with CFR.

Conclusions: Healthcare-associated infections caused by L. monocytogenes are associated with high CFR. Adequate initial empirical treatments could reduce CFR, suggesting that careful consideration of an empirical antimicrobial regimen is warranted for elderly or immunocompromised patients admitted to the hospital.

Key Words: Listeria monocytogenes, Listeriosis, Incidence, Outcome, Empirical treatment

INTRODUCTION

Listeriosis caused by Listeria monocytogenes is a bacterial infection with a high case-fatality rate (CFR) of approximately 20% to 30%; listeriosis occurs mainly in the elderly, neonates, immunocompromised patients, and pregnant women via central nervous system (CNS) infection and bloodstream infection (BSI) [1-4]. This gram-positive intracellular bacterium is widespread in the natural environment [5], and infections mostly arise following the consumption of contaminated food, such as unheated ready-to-eat meals and dairy products [6-8], because of the ability of L. monocytogenes to survive under salty or acidic conditions and grow at refrigeration temperatures [9].

An increase in the annual incidence of listeriosis has been reported in many countries recently [1, 7, 10-12]. Although a number of listeriosis outbreaks have been reported [13], most cases are sporadic. In addition, there is an increasing concern regarding the emergence of healthcare-associated listeriosis [11]. How-
ever, *L. monocytogenes* infection is difficult to diagnose and treat with appropriate initial empiric treatments because it does not produce any specific symptoms [14].

Large-scale multilocus sequence typing (MLST) has been performed in a number of European countries to investigate the genotypic-related characteristics of strains [1, 4, 6, 15]. However, only a few groups have performed MLST studies of *L. monocytogenes* in Asian countries [16], and the available data is too limited for comparisons with other regions.

We investigated the annual incidence, clinical characteristics, and outcomes of listeriosis at three different hospitals in Korea and evaluated the effects of appropriate empiric antimicrobial treatments on patient outcomes. In addition, we analyzed MLST profiles of a subset of *L. monocytogenes* isolates to determine which strains caused outbreaks and compared our data with the results of previous studies. We aimed to determine whether listeriosis incidence increased in Korea and to analyze the risk factors associated with treatment outcome.

**METHODS**

We retrospectively collected the data pertaining to all culture-positive cases of human listeriosis from three hospitals of different sizes (38 cases from hospital “A” [>2,000 beds; tertiary university hospital, Seoul], 10 cases from hospital “B” [>800 beds; tertiary university hospital, Seoul], and 10 cases from hospital “C” [>700 beds; secondary national hospital, Goyang]) in Korea during 2006–2016 and calculated the annual number of cases and incidence per 100,000 admissions at the three hospitals. We excluded duplicate cases.

The following clinical data were collected from electronic medical records: age at diagnosis, sex, underlying diseases, date of patient death or most recent visit, sampling sites, date of sample collection and report of culture results, and any antimicrobial agents administered during hospitalization. Available laboratory findings at the time of sample collection, including C-reactive protein (CRP) level, erythrocyte sedimentation rate (ESR), white blood cell (WBC) count, neutrophil percent, and antimicrobial susceptibility test results, were also obtained.

We performed MLST analysis for 19 isolates collected from hospital “A”, as described by Ragon et al [6]. The sequences of seven housekeeping genes (*abcZ*, *bglA*, *cat*, *dapE*, *dat*, *ldh*, and *IhkA*) were analyzed, and the sequence type (ST) and clonal complex (CC) of the obtained data were assigned using the *Listeria* MLST database hosted by the Institut Pasteur (http://big-sdb.pasteur.fr/listeria).

This retrospective study was approved by the Institutional Review Board at Shinchon and Gangnam Severance Hospital (Seoul, Korea) and the National Health Insurance Service of Ilsan Hospital (Goyang, Korea).

1. **Definitions**

Cases were categorized as CNS infections, BSIs, pregnancy-associated infections, or other infections based on the site of isolation of *L. monocytogenes* and clinical diagnosis. Pregnancy-associated infections were defined as listeriosis in <30-day-old newborn infants with maternal-fetal infections.

The presence of the following immunocompromised conditions was documented: solid organ cancer, hematologic malignancy, type 2 diabetes mellitus (DM), chronic kidney disease, chronic respiratory disease, chronic liver disease, stroke, and autoimmune disease treated with corticosteroids.

The term CFR refers to non-pregnancy associated mortality within 30 days of the sample collection date.

Listeriosis was considered to be “healthcare-associated” if (a) the onset of listeriosis symptoms occurred 48 hours post admission and there was no evidence of infection at admission; if (b) infections were acquired at other hospitals prior to transfer to the study hospitals; or if (c) infections were acquired during a previous admission within two weeks of presentation. Otherwise, listeriosis was considered to be community-associated, as previously reported [17, 18].

Antimicrobial agents were categorized into three groups: first-line antimicrobial agents, defined as monotherapy or combinations of penicillin or ampicillin and gentamicin; alternative antimicrobial agents including trimethoprim-sulfamethoxazole, erythromycin (excluding ineffective use for pregnancy-associated infections) [19], vancomycin (excluding ineffective use for CNS infections) [20], imipenem, or meropenem; and other drugs classified as inadequate antimicrobial agents [10].

2. **Statistical analysis**

Incidence rates ratios (RRs) and 95% confidence intervals (CIs) were calculated by comparing the mean incidence between 2006–2013 and 2014–2016.

In all variables included in the statistical analysis, we assessed whether they followed a Gaussian distribution using the Shapiro-Wilk test. We described the case characteristics using medians and interquartile ranges (IQRs). The significance of the differences between groups was tested with Fisher’s exact test for qualitative data and the Mann-Whitney U test for quantitative data.
To obtain odds ratios (ORs), univariate and multivariate regressions were performed using logistic regression. Dependent variables included in the multivariate regressions were selected using Akaike's information criterion (AIC) based on forward stepwise logistic regression. The presence of variance inflation factors was also examined for all parameters of the multiple regression models.

All reported \( P \) values are two-tailed, and \( P \) values <0.05 were considered to indicate statistical significance. All statistical analyses were performed using the R statistical software (Version 0.99.893—2009–2016; R Studio, Boston, MA, USA).

RESULTS

Although the annual incidence of listeriosis was stable from 2006–2012, it has increased since 2013 (Fig. 1). The incidence of listeriosis was significantly higher in 2013–2016 than in 2006–2012 (RR 3.1; 95% CI 1.79–5.36; \( P < 0.001 \)), mainly because of the increase in patients > 60 years of age (RR 3.69; 95% CI 1.70–8.02; \( P < 0.001 \)) and those with underlying diseases such as solid organ cancer and DM (Fig. 2).

Table 1 describes the clinical characteristics of cases by year. No statistically significant differences were observed in patient sex, infection type, isolate source, or CFR. Fig. 2 illustrates the increased annual incidence of three groups: pregnancy-associated infections, patients > 60 years of age, and patients < 60 years of age. There was no significant difference in pregnancy-associated infections; however, the incidence of patients > 60 years of age increased.

The median age of all 58 patients was 62 years (IQR, 52–72 years). Thirty-one (53.4%) patients were males. Patient demographic and baseline characteristics according to community- and healthcare-associated infections are summarized in Table 2. Forty-two cases were classified as community-associated infection, and 16 cases were classified as healthcare-associated infection. Of the infections, 58.6% were BSIs, 25.9% were CNS infections, 8.6% were pregnancy-associated infections, and 6.9% consisted of other infections such as peritonitis (three of four cases) and pneumonia (one of four cases). Inadequate antimicrobial agents were most frequently observed in initial em-
Increased incidence of listeriosis in Korea

Human listeriosis is a rare disease; however, its incidence has increased in recent years in many countries [1, 15, 21]. Our data also demonstrated a significant increase of listeriosis at three Korean hospitals since 2013. It was mainly due to an increase in patients over the age of 60 years and patients in an immunocompromised state due to conditions such as solid or organ cancer or type 2 DM. Listeriosis exhibited a high CFR (22.0%–71.5%) in our study. Using multivariate analysis, we found that healthcare-associated infections were the main risk factor related to higher CFR compared with community-associated infections. In addition, the initial selection of appropriate empiric antimicrobial agents was associated with a lower CFR. Table 1 shows characteristics of yearly isolated listeriosis cases.

DISCUSSION

Human listeriosis is a rare disease; however, its incidence has increased in recent years in many countries [1, 15, 21]. Our data also demonstrated a significant increase of listeriosis at three Korean hospitals since 2013. It was mainly due to an increase in patients over the age of 60 years and patients in an immunocompromised state due to conditions such as solid or organ cancer or type 2 DM. Listeriosis exhibited a high CFR (22.0%–71.5%) in our study. Using multivariate analysis, we found that healthcare-associated infections were the main risk factor related to higher CFR compared with community-associated infections. In addition, the initial selection of appropriate empiric antimicrobial agents was associated with a lower CFR. Table 1 shows characteristics of yearly isolated listeriosis cases.

Table 1. Characteristics of yearly isolated listeriosis cases

| Year | N   | Incidence/100,000 inpatients | Age (yr) | Male sex | Community-associated infection | BSI | CNS | Pregnancy-associated infection | Other* | No. of deaths | Culture results report time post sample collection (days) | Susceptibility (%) |
|------|-----|----------------------------|---------|----------|-------------------------------|-----|-----|--------------------------------|--------|--------------|---------------------------------------------------------|------------------|
| 2006 | 3   | 2.3                        | 62.0 [57.0–65.5] | 2        | 2                             | 0   | 3   | 0                              | 0      | 1            | 4.0 [3.5–5.5]                                             | Ampicillin (3 [0.00–0.03]) |
| 2007 | 4   | 3.0                        | 62.5 [29.0–70.5] | 2        | 3                             | 2   | 1   | 1                              | 1      | 2            | 5.0 [4.0–6.5]                                             | Penicillin (1 [0.00–0.03]) |
| 2008 | 3   | 2.0                        | 48.0 [24.0–60.0] | 1        | 2                             | 1   | 1   | 1                              | 0      | 1            | 4.0 [3.0–5.5]                                             | Trimethoprim-sulfamethoxazole (1 [0.00–0.03]) |
| 2009 | 1   | 0.6                        | 22.0 [22.0–22.0] | 0        | 1                             | 0   | 1   | 1                              | 0      | 0            | 2.0 [2.0–2.0]                                             | NA (1 [0.00–0.03]) |
| 2010 | 1   | 0.6                        | 45.0 [45.0–45.0] | 1        | 1                             | 0   | 0   | 0                              | 0      | 0            | 6.0 [6.0–6.0]                                             | Ampicillin (1 [0.00–0.03]) |
| 2011 | 4   | 2.4                        | 71.5 [44.0–74.5] | 3        | 3                             | 3   | 1   | 1                              | 0      | 1            | 3.5 [2.5–4.0]                                             | Penicillin (1 [0.00–0.03]) |
| 2012 | 3   | 1.7                        | 59.0 [56.0–61.0] | 2        | 1                             | 2   | 1   | 1                              | 0      | 1            | 3.0 [3.0–4.0]                                             | Trimethoprim-sulfamethoxazole (1 [0.00–0.03]) |
| 2013 | 8   | 4.7                        | 55.5 [25.0–65.0] | 6        | 3                             | 5   | 1   | 1                              | 1      | 4            | 3.0 [2.5–6.0]                                             | NA (1 [0.00–0.03]) |
| 2014 | 7   | 4.1                        | 56.0 [53.5–66.0] | 4        | 6                             | 5   | 1   | 1                              | 0      | 2            | 2.0 [2.0–2.5]                                             | NA (1 [0.00–0.03]) |
| 2015 | 10  | 5.6                        | 74.0 [57.0–80.0] | 5        | 8                             | 7   | 2   | 1                              | 0      | 2            | 3.0 [2.0–4.0]                                             | NA (1 [0.00–0.03]) |
| 2016 | 14  | 7.5                        | 62.5 [57.0–74.0] | 5        | 12                            | 9   | 2   | 0                              | 3      | 4            | 3.0 [2.0–4.0]                                             | NA (1 [0.00–0.03]) |

Data are presented as numbers (%) or medians [interquartile range].

*Includes peritonitis and pneumonia.

Abbreviations: BSI, blood stream infection; CNS, central nervous system; CFR, case-fatality rate; NA, not available.

MST analysis of 19 available L. monocytogenes isolates from hospital “A” revealed that seven isolates belonged to genetic lineage II and that there were 13 different sequence types (ST). The most commonly identified genotypes were ST9 (four isolates), followed by ST7, ST1, and ST2 (two isolates each). No dominant sequence type was apparent.

Variables associated with CFR are described in Table 4. Univariate analysis showed that healthcare-associated infection was associated with CFR (OR, 5.51; 95% CI, 1.57–21.04; P = 0.0093). Multivariate analysis showed that healthcare-associated infection (adjusted OR, 12.15; 95% CI, 2.56–86.01; P = 0.004) and empirical treatment with first-line antimicrobial agents (adjusted OR, 0.08; 95% CI, 0.00–0.63; P = 0.044) were associated with CFR.


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However, it is difficult to select an adequate initial regimen because listeriosis does not present with any specific symptoms, and many classes of antimicrobial agents that are widely used

| Table 2. Baseline characteristics of patients with listeriosis |
|---------------|-----------------|-----------------|-----------------|-----|
|               | Total (N=58)    | Community-associated infection (N=42) | Healthcare-associated infection (N=16) | P  |
| Age (yr)      | 62.0 [52.0–72.0] | 62.0 [47.0–72.0] | 61.0 [55.0–70.0] | 0.754 |
| Male sex      | 31 (53.4)       | 20 (47.6)       | 11 (68.8)       | 0.251 |
| Infection type| BSI 34 (58.6)   | 24 (57.1)       | 10 (62.5)       | 0.396 |
|               | CNS 15 (25.9)   | 11 (26.2)       | 4 (25.0)        | 0.396 |
|               | Pregnancy-associated 5 (8.6) | 5 (11.9) | 0 (0.0) | 0.396 |
|               | Other 4 (6.9)   | 2 (4.8)         | 2 (12.5)        | 0.396 |
| CFR           | 17 (29.3)       | 8 (21.6)        | 9 (56.2)        | 0.014 |
| Culture results report time post sample collection (day) | 3.0 [2.0–4.0] | 3.0 [2.0–4.0] | 3.0 [2.0–6.0] | 0.404 |
| Duration of inadequate antimicrobial treatment (day) | 2.0 [0.0–4.0] | 2.5 [0.0–4.0] | 2.0 [0.0–3.5] | 0.605 |
| Underlying disease | BSI 24 (41.4) | 14 (33.3) | 10 (62.5) | 0.270 |
|               | Hematologic malignancy 3 (5.2) | 2 (4.8) | 1 (6.2) | 0.270 |
|               | Other immunocompromised conditions 22 (37.9) | 17 (40.5) | 5 (31.2) | 0.270 |
|               | Pregnancy-associated 5 (8.6) | 5 (11.9) | 0 (0.0) | 0.270 |
|               | Other 4 (6.9)   | 4 (9.5)         | 0 (0.0)         | 0.270 |
| Laboratory findings | C reactive protein (mg/L) 52.1 [16.4–176.9] | 66.1 [14.1–164.4] | 35.5 [20.3–229.8] | 0.515 |
|               | Erythrocyte sedimentation rate (mm/hr) 48.5 [15.0–71.0] | 48.5 [22.0–71.0] | 32.5 [11.5–71.5] | 0.586 |
|               | WBC count (10³/L) 11.1 [4.9–17.1] | 12.3 [4.9–17.8] | 10.3 [5.4–13.4] | 0.439 |
|               | Neutrophils (%) 86.0 [77.0–91.5] | 86.0 [74.4–91.5] | 86.1 [81.2–91.7] | 0.638 |
| Initial empiric treatments | First-line antimicrobial agents* 18 (31.0) | 13 (31.0) | 5 (31.2) | 0.339 |
|               | Alternative antimicrobial agents† 5 (8.6) | 5 (11.9) | 0 (0.0) | 0.339 |
|               | Inadequate antimicrobial agents 35 (60.3) | 24 (57.1) | 11 (68.8) | 0.339 |
| Treatments post bacterial identification | First-line antimicrobial agents* 39 (67.2) | 27 (64.3) | 12 (75.0) | 0.650 |
|               | Alternative antimicrobial agents† 7 (12.1) | 6 (14.3) | 1 (6.2) | 0.650 |
|               | Inadequate antimicrobial agents 12 (20.7) | 9 (21.4) | 3 (18.8) | 0.650 |
| Antibiotic susceptibility test (n-%susceptibility) | Ampicillin 14 (100.0) | 8 (100.0) | 6 (100.0) | 0.593 |
|               | Penicillin 35 (89.7) | 24 (85.7) | 11 (100.0) | 0.461 |
|               | Trimethoprim-sulfamethoxazole 37 (94.9) | 28 (96.6) | 9 (90.0) | 0.194 |

Data are presented as numbers (%) or medians [interquartile range].

*First-line antimicrobial agents: ampicillin or penicillin alone or in combination with gentamicin; †Alternative antimicrobial agents: trimethoprim-sulfamethoxazole, imipenem, meropenem, or vancomycin (excluding use in CNS infection).

Abbreviations: CFR, case-fatality rate; BSI, blood stream infection; CNS, central nervous system; WBC, white blood cell.
Table 3. Available MLST test results for *Listeria monocytogenes* isolates

| N  | ST/CC | Genetic lineage | Year(s)  |
|----|-------|-----------------|----------|
| 4  | 9/9   | II              | 2014–2016|
| 2  | 7/7   | II              | 2011, 2014|
| 2  | 1/1   | I               | 2014, 2016|
| 2  | 59/59 | I               | 2016     |
| 1  | 224/224 | II          | 2009    |
| 1  | 91/14 | II              | 2011     |
| 1  | 101/101 | II          | 2013    |
| 1  | 121/121 | II           | 2013    |
| 1  | 8/8   | II              | 2014     |
| 1  | 5/5   | I               | 2015     |
| 1  | 87/87 | I               | 2016     |
| 1  | 18/18 | II              | 2016     |
| 1  | 155/155 | II          | 2016    |

Abbreviations: MLST, multilocus sequence typing; ST, sequence type; CC, clonal complex.

Table 4. Results of univariate and multivariate analyses of risk factors for case-fatality due to Listeriosis

| Variables                                                                 | Survived (N = 37) | Died*(N = 16) | Univariate analysis | Multivariate analysis |
|---------------------------------------------------------------------------|-------------------|---------------|--------------------|-----------------------|
|                                                                           | OR (95% CI)       | P             | OR (95% CI)        | P                     |
| Age (≥ 60 yr)*                                                            | 1.14 (0.34–3.74)  | 0.828         |                    |                       |
| Sex, female*                                                              | 1.31 (0.40–4.32)  | 0.650         |                    |                       |
| Healthcare-associated infection*                                          | 5.51 (1.57–21.04) | 0.009         | 12.15 (2.56–86.01) | 0.004                 |
| Immunocompromised state*                                                  | 1.0               | NA            |                    |                       |
| Prior history of solid organ or hematologic malignancy*                   | 2.89 (0.87–10.75) | 0.094         |                    |                       |
| Bacterial identification report time post sample collection (+1 day)       | 0.81 (0.53–1.14)  | 0.279         | 0.67 (0.41–1.01)*  | 0.0674                |
| Duration of inadequate antibiotic treatment (+1 day)                      | 1.06 (0.82–1.34)  | 0.650         |                    |                       |
| Infection type*                                                           |                   |               |                    |                       |
| BSI                                                                       | 25 (67.6)         | 9 (56.2)      | 1.0                |                       |
| CNS                                                                       | 11 (29.7)         | 4 (25.0)      | 0.79 (0.19–2.86)   | 0.726                 |
| Other                                                                     | 1 (2.7)           | 3 (18.8)      | 8.31 (0.97–176.48) | 0.078                 |
| Initial empiric treatment*                                                |                   |               |                    |                       |
| First-line antimicrobial agents†                                          | 12 (32.4)         | 2 (12.5)      | 0.14 (0.01–0.85)   | 0.074                 |
| Alternative antimicrobial agents§                                         | 3 (8.1)           | 2 (12.5)      | 1.13 (0.14–7.70)   | 0.902                 |
| Inadequate regimens                                                       | 22 (59.5)         | 12 (75.0)     | 1.0                |                       |
| Treatment following bacterial identification*                             |                   |               |                    |                       |
| First-line antimicrobial agents†                                          | 27 (73.0)         | 9 (56.2)      | 0.58 (0.14–2.65)   | 0.464                 |
| Alternative antimicrobial agents§                                         | 3 (8.1)           | 3 (18.8)      | 1.75 (0.23–14.22)  | 0.587                 |
| Inadequate antimicrobial agents                                          | 7 (18.9)          | 4 (25.0)      | 1.0                |                       |

Data are presented as numbers (%) or medians (interquartile range).
*Categorical variables included in logistic regression; †Variables included in the multivariable model were selected using the Akaike's Information Criterion (AIC) value based on forward stepwise logistic regression (AIC = 56.046); ‡First-line antimicrobial agents: ampicillin or penicillin alone or in combination with gentamicin; §Alternative antimicrobial agents: trimethoprim-sulfamethoxazole, imipenem, meropenem, or vancomycin (excluding use in CNS infection); ††Included non-pregnancy associated mortality within 30 days of the sample collection date.

Abbreviations: OR, odds ratio; CI, confidence interval; NA, not available; BSI, blood stream infection; CNS, central nervous system.
tive campaigns aimed at pregnant women [24-26]. However, an increased incidence of listeria in adults over 60 years of age has been reported in several studies [1, 15, 27]. Therefore, the initial empiric treatment against L. monocytogenes, especially in healthcare-associated infections, should be carefully considered in groups at high-risk for listeriosis such as elderly and immunocompromised patients.

Because no major STs were found in the MLST analysis, the increased incidence we observed was likely due to sporadic cases rather than an outbreak. We compared the STs of L. monocytogenes obtained by MLST with those reported in previous studies in other countries [28, 29]. CC8 was a major global L. monocytogenes isolate because of its high biofilm forming capacity and its ability to persist in food industrial processes and subsequently contaminate food [30]. According to our results, only one of the 19 isolates was identified as CC8, while the most common ST (four of 19 isolates) was CC9, consistent with the frequency described by Cantinelli et al [28]. The fact that CC8 was not the major ST in our study may be due to differences in regional or dietary habits in Korea.

Our study had a number of limitations. It was a retrospective study, and only 19 of 58 isolates were subjected to MLST analysis, which could have biased the results and decreased the likelihood of identifying major type isolates. In addition, several important medical record details, such as infection source of listeriosis, were not available for most patients. However, although human listeriosis is a food-borne disease, it is difficult to determine the food source of infection because of the long incubation time of L. monocytogenes [7].

This study demonstrated an increased incidence of listeriosis in elderly patients and those in an immunocompromised state at three Korean hospitals. Healthcare-associated infections caused by L. monocytogenes were associated with a high CFR and adequate initial empirical treatments appeared to reduce CFR, suggesting that careful consideration of the empirical antimicrobial regimen for elderly or immunocompromised patients admitted to the hospital is warranted. Multi-center, prospective studies including a larger number of patients with listeriosis would help support our recommendations concerning careful initial empiric treatment of healthcare-associated infections.

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