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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

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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 genotype-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 *lhkA*) 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://bigsdb.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 (CI) 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-Wilks 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).

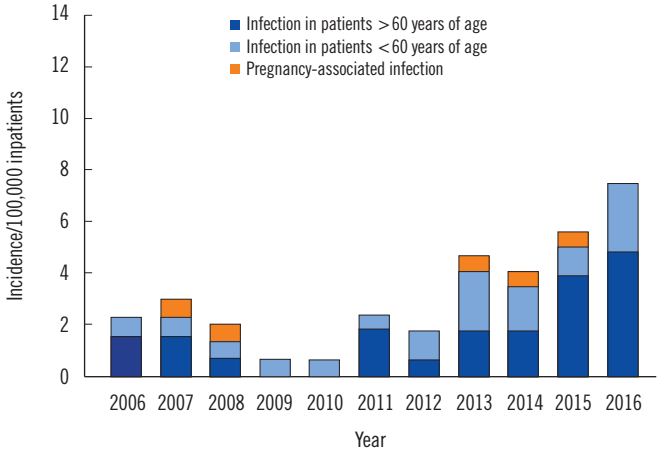

Fig. 1. Increase in the number of *Listeria monocytogenes* isolates according to age distribution, 2006–2016.

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-

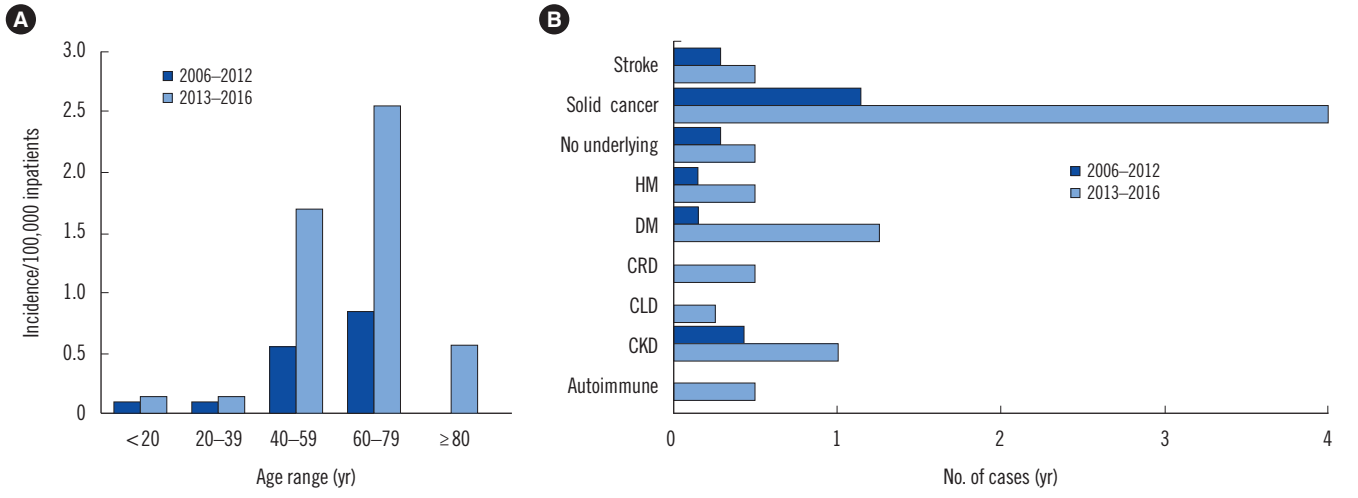

Fig. 2. Trends in non-pregnancy-associated listeriosis categorized by (A) age distribution and (B) underlying disease, 2006–2012 vs 2013–2016.
Abbreviations: Postop, postoperative states; HM, hematologic malignancies; DM, diabetes mellitus; CRD, chronic respiratory diseases; CLD, chronic liver diseases; CKD, chronic kidney diseases.

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Table 1. Characteristics of yearly isolated listeriosis cases

Year	N	Incidence/ 100,000 inpatients	Age (yr)	Male sex	Community-associated infection	Infection types				No. of deaths	Culture results report time post sample collection (days)	Susceptibility (%)		
						BSI	CNS	Pregnancy-associated	Other*			Ampicillin	Penicillin	Trimethoprim-sulfamethoxazole
2006	3	2.3	62.0 [57.0–65.5]	2	2	0	3	0	0	1	4.0 [3.5–5.5]	3 (100)	1 (33.3)	3 (100)
2007	4	3.0	62.5 [29.0–70.5]	2	3	2	1	1	0	2	5.0 [4.0–6.5]	3 (100)	2 (66.7)	3 (100)
2008	3	2.0	48.0 [24.0–60.0]	1	2	1	1	1	0	1	4.0 [3.0–5.5]	2 (100)	2 (100)	2 (100)
2009	1	0.6	22.0 [22.0–22.0]	0	1	0	1	0	0	0	2.0 [2.0–2.0]	1 (100)	1 (100)	1 (100)
2010	1	0.6	45.0 [45.0–45.0]	1	1	0	1	0	0	0	6.0 [6.0–6.0]	2 (100)	0 (0)	1 (100)
2011	4	2.4	71.5 [44.0–74.5]	3	3	3	1	0	0	1	3.5 [2.5–4.0]	1 (100)	4 (100)	4 (100)
2012	3	1.7	59.0 [56.0–61.0]	2	1	2	1	0	0	1	3.0 [3.0–4.0]	2 (100)	2 (100)	2 (100)
2013	8	4.7	55.5 [25.0–65.0]	6	3	5	1	1	1	4	3.0 [2.5–6.0]	NA	5 (100)	3 (100)
2014	7	4.1	56.0 [53.5–66.0]	4	6	5	1	1	0	1	2.0 [2.0–2.5]	NA	6 (100)	4 (66)
2015	10	5.6	74.0 [57.0–80.0]	5	8	7	2	1	0	2	3.0 [2.0–4.0]	NA	3 (100)	5 (100)
2016	14	7.5	62.5 [57.0–74.0]	5	12	9	2	0	3	4	3.0 [2.0–4.0]	NA	9 (100)	9 (100)

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.

piric treatment (60.3%), and first-line antimicrobial agents were selected in 31% (18 of 58) of cases; treatment regimen was mostly altered to first-line antimicrobial agents after obtaining culture results (median delay of 0 day; IQR, 0–2 days). All 14 isolates tested for antimicrobial susceptibility were susceptible to ampicillin, whereas only two of the 39 isolates showed resistance to trimethoprim-sulfamethoxazole and four of the 39 isolates were resistant to penicillin. There were no statistically significant differences between the community- and healthcare-associated infection groups in terms of median age at diagnosis, sex, or infection type. Of the non-pregnancy associated cases, 17 patients died within 30 days of sample collection. The healthcare-associated infection group showed a higher mortality rate than the community-associated infection group (56.2% vs 21.6%, $P=0.014$).

MLST analysis of 19 available *L. monocytogenes* isolates from hospital "A" revealed that seven isolates belonged to genetic lineage I and 12 isolates belonged to genetic lineage II and that there were 13 different sequence types (ST) present (Table 3). The remaining 39 isolates had not been frozen and therefore could not be analyzed. The most commonly identified genotype was 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.

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 organ cancer or type 2 DM.

Listeriosis exhibited a high CFR (29.3%) in our study. Using multivariate analysis, we found that healthcare-associated infections constitute a risk factor related to higher CFR compared with community-associated infections. In addition, the initial selection of appropriate empiric antimicrobial agents was associ-

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				0.396
BSI	34 (58.6)	24 (57.1)	10 (62.5)	
CNS	15 (25.9)	11 (26.2)	4 (25.0)	
Pregnancy-associated	5 (8.6)	5 (11.9)	0 (0.0)	
Other	4 (6.9)	2 (4.8)	2 (12.5)	
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				0.270
Solid cancer	24 (41.4)	14 (33.3)	10 (62.5)	
Hematologic malignancy	3 (5.2)	2 (4.8)	1 (6.2)	
Other immunocompromised conditions	22 (37.9)	17 (40.5)	5 (31.2)	
Pregnancy-associated	5 (8.6)	5 (11.9)	0 (0.0)	
Other	4 (6.9)	4 (9.5)	0 (0.0)	
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 (10^9/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				0.339
First-line antimicrobial agents*	18 (31.0)	13 (31.0)	5 (31.2)	
Alternative antimicrobial agents†	5 (8.6)	5 (11.9)	0 (0.0)	
Inadequate antimicrobial agents	35 (60.3)	24 (57.1)	11 (68.8)	
Treatments post bacterial identification				0.650
First-line antimicrobial agents*	39 (67.2)	27 (64.3)	12 (75.0)	
Alternative antimicrobial agents†	7 (12.1)	6 (14.3)	1 (6.2)	
Inadequate antimicrobial agents	12 (20.7)	9 (21.4)	3 (18.8)	
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.

ated with a low CFR. Therefore, initial empiric treatment should be chosen carefully in patients with healthcare-associated listeriosis.

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

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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	I	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.

in clinical settings, such as cephalosporins [15] and quinolones [22], are not effective against *L. monocytogenes* infection. In our study, only 18 of 58 (31.0%) patients were treated initially with ampicillin- or penicillin-based regimens, whereas 35 patients (60.3%) were treated with inadequate empirical regimens, including cephalosporins (18 patients, 27.6%), quinolones (nine patients, 15.5%) and no empirical antibiotics (eight patients, 13.8%). Although 24 of 35 patients who received inadequate initial empirical regimens were immediately changed over to adequate drugs (median, 2.0 day), such as ampicillin or penicillin once culture results were obtained, this was not reflected by a statistically significant difference in CFR.

A previous meta-analysis has suggested that *L. monocytogenes* should not be considered in febrile infants because of the very rare incidence of listeriosis at that age [23]. In addition, the annual incidence of pregnancy-associated listeriosis has decreased significantly since 1985, presumably because of preven-

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)*	15 (40.5)	7 (43.8)	1.14 (0.34–3.74)	0.828		
Sex, female*	16 (43.2)	8 (50.0)	1.31 (0.40–4.32)	0.650		
Healthcare-associated infection*	7 (18.9)	9 (56.2)	5.51 (1.57–21.04)	0.009	12.15 (2.56–86.01)[†]	**0.004**
Immunocompromised state*	33 (89.2)	16 (100.0)	NA			
Prior history of solid organ or hematologic malignancy*	16 (43.2)	11 (68.8)	2.89 (0.87–10.75)	0.094		
Bacterial identification report time post sample collection (+1 day)	3.0 [2.0–4.0]	3.0 [2.0–3.5]	0.81 (0.53–1.14)	0.279	0.67 (0.41–1.01)[†]	0.0674
Duration of inadequate antibiotic treatment (+1 day)	4.0 [2.0–6.0]	3.0 [3.0–5.0]	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	0.08 (0.00–0.63)[†]	**0.044**
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.

Authors' disclosures of potential conflict of interest

We declare that we have no conflicts of interest.

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