Infection (2017) 45:67–74
DOI 10.1007/s15010-016-0939-2

ORIGINAL PAPER

Predictive risk factors for *Listeria monocytogenes* meningitis compared to pneumococcal meningitis: a multicenter case–control study

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Received: 15 April 2016 / Accepted: 8 August 2016 / Published online: 19 August 2016

Abstract

Purpose Various immunocompromised conditions increase the risk of meningitis caused by *Listeria monocytogenes*. However, the relative importance of these risk factors has not been well established. We determined the risk factors that predict meningitis due to *L. monocytogenes* compared to that caused by *Streptococcus pneumoniae*.

Methods A nationwide multicenter case–control study was conducted in Korea. Cases of meningitis caused by *L. monocytogenes* between 1998 and 2013 were included. Patients with pneumococcal meningitis were included as controls. Multivariate logistic regression analysis was used to predict the risk factors of *Listeria* meningitis.

Results A total of 36 cases and 113 controls were enrolled. The most significant predictive risk factor of *Listeria* meningitis was a prior history of receiving immunosuppressive therapy (odds ratio 8.12, 95 % CI 2.47–26.69). Chronic liver disease was the second most important predictive risk factor (OR 5.03, 95 % CI 1.56–16.22). Delaying appropriate antibiotic therapy by more than 6 h (hazard ratio 2.78) and fatal underlying disease (hazard ratio 2.88) were associated with increased mortality.

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Conclusions Patients with a prior history of receiving immunosuppressive therapy within 1 month and chronic liver disease have 8.1-fold and 5-fold increased risk of meningitis by *L. monocytogenes* compared to *S. pneumoniae*, respectively.

Keywords Immunocompromised host · Liver diseases · Elderly · *Streptococcus pneumoniae* · Listeriosis

Introduction

Clinical infection with *Listeria monocytogenes* is well recognized to occur in particular groups including the immunocompromised, pregnant women, elderly, and neonates [1]. The incidence of listeriosis is increasing in the USA and Europe [1]. Around 20–25 % of listeriosis cases involve the central nervous system [2]. *L. monocytogenes* is the second or third most frequent cause of bacterial meningitis in American and European adults [3, 4]. Among Korean adults, *L. monocytogenes* is the fourth most common etiology of community-acquired bacterial meningitis [5]. Meningitis due to *L. monocytogenes* has been mostly reported in immunocompromised hosts and elderly patients [6].

There are several predisposing conditions to increase the susceptibility for bacterial meningitis [7]. In particular, the common risk factors of pneumococcal and *Listeria* meningitis in adults include age older than 65 years, alcoholism, diabetes mellitus, cancer, and organ transplantation [7]. In this study, we determined the risk factors for predicting *L. monocytogenes* as the etiology of bacterial meningitis in adults compared to that due to *S. pneumoniae*.

Patients and methods

Study population

We conducted a multicenter, retrospective case–control study at 16 teaching hospitals in Korea. All patients were 18 years or older and were discharged with a diagnosis of bacterial meningitis between 1998 and 2013. The diagnoses were identified using ICD10 codes (G00–G03, A32.1). Bacterial meningitis was defined with clinical manifestations and cerebrospinal fluid (CSF) abnormalities compatible with meningitis and with a confirmed bacterial pathogen by cultures of CSF or blood or bacterial antigen testing. Cases were defined as patients with meningitis caused by *L. monocytogenes*. *Listeria* meningitis was diagnosed when *L. monocytogenes* was identified in the culture of the CSF and/or blood. Controls were cases of pneumococcal meningitis, diagnosed either by culture of the CSF and/or blood or by a bacterial antigen test. Some data of the meningitis cases between 1998 and 2008 were collected from a prior study's database of bacterial meningitis cases in adults [5]. This study was approved by the Samsung Medical Center Institutional Review Board (2008-06-052-001).

Clinical and microbiological data

Demographic and clinical information including age, gender, underlying medical conditions, neurologic manifestations, CSF profile, brain imaging, and antibiotic treatment were collected from the medical records. Immunosuppressive agents included anti-cancer drugs, corticosteroids, purine pathway inhibitors (azathioprine, mycophenolate mofetil), leflunomide, calcineurin inhibitors (cyclosporine, tacrolimus), mammalian target of rapamycin (mTOR) inhibitors (sirolimus) and tumor necrosis factor-alpha blockers. The McCabe classification was used to categorize the severity of the underlying medical condition as nonfatal, ultimately fatal, or rapidly fatal [8]. Septic shock and severe sepsis were defined by the Society of Critical Care Medicine/American College of Chest Physicians criteria [9]. Based on data from the medical record and according to the definition from the Centers for Disease Control and Prevention (CDC), heavy alcohol drinking was defined as ingestion of five or more glasses of alcohol at one time (or four or more in women) [10].

The empirical antibiotic regimen was considered appropriate in cases if it included ampicillin/other penicillins or meropenem. In controls, concordant antibiotic therapy based on the in vitro susceptibility of the isolated *S. pneumoniae* strain was considered appropriate. The antimicrobial susceptibility of *S. pneumoniae* was determined according to the criteria of the Clinical and Laboratory Standards Institute [11].

Outcome variables

Early clinical outcome was evaluated at 3 days of treatment. All-cause mortality and infection-related mortality were assessed at 30 days of treatment. Neurological complications were evaluated at the time of discharge. The length of hospital stay was defined as the time between admission and discharge.

Statistical analysis

All statistical analyses were performed using Stata version 11.2 (StataCorp, College Station, TX, USA). All tests of significance were two tailed. P values <0.05 were

considered to be statistically significant. Categorical variables were compared between the groups using Chi square test or Fisher's exact test. Continuous variables were compared using the Mann–Whitney *U* test.

Multivariate logistic regression analysis was used to determine the risk factors of *Listeria* meningitis compared to those of pneumococcal meningitis. Independent variables were selected for backward stepwise regression and included age 50 years or older, chronic kidney disease, chronic liver disease, malignancy, and prior history of receiving immunosuppressive therapy. The covariants showing $P \geq 0.2$ were removed from the final model. Time to death curves during the follow-up period were calculated using the Kaplan–Meier method and compared between groups using the log-rank test. Multivariate cox regression analysis was used to determine the risk factors of mortality.

Results

Demographic characteristics and underlying diseases

A total of 36 meningitis cases caused by *L. monocytogenes* were included in the cases, and the controls included 113 cases of pneumococcal meningitis (Table 1). Among cases of *L. monocytogenes* meningitis, 9 had positive cultures in both CSF and blood, 20 had positive CSF culture only, and 7 had positive blood culture only. The cases of pneumococcal meningitis comprised 31 with positive cultures in both CSF and blood, 71 with positive cultures in CSF only (39 were also antigen positive), 8 with positive cultures in blood only, and 3 with antigen-positive test only. There were more patients who were ≥50-year-old in the cases than in the controls. Hypertension, chronic kidney disease, chronic

Table 1 Comparison of demographic characteristics and underlying diseases between patients with *Listeria* meningitis (cases) and pneumococcal meningitis (controls)

Variable	No. (%)		*P* value
	Cases ($n = 36$)	Controls ($n = 113$)	
Age in years, median (IQR)	63.5 (53.5–73)	59 (42–68)	0.056
Age 50 years or older	30 (83.3)	73 (64.6)	0.034
Age 65 years or older	17 (47.2)	39 (34.5)	0.170
Gender, male	22 (61.1)	68 (60.2)	0.921
Underlying diseases			
Diabetes mellitus	11 (30.6)	28 (24.8)	0.492
Hypertension	13 (36.1)	20 (17.7)	0.021
Chronic liver disease	9 (25.0)	7 (6.2)	0.002
Malignancy (solid tumor)	6 (16.7)	8 (7.1)	0.086
Cerebrovascular disease	3 (8.3)	7 (6.2)	0.655
Chronic kidney disease	4 (11.1)	1 (0.9)	0.012
Hematologic malignancy	1 (2.8)	2 (1.8)	0.567
Chronic lung disease or asthma	0 (0)	1 (0.9)	1.000
Autoimmune disease	7 (19.4)	1 (0.9)	<0.001
Asplenia	2 (5.6)	1 (0.9)	0.145
Heavy alcohol drinking	10 (27.8)	23 (20.3)	0.350
Pregnancy	0 (0)	1 (0.9)	1.000
History of receiving	12 (33.3)	7 (6.2)	<0.001
Immunosuppressive therapy within 1 month			
Corticosteroid	8 (22.2)	4 (3.5)	<0.001
Other immunosuppressant	11 (29.7)	7 (6.3)	<0.001
History of receiving antibiotic therapy within 1 month	5 (13.9)	22 (19.5)	0.449
Residence in chronic care facility	3 (8.6)	1 (1.1)	0.069
Severity of underlying disease (McCabe classification)			0.709
Nonfatal	32 (88.9)	100 (88.5)	
Ultimately fatal	4 (11.1)	11 (9.7)	
Rapidly fatal	0 (0)	2 (1.8)	

Data are expressed as no. (%) of patients, unless indicated otherwise

IQR interquartile range

Table 2 Risk factors for *Listeria* meningitis compared with pneumococcal meningitis

Variables	Univariate		Multivariate	
	OR (95 % CI)	*P* value	OR (95 % CI)	*P* value
Age 50 years or older	2.74 (1.05–7.14)	0.0273	1.84 (0.58–5.79)	0.299
Chronic kidney disease	14.0 (1.51–129.71)	0.0072	9.86 (0.89–109.79)	0.063
Chronic liver disease	5.05 (1.72–14.78)	0.0033	5.03 (1.56–16.22)	0.007
Hypertension	2.62 (1.14–6.05)	0.0256	2.40 (0.88–6.57)	0.088
Malignancy (solid tumor)	2.63 (0.84–8.16)	0.1048	1.62 (0.42–6.25)	0.480
History of receiving immunosuppressive therapy within 1 month	7.57 (2.70–21.25)	0.0001	8.12 (2.47–26.69)	0.001

OR odds ratio, *CI* confidence interval

liver disease, autoimmune disease, and a prior history of receiving immunosuppressive therapy were also more frequent in the cases than in the controls.

Predictive risk factors of *Listeria* meningitis

The most significant risk factor of *Listeria* meningitis was a prior history of receiving immunosuppressive therapy (odds ratio 8.12) (Table 2). Chronic liver disease was the second most important risk factor associated with the cases (OR 5.03). Chronic kidney disease also had a tendency to be associated with *Listeria* meningitis (OR 9.86, $P = 0.063$).

Clinical characteristics of *Listeria* meningitis

At the time of diagnosis, there were no significant differences between the two groups with regard to frequency of neurological abnormalities including seizure, cranial nerve palsy, aphasia, hemiparesis, and other neurological deficits (Table 3). Similarly, there were no differences between the two groups with regard to brain imaging results. The CSF profile of the cases was quite different from that of the controls (Table 3). The median white blood cell (WBC) count, neutrophil percentage, and protein level were much lower in the cases than in the controls. The median CSF/serum glucose ratio was 0.28 in the cases, but only 0.07 in the controls. The frequency with which the microscopic examination of Gram-stained concentrated CSF showed the presence of microorganisms was much lower in the cases than in the controls (12.5 vs. 79.1 %).

Treatment and clinical outcome of *Listeria* meningitis

In the case, the most frequent initial empirical antibiotic regimen was a combination of vancomycin, third- or fourth-generation cephalosporin, and ampicillin. In contrast, the most frequent regimen in the controls was a combination of vancomycin and third- or fourth-generation cephalosporin (Table 4). The frequency of appropriate empirical antibiotic therapy was significantly lower in the cases than in the controls (63.9 vs. 96.1 %). The time to appropriate antibiotic therapy was also significantly longer in the cases than in the controls.

Early outcome assessment in the cases at 3 days showed no mortality; however, 54.8 % of the cases had worsened. In contrast, the fatality rate was 11.6 % in the controls. The overall 30-day mortality rate was higher in the cases than in the controls, although the difference was not significant (Table 4). There were no differences between the two groups with regard to neurological complications at discharge. The length of hospital stay was longer in the cases than in the controls.

Comparison of the Kaplan–Meier curves using a log-rank test demonstrated a significant difference in survival between the two groups (Fig. 1). There was a lower number of patient survival among the *Listeria* cases than among the controls. However, multivariate Cox regression analysis found that *Listeria* versus *S. pneumoniae* was not a significant risk factor of mortality. In contrast, delaying appropriate antibiotic therapy by more than 6 h had a 2.78-fold increased risk of mortality compared to cases in which the patient received appropriate therapy within 6 h (95 % CI 1.13–6.87, $P = 0.027$). Fatal underlying disease was also associated with increased fatality rate (hazard ratio 2.88, 95 % CI 1.16–7.18, $P = 0.023$).

Among the 13 cases of *Listeria* meningitis in which patients received inappropriate initial empirical antibiotic therapy, the inappropriate therapy was continued in four cases even after *L. monocytogenes* was identified. Three of these four patients died. The median time to appropriate antibiotic therapy in the nine remaining cases was 72 h (range 24–288 h). Two of these nine patients died. Nine of 13 patients developed neurological complications.

Table 3 Comparison of clinical characteristics of patients with *Listeria* meningitis (cases) and patients with pneumococcal meningitis (controls)

Variable	No. (%)		*P* value
	Cases ($n = 36$)	Controls ($n = 113$)	
Length of symptoms prior to diagnosis (days), median (IQR)	2 (1–5)	1 (1–2)	0.162
Sepsis			0.265
Sepsis	17 (47.2)	39 (34.5)	
Severe sepsis	0 (0)	6 (5.3)	
Septic shock	1 (2.8)	8 (7.1)	
Neurologic manifestations at diagnosis			
Seizure	5 (13.9)	24 (21.2)	0.365
Neurological deficit	5 (13.9)	7 (6.2)	0.140
Third cranial nerve palsy	0 (0)	2 (1.8)	1.000
Sixth cranial nerve palsy	2 (5.6)	0 (0)	0.057
Seventh cranial nerve palsy (peripheral type)	2 (5.6)	2 (1.8)	0.246
Aphasia	1 (2.8)	2 (1.8)	0.567
Hemiparesis	1 (2.8)	3 (2.7)	1.000
Incontinence	1 (2.8)	2 (1.8)	0.567
Initial CSF study			
Opening pressure (cmH_2O), median (IQR)	20.0 (16.0–29.0)	27.0 (17.0–31.0)	0.207
WBC ($/mm^3$) in CSF, median (IQR)	805 (162–1220)	1750 (300–5472)	0.0037
Neutrophil (%), median (IQR)	70 (52–80)	90 (80–95)	<0.0001
Lymphocyte (%), median (IQR)	19 (10–38)	10 (3–10)	<0.0001
Protein (mg/dl), median (IQR)	203.5 (109.5–300)	300 (283–498)	0.0001
Glucose ratio (CSF/serum), median (IQR)	0.28 (0.20–0.40)	0.07 (0.03–0.20)	<0.0001
Bacteria on Gram stain	4/32 (12.5)	87/110 (79.1)	<0.001
Initial brain imaging			
Meningeal enhancement	8 (22.2)	10 (8.9)	0.032
Cerebritis	5 (13.9)	10 (8.9)	0.382
Cerebellitis	0 (0)	1 (0.9)	1.000
Brain stem encephalitis	2 (5.6)	0 (0)	0.057
Brain abscess	2 (5.6)	2 (1.8)	0.246
Infarction	2 (5.6)	14 (12.4)	0.359
Hydrocephalus	2 (5.6)	6 (5.3)	1.000

Data are expressed as no. (%) of patients, unless indicated otherwise

Reference range CSF WBC $\leq$5 cells/mm^3, neutrophil 0–6 %, lymphocyte 40–80 %, proteins 20–40 mg/dL, CSF/serum glucose ratio 0.6–0.8

IQR interquartile range, *WBC* white blood cell, *CSF* cerebrospinal fluid

Discussion

Adult meningitis patients with a prior history of receiving immunosuppressive therapy had an 8.1-fold increased risk of infection with *L. monocytogenes* versus with *S. pneumoniae*. Chronic liver disease also increased the risk of *L. monocytogenes* by fivefold.

Previous studies have found that most patients (>60 %) with *Listeria* meningitis are immunocompromised or elderly [6, 12]. There were many reported immunocompromised conditions, including immunosuppressive therapy, malignancy, connective tissue disease, diabetes mellitus, alcoholism, asplenia, liver cirrhosis, end-stage renal disease, and HIV infection [6]. However, those factors in addition to old age have long been recognized as important risks predisposing to pneumococcal meningitis [13]. To the best of our knowledge, there is only one prior report that compares the risk factors between *Listeria* and pneumococcal meningitis. A prospective observational study in Italian patients older than 50 years at a single center compared 22 cases of *Listeria* meningitis and 109 cases of pneumococcal meningitis. The group found an association between *Listeria* and current immunosuppressive therapy (OR 4.0, 95 % CI 1.2–6.9, $P = 0.008$) [14].

Table 4 Comparison of antibiotic regimen and clinical outcome of patients with *Listeria* meningitis (cases) and pneumococcal meningitis (controls)

Variable	No. (%)		*P* value
	Cases ($n = 36$)	Controls ($n = 113$)	
Empirical antibiotics			0.003
Vancomycin + 3rd/4th cephalosporin + ampicillin	13 (37.1)	23 (20.5)	
Vancomycin + 3rd/4th cephalosporin	6 (17.1)	56 (50.0)	
3rd/4th cephalosporin + ampicillin	1 (2.9)	4 (3.6)	
3rd/4th cephalosporin	4 (11.4)	2 (1.8)	
Vancomycin + 3rd/4th cephalosporin + ampicillin + rifampicin	1 (2.9)	4 (3.6)	
Others	11 (30.6)	23 (20.5)	
Empirical use of penicillin class	20 (55.6)	36 (32.1)	0.012
Appropriateness of empirical antibiotics	23 (63.9)	99 (96.1)	<0.001
Intraventricular antibiotic use	2 (5.6)	1 (0.9)	0.145
Adjunctive corticosteroid			0.088
None	13 (36.1)	33 (29.2)	
Before or with starting antibiotics	20 (55.6)	51 (45.1)	
After starting antibiotics	3 (8.3)	29 (25.7)	
Definitive use of ampicillin	27 (75.0)	25 (22.1)	<0.001
Definitive use of vancomycin	2 (5.6)	80 (70.8)	<0.001
Definitive use of 3rd/4th cephalosporin	4 (11.1)	93 (82.3)	<0.001
Appropriateness of definitive antibiotics	31 (86.1)	97 (92.4)	0.262
Time to appropriate antibiotic therapy*			<0.001
3 h or less	6 (23.1)	63 (64.3)	
3–6 h	1 (3.9)	13 (13.3)	
6–12 h	5 (19.2)	11 (11.2)	
12–24 h	3 (11.5)	6 (6.1)	
>24 h	11 (42.3)	5 (5.1)	
Early outcome at 3 days**			0.011
Improving	14 (45.2)	60 (63.2)	
Worsening	17 (54.8)	24 (25.3)	
Meningitis-related death	0 (0)	10 (10.5)	
Meningitis-unrelated death	0 (0)	1 (1.1)	
Overall mortality within 30 days	10/32 (31.3)	18/103 (17.5)	0.093
Infection-related mortality within 30 days	8/32 (25.0)	17/103 (16.5)	0.280
Neurological complications at discharge	20 (55.6)	62 (54.9)	0.942
Seizure	6 (16.7)	26 (23.0)	0.420
Hearing loss	1 (2.8)	11 (9.7)	0.182
Motor weakness	2 (5.6)	4 (3.5)	0.592
Cranial nerve palsy	4 (11.1)	3 (2.7)	0.037
Hydrocephalus	6 (16.7)	11 (9.7)	0.255
Acute infarction	2 (5.6)	13 (11.5)	0.302
Length of stay (days), median (IQR)	24 (15–38)	17 (13–26)	0.0393

Data are expressed as no. (%) of patients, unless indicated otherwise

* $n = 26$ for *Listeria*, $n = 98$ for *S. pneumoniae*

** $n = 31$ for *Listeria*, $n = 95$ for *S. pneumoniae*

In the present study, other risk factors such as old age, diabetes mellitus, and malignancy were not different in association with the etiology between *Listeria* and pneumococcal meningitis. In univariate analysis, the proportion of persons aged 50 years or elder was higher in *Listeria* meningitis than in pneumococcal meningitis.

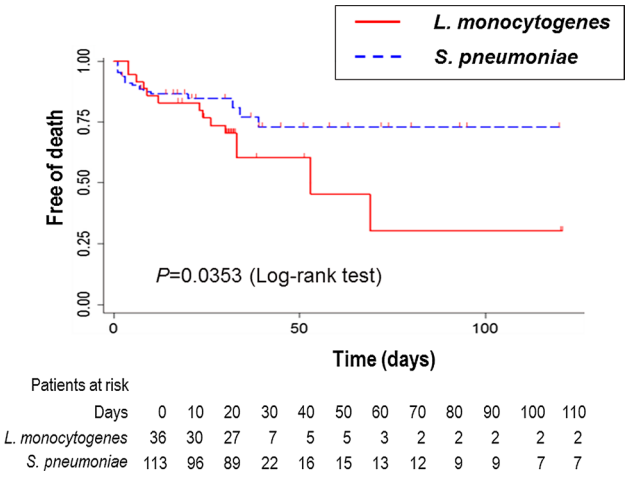

Fig. 1 Comparison of the Kaplan–Meier *curves* showing the cumulative probability of survival between *Listeria* and pneumococcal meningitis cases. The *numbers below* the *plots* indicate the number of patients at risk in each group at the given time points

However, this difference was not significant in multivariate analysis. Chronic kidney disease tended to be associated with *Listeria* meningitis. Therefore, it may be a risk factor predicting *Listeria* (versus *S. pneumoniae*) as the etiology of bacterial meningitis in adults.

In our study, the initial empirical antibiotic treatment was inappropriate in 36.1 %. Previous studies found that 30–50 % of patients with *Listeria* meningitis initially received inappropriate empiric treatment [6, 15]. A delay in treatment increased mortality and the risk of developing neurologic sequelae [15]. Interestingly, 55 % of *Listeria* cases in this study worsened clinically at 3 days of treatment, although there was no mortality. However, this finding is not unexpected, as 42 % of the patients did not receive appropriate antibiotic therapy for at least 24 h. The fatality rate in our study was similar to that of the previous reports (17–27 %) [13]. Vancomycin had been suggested as an alternative agent for treatment of *Listeria* meningitis in some recommendations due to in vitro susceptibility of vancomycin against *L. monocytogenes* [16]. However, the practice guidelines for the management of bacterial meningitis proposed by the Infectious Diseases Society of America (IDSA) in 2004 do not recommend the use of vancomycin for either empirical or definitive therapy of *Listeria* meningitis [17], and vancomycin has been associated with treatment failures in patients [13]. Therefore, vancomycin use was determined to be inappropriate for *Listeria* meningitis in our study. There were high rates (55.6 %) of neurological complications in this study. This may have occurred because we included the patients with neurological complications who eventually died. In contrast, Brouwer reported that neurological sequelae occurred in 25 % of patients who survived *Listeria* meningitis [13].

This study has several limitations. First, this was a retrospective study based on medical records. Therefore, our results may have been susceptible to information bias. For example, time to appropriate antibiotic therapy could not be calculated from all the enrolled patients. Secondly, the sample size of cases was small. Therefore, we were unable to analyze independent risk factors of mortality or neurological complications in patients with *Listeria* meningitis. Thirdly, the controls in this study were patients with pneumococcal meningitis. Therefore, we were not able to address the common risk factors shared by *Listeria* and pneumococcal meningitis. Fourthly, our study did not analyze any genotypic information of *L. monocytogenes* isolates. A recent report showed that the clinical outcomes differed according to the genotype of the *L. monocytogenes* strains [18]. Therefore, genotypic difference between the *L. monocytogenes* strains could have affected our analysis. Lastly, our data on the underlying diseases did not include sinusitis or mastoiditis, which are known to be important foci of infection in pneumococcal meningitis [13]. As our study was a retrospective design, consultation of the cases with the otorhinolaryngologists for examination was not done. This might have affected the risk factor analysis.

In conclusion, adult patients with a prior history of receiving immunosuppressive therapy within 1 month and those with chronic liver disease have 8.1-fold and fivefold increased risk of meningitis caused by *L. monocytogenes* compared to *S. pneumoniae*, respectively. Empirical antibiotic coverage targeting *L. monocytogenes* should be considered in the treatment of meningitis in patients with such risk factors.

Acknowledgments This study was supported by a grant from the Korean Health Technology R&D Project, Ministry of Health and Welfare, Republic of Korea (Grant No. HI12C0756).

Compliance with ethical standards

This study was approved by the Samsung Medical Center Institutional Review Board (2008-06-052-001).

Conflict of interest All authors have nothing to declare.

References

1. Maertens de Noordhout C, Devleesschauwer B, Angulo FJ, Verbeke G, Haagsma J, Kirk M, Havelaar A, Speybroeck N. The global burden of listeriosis: a systematic review and meta-analysis. Lancet Infect Dis. 2014;14:1073–82.
2. Disson O, Lecuit M. Targeting of the central nervous system by *Listeria monocytogenes*. Virulence. 2012;3:213–21.
3. van de Beek D, de Gans J, Spanjaard L, Weisfelt M, Reitsma JB, Vermeulen M. Clinical features and prognostic factors in adults with bacterial meningitis. N Engl J Med. 2004;351:1849–59.
4. Thigpen MC, Whitney CG, Messonnier NE, Zell ER, Lynfield R, Hadler JL, Harrison LH, Farley MM, Reingold A, Bennett NM, Craig AS, Schaffner W, Thomas A, Lewis MM, Scallan

E, Schuchat A. Bacterial meningitis in the United States, 1998–2007. N Engl J Med. 2011;364:2016–25.
5. Moon SY, Chung DR, Kim SW, Chang HH, Lee H, Jung DS, Kim YS, Jung SI, Ryu SY, Heo ST, Moon C, Ki HK, Son JS, Kwon KT, Shin SY, Lee JS, Lee SS, Rhee JY, Lee JA, Joung MK, Cheong HS, Peck KR, Song JH. Changing etiology of community-acquired bacterial meningitis in adults: a nationwide multicenter study in Korea. Eur J Clin Microbiol Infect Dis. 2010;29:793–800.
6. Brouwer MC, van de Beek D, Heckenberg SG, Spanjaard L, de Gans J. Community-acquired *Listeria monocytogenes* meningitis in adults. Clin Infect Dis. 2006;43:1233–8.
7. Adriani KS, Brouwer MC, van de Beek D. Risk factors for community-acquired bacterial meningitis in adults. Neth J Med. 2015;73:53–60.
8. Mc CW, Jackson G. Gram-negative bacteremia: I. Etiology and ecology. Arch Intern Med. 1962;110:847–55.
9. Bone RC, Balk RA, Cerra FB, Dellinger RP, Fein AM, Knaus WA, Schein RM, Sibbald WJ. Definitions for sepsis and organ failure and guidelines for the use of innovative therapies in sepsis. The ACCP/SCCM Consensus Conference Committee. American College of Chest Physicians/Society of Critical Care Medicine. Chest. 1992;101:1644–55.
10. Stahre M, Naimi T, Brewer R, Holt J. Measuring average alcohol consumption: the impact of including binge drinks in quantity–frequency calculations. Addiction. 2006;101:1711–8.
11. Clinical and Laboratory Standards Institute. Performance standards for antimicrobial susceptibility testing; twenty-fourth informational supplement. M100-S24. Wayne, PA, USA:CLSI; 2014.
12. Laguna-Del Estal P, Lledo-Ibanez GM, Rios-Garces R, Pintos-Pascual I. Meningitis due to *Listeria monocytogenes* in adults. Rev Neurol. 2013;56:13–8.
13. Brouwer MC, Tunkel AR, van de Beek D. Epidemiology, diagnosis, and antimicrobial treatment of acute bacterial meningitis. Clin Microbiol Rev. 2010;23:467–92.
14. Pagliano P, Attanasio V, Rossi M, Carleo MA, Carannante N, Ascione T, Tuccillo F, Fraganza F. *Listeria monocytogenes* meningitis in the elderly: distinctive characteristics of the clinical and laboratory presentation. J Infect. 2015;71:134–6.
15. Arslan F, Meynet E, Sunbul M, Sipahi OR, Kurtaran B, Kaya S, Inkaya AC, Pagliano P, Sengoz G, Batirel A, Kayaaslan B, Yildiz O, Guven T, Turker N, Midi I, Parlak E, Tosun S, Erol S, Inan A, Oztoprak N, Balkan I, Aksoy Y, Ceylan B, Yilmaz M, Mert A. The clinical features, diagnosis, treatment, and prognosis of neuroinvasive listeriosis: a multinational study. Eur J Clin Microbiol Infect Dis. 2015;34:1213–21.
16. Bartlett JG. *Listeria monocytogenes*. In: Johns Hopkins antibiotic (ABX) guide. Johns Hopkins Medicine. 2016. http://www.hopkinsguides.com/hopkins/view/Johns_Hopkins_ABX_Guide/540318/all/Listeria_Monocytogenes. Accessed 03 July 2016.
17. Tunkel AR, Hartman BJ, Kaplan SL, Kaufman BA, Roos KL, Schel WM, Whitley RJ. Practice guidelines for the management of bacterial meningitis. Clin Infect Dis. 2004;39:1267–84.
18. Koopmans MM, Brouwer MC, Bijlsma MW, Bovenkerk S, Keijzers W, van der Ende A, van de Beek D. *Listeria monocytogenes* sequence type 6 and increased rate of unfavorable outcome in meningitis: epidemiologic cohort study. Clin Infect Dis. 2013;57:247–53.