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Original Article

Epidemiology and Clinical Characteristics of *Listeria monocytogenes* Bacteremia in a Taiwanese Medical Center

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BACKGROUND/PURPOSE: There have been many reported cases of *Listeria monocytogenes* bacteremia in Europe and the United States, but only a few from Taiwan. The present study was undertaken to analyze the clinical characteristics of patients with *L. monocytogenes* bacteremia in Taiwan.

METHODS: Patients with culture-confirmed *L. monocytogenes* bacteremia were identified at Chang Gung Memorial Hospital between January 2001 and December 2008. The clinical features and outcomes of the patients and the antimicrobial susceptibilities of the clinical isolates were analyzed.

RESULTS: Forty-three patients, including two newborn babies (4.7%) and 41 adults (95.3%), with at least one episode of *Listeria* bacteremia were identified. Forty-two (97.7%) of these patients had underlying diseases. Thirty-three patients (76.7%) had fever, 14 (32.6%) had experienced respiratory distress, and 11 (25.6%) had reported changes in consciousness. Twelve patients died within 14 days of infection, corresponding to a case-fatality rate of 27.9%. All the clinical isolates tested were susceptible to ampicillin, penicillin and vancomycin.

CONCLUSION: Most cases of *L. monocytogenes* infection occurred in adults with underlying diseases, especially malignancy, and only two cases of neonatal *L. monocytogenes* bacteremia were identified over the 8-year period. Penicillin, ampicillin and vancomycin could be used for the treatment of *L. monocytogenes* bacteremia, with the case-fatality rate lower for patients who received appropriate treatment.

KEYWORDS: bacteremia, *Listeria monocytogenes*, mortality, Taiwan

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Introduction

Listeria monocytogenes is an aerobic and facultatively anaerobic, motile, Gram-positive rod that infects humans. *Listeria* infection is an uncommon disease in the general population, usually causing self-limited febrile gastroenteritis in previously healthy individuals who ingest high numbers of *Listeria*. However, *L. monocytogenes* infection can cause death in specific groups, including elderly adults, pregnant women, neonates and immunocompromised patients. In these hosts, *listeria* infection may develop into sepsis or central nervous system infection (meningitis or meningoencephalitis).[1–3]

Although there have been several reports from Europe and the United States on the clinical manifestations of *Listeria* bacteremia,[4–6] only one report has come from Taiwan.[7] Therefore, we reviewed the medical records of 43 patients with *L. monocytogenes* bacteremia at Chang Gung Memorial Hospital (CGMH) from 2001 to 2008. The goal of the present study was to analyze the clinical manifestations of patients with *L. monocytogenes* bacteremia in a medical center from Taiwan.

Methods

Patients and bacterial isolates

Patients with *L. monocytogenes* bacteremia were identified retrospectively from blood culture reports received from the clinical microbiology laboratory at CGMH from January 2001 to December 2008. All the medical records of patients with blood cultures that grew *L. monocytogenes* were studied retrospectively. For this cohort, we reviewed the underlying host conditions (age, underlying diseases and immunosuppressed status), laboratory data [hemogram, C-reactive protein (CRP), cerebrospinal fluid (CSF) analyses, and antimicrobial susceptibilities], clinical presentations, treatments and outcomes.

We classified the patients into groups based on age and time of onset, to identify the age and year distributions of *listeria* infection, and compared the fatality rates of the groups. The clinical symptoms and signs, including fever, respiratory distress and consciousness changes, were recorded. Infections were considered nosocomial if they first appeared 48 hours or more after hospital admission or within 30 days after discharge.[8] Antimicrobial susceptibility of the *L. monocytogenes* isolates from the patients was reviewed. The susceptibilities of the bacterial isolates to ampicillin, penicillin and vancomycin were determined by the E-test (AB Biodisk, Solna, Sweden), and the results were interpreted according to Clinical and Laboratory Standards Institute guidelines.[9] We reviewed the treatment course administered to each patient, to determine whether the patient received appropriate antibiotic therapy and the post-treatment outcomes were analyzed.

Identification

Simplified identification of *L. monocytogenes* was based on the following tests: Gram staining, observation of trembling motility in a wet mount, positive catalase reaction, and esculin hydrolysis. *L. monocytogenes* is Gram-positive and rod-shaped, usually non-motile and catalase negative. The CAMP test uses a β-lysin-producing *Staphylococcus aureus* strain streaked in one direction on a sheep blood agar plate and test cultures of *L. monocytogenes* streaked at right angles (but not touching) the *S. aureus* culture streaks. An identical broth culture incubated at 37°C shows considerably less motility. This motility pattern is also illustrated by an "umbrella-shaped" pattern that develops after overnight incubation at room temperature of an agar stab culture.[10]

Definitions

An episode of significant bacteremia was defined as one or more *L. monocytogenes*-positive blood cultures, in combination with clinical sepsis. A case was considered maternal/neonatal when a pregnant woman, a miscarriage, a stillbirth, or a newborn of less than 1 month of age was involved.[11] Meningitis was defined by the growth of *L. monocytogenes* in the CSF, elevated CSF protein (>45 mg/dL) or pleocytosis (white blood cells >100 cells/μL in CSF) with *L. monocytogenes* sepsis.[12] Sepsis was defined as a positive blood culture sample with systemic inflammatory response syndrome.[13] Leukocytosis was defined by a white blood cell count greater than 10,000 cells/μL in the peripheral blood. Neutrophilia was defined as an absolute neutrophil count greater than 7,500/μL in the peripheral blood, and neutropenia was defined as an absolute neutrophil count of less than 500/μL.[14] Fatality was defined as death within 14 days of a blood culture showing *listeria* infection. Appropriate treatment was defined as therapy with ampicillin, penicillin, vancomycin, macrolides (erythromycin or azithromycin),

imipenem, meropenem, linezolid, teicoplanin or rifampin.[15] Gentamicin was considered to have a synergistic effect and cephalosporins were considered to be ineffective in these patients.[15]

Statistical analysis

Categorical variables were analyzed by Fisher's exact test. Continuous variables were analyzed by Student's *t* test. A *p* value less than 0.05 was considered statistically significant. Statistic analysis was performed using SPSS version 15 (SPSS Inc., Chicago, IL, USA).

Results

Demographic data

Forty-three patients with at least one episode of *L. monocytogenes* bacteremia were identified at CGMH between January 2001 and December 2008, and were assigned to the following age groups: neonates ($n=2$); 6–18 years ($n=1$); 19–50 years ($n=9$, 20.9%); 51–60 years ($n=13$, 30.2%); 61–70 years ($n=7$, 16.3%); 71–80 years ($n=8$, 18.6%); and 81–90 years ($n=3$, 7.0%) (Table 1). The ratio of males to females was 1.05 (22 *vs.* 21 patients). The numbers of years from onset of infection are shown in the Figure.

Diagnosis

For the 41 adult patients, 37 (90.2%) had a diagnosis of sepsis and 3 (7.3%) had meningitis and sepsis. Only one patient had pneumonia, with a chest X-ray showing left lower lobe pneumonia. The two neonatal patients suffered from listeriosis within 1 day of birth (early onset disease). However, one neonatal patient had meningitis and sepsis, while the other had sepsis only. The baby with a diagnosis of sepsis had a history of maternal fever.

Underlying diseases

All cases except one newborn patient had an underlying disease, such as solid tumors ($n=15$, 34.9%), renal failure ($n=13$, 30.2%), type II diabetes mellitus ($n=11$, 25.6%). One neonatal patient was born prematurely with a gestation age of 29 weeks (Table 2).

Clinical symptoms, signs and outcomes

Thirty-three patients (76.7%) had fever, 14 (32.6%) had respiratory distress, 12 (27.9%) experienced consciousness

Table 1. Age distribution of the 43 cases of *Listeria monocytogenes* infection

Age	*n* (%)	Case-fatality rate (%)
0–7 d	2 (4.7)	0
8 d to 3 mo	0 (0)	0
4 mo to 5 yr	0 (0)	0
6–18 yr	1 (2.3)	0
19–50 yr	9 (20.9)	11.1
51–60 yr	13 (30.2)	38.5
61–70 yr	7 (16.3)	42.8
71–80 yr	8 (18.6)	12.5
81–90 yr	3 (7.0)	66.7

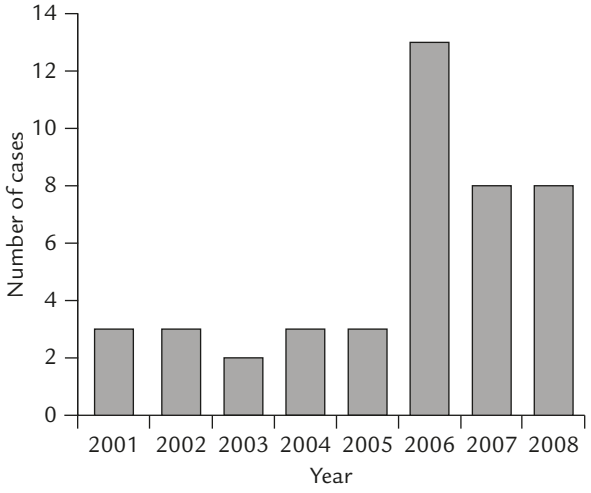

Figure. Numbers of cases of *Listeria monocytogenes* infection from 2001 to 2008 diagnosed at Chang Gung Memorial Hospital, Taoyuan, Taiwan.

Table 2. Underlying conditions of the 43 patients with *Listeria monocytogenes* infection

Underlying diseases ($n=43$)	*n* (%)
Solid tumors	15 (34.9)
Renal failure	13 (30.2)
Type 2 diabetes mellitus	11 (25.6)
Lymphoid and hematopoietic malignancy	6 (14.0)
Systemic lupus erythematosus	4 (9.3)
Chronic hepatitis	3 (7.0)
Liver cirrhosis	3 (7.0)
Asthma under steroid treatment	2 (4.7)
Chronic obstructive pulmonary disease	2 (4.7)
Prematurity	1 (2.3)
Pregnancy	1 (2.3)

changes, and six (13.9%) appeared lethargic. Twelve patients died within 14 days (fatality rate 27.9%). The highest case-fatality rate (66.7%) was noticed in patients aged 80–90 years. There were no deaths among the two pediatric patients (Table 1).

Antimicrobial susceptibilities and laboratory data

The blood isolates were tested for susceptibility to penicillin ($n=40$), vancomycin ($n=14$) and ampicillin ($n=10$) (Table 3). Among the 43 patients, seven patients did not receive appropriate treatment (ceftriaxone or cefazolin was used) and four patients died (57.1%). In contrast, 36 patients received at least one appropriate antibiotic, however eight patients (22.2%) subsequently died ($p=0.081$).

Laboratory tests showed that 19 patients (46.3%) had leukocytosis, 18 (45.0%) had neutrophilia, and five had neutropenia (11.6%). Thirteen (44.8%) of the 29 patients who received CRP testing had a CRP level greater than 100 mg/L.

Characteristics for fatal and surviving cases

Table 4 demonstrates the characteristics for fatal and surviving cases. It would appear that people with type 2 diabetes mellitus or respiratory distress may have increased fatality rates in cases of *L. monocytogenes* bacteremia.

Table 3. Minimum inhibitory concentrations of antibiotics against *Listeria monocytogenes* isolates

	MIC_{50}	MIC_{90}	Susceptible, *n* (%)	Isolates tested, *n*
Penicillin	0.38	0.75	40 (100)	40
Vancomycin	0.50	1	14 (100)	14
Ampicillin	0.25	0.25	10 (100)	10

MIC = minimum inhibitory concentration.

Table 4. Characteristics between the fatal and survival cases[a]

	Fatality ($n=23$)	Survival ($n=31$)	*p*
Age[c]	60.2±14.5	52.2±21.8	0.25
Sex			0.56[b]
Female	5 (41.7)	16 (51.6)	
Male	7 (58.3)	15 (48.4)	
M:F	1.4	0.94	
Underlying diseases			
Solid tumors	6 (50.0)	9 (29.0)	0.29
Renal failure	4 (33.3)	10 (32.3)	1.00[b]
Type 2 diabetes mellitus	1 (8.3)	10 (32.3)	0.14[b]
Lymphoid and hematopoietic malignancy	1 (8.3)	5 (16.1)	0.66[b]
Clinical symptoms			
Fever	6 (50.0)	24 (77.4)	0.14[b]
Respiratory distress	1 (8.3)	13 (41.9)	0.07[b]
Consciousness change	3 (25.0)	9 (29.0)	1.00[b]
Laboratory data			
WBC[c,d]	8,133.3±6,964.6	12,880.0±14,367.3	0.28
CRP[c,e]	139.0±94.2	91.5±95.5	0.26

[a]Data presented as *n* (%) or mean±standard deviation; [b]Fisher's exact test; [c]Student's *t* test; [d]not all cases had white blood cell laboratory data available (fatal, $n=12$; surviving, $n=30$); [d]not all cases had CRP laboratory data (fatal, $n=7$; surviving, $n=23$). CRP = C-reactive protein; F = female; M = male; WBC = white blood cell.

However, both these factors did not show a statistically significant difference ($p = 0.14$ and $p = 0.07$). According to the definition, there were 22 cases (51.1%) of nosocomial infection and nine of the 22 cases (40.9%) died.

Discussion

The present study included only two neonatal patients (4.7%), both of whom were treated. A surveillance study in Spain ($n = 40$) comprised 32.5% newborn patients, and the mortality rate was as high as 61.5%.[5] A study conducted in Israel ($n = 1,149$) showed 43% perinatal infections, and the perinatal patient case-fatality rate was up to 36%.[16] However, the patient populations in the Spanish study and our present study are not sufficiently large to give statistically meaningful results. The two newborns in the present study were cured, and it is reasonable to assume that almost all newborn babies in Taiwan who have an unstable clinical condition, such as fever, poor activity or poor appetite, receive empirical treatment with ampicillin and gentamicin. The two newborn babies in the present study received ampicillin and gentamicin after birth due to fever and respiratory distress. These two drugs generally show *in vitro* and *in vivo* activities against *L. monocytogenes*.[9] According to a study at a national Taiwanese university,[7] most neonatal cases with listeriosis also had respiratory distress (11/14) and half of the cases had involvement of the central nervous system, observations similar to those seen in our study.

In the present study, only three adult patients (7.3%) and one newborn baby (50%) were diagnosed with meningitis, with these percentages lower than the corresponding values from studies conducted in England (24%) and Israel (28%).[16,17] The low rate of meningitis may be due to the low rate of CSF analysis in the present study. Only 11 (25.6%) patients underwent a CSF survey; the rate of meningitis might be increased if all the patients underwent this test.

All but one of the newborn patients had an underlying disease, and this rate was higher than those reported for studies conducted in England (75%) and Israel (74%).[16,17] Malignancy, diabetes mellitus and renal disease were also identified as risk factors in another country,[16–18] whereas human immunodeficiency virus infection seems to be less common in Taiwan. Connective tissue disease, including systemic lupus erythematosus, with previously accompanied listeriosis as either a comorbid or pre-existing condition, was noted in two case series and one outbreak.[19] Viral hepatitis has also been linked to *Listeria* infection in case studies,[20,21] and systemic lupus erythematosus and viral hepatitis were implicated in the present study.

In the present study, the number of patients with listeriosis increased during the period from 2006 to 2008; this pattern of increased incidence was also noted in England and France,[11,17] however the reason for the increase in incidence remains unclear. It may be linked to improvements in laboratory methods (especially in the isolation of *L. monocytogenes* from blood samples) or changes in local clinical practices.

Historically, *L. monocytogenes* has been linked more often to infections among men than women,[22] although this gap has narrowed in recent years, in agreement with our data. In the present study, all *L. monocytogenes* isolates showed *in vitro* susceptibility to nearly all the common antibiotics; similar to what has been reported previously.[23] The optimal antimicrobial therapy for listeriosis has not been established in controlled clinical trials. An overall mortality rate for *L. monocytogenes* bacteremia of 21–44% has been reported,[24,25] and our case-fatality rate of 27.9% falls within this range.

In conclusion, *L. monocytogenes* bacteremia in newborn babies is not common in Taiwan, but the recovery rate is high. *L. monocytogenes* bacteremia was diagnosed in immunocompromised patients and elderly individuals, with ampicillin, penicillin and vancomycin found to be active against the *L. monocytogenes* isolates in the present study. Appropriate antibiotic treatment may decrease the *L. monocytogenes* bacteremia-related mortality rate.

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