Listeriosis at a Tertiary Care Hospital in Beijing, China: High Prevalence of Nonclustered Healthcare-Associated Cases Among Adult Patients

Huan-ling Wang,1 Khalil G. Ghanem,2 Peng Wang,3 Shuang Yang,4 and Tai-sheng Li5

1Department of Infectious Diseases, Peking Union Medical College Hospital, Chinese Academy of Medical Sciences, Beijing, People’s Republic of China; 2Department of Medicine, Division of Infectious Diseases, Johns Hopkins University School of Medicine, Baltimore, Maryland; 3Department of Microbiology, Peking Union Medical College Hospital, 4Department of Medicine, Peking Union Medical College, and 5Department of Infectious Diseases, Peking Union Medical College Hospital, Chinese Academy of Medical Sciences, Beijing, People’s Republic of China

Background. Listeriosis is an emerging infectious disease associated with high mortality. There are few published reports from East Asia and developing countries. Our goal was to describe the clinical characteristics and outcomes of patients diagnosed with Listeria monocytogenes at a tertiary care hospital in Beijing, China.

Methods. Peking Union Medical College Hospital (PUMCH), an 1800-bed hospital, consists of 2 campuses that house different medical departments. We retrospectively reviewed all culture-proven cases of listeriosis occurring at PUMCH between 1999 and 2011. Point estimates and 95% confidence intervals are presented.

Results. There were 38 patients with listeriosis: 5 neonatal, 8 maternal, and 25 nonmaternal. The median age of the adult nonmaternal patients was 47 (range, 18–79) years with a female predominance (72%). Forty percent (n = 10) had an underlying rheumatic disease. Forty-four percent of cases (n = 11) were healthcare-associated infections occurring a median of 20 (range, 3–44) days after hospital admission. Only 2 of the 11 healthcare-associated cases clustered in space and time. One healthcare-associated case occurred in a patient receiving KHI-272 therapy, an oral, irreversible dual EGFR/HER2 inhibitor. The neonatal and maternal listeriosis cases were similar to those reported in the literature.

Conclusions. Nonclustered healthcare-associated cases of L. monocytogenes occurred at a large tertiary care hospital in Beijing, China. The source of these infections is unclear. Although rare, in the setting of immunosuppression, Listeria should be considered in the differential diagnosis of healthcare-associated infections, even in the absence of a point-source outbreak.

Keywords. Listeria monocytogenes; immunocompromised host; healthcare-associated infection; neonatal; maternal.

Listeriosis is a relatively uncommon but serious infection caused by Listeria monocytogenes. This organism is ubiquitous in the environment and can survive at temperatures ranging from −7°C to body temperature [1]. The main route of transmission is believed to be through the consumption of contaminated food (processed meats, unpasteurized milk, soft cheeses, and cantaloupes) [2–7] and vertical transmission from mother to child [8, 9]. However, healthcare-associated transmission has also been reported through patient-to-patient transmission, mineral bathing oil, contaminated resuscitation equipment, and the contaminated hands
of medical personnel [10–14]. Most of the healthcare-associated infections are clustered and related to food processing [11–13].

Gastroenteritis, bacteremia, and meningitis are the most common manifestations of listeriosis. Because *L. monocytogenes* has a strong predilection for elderly and immunocompromised persons [15–18], results in poor fetal outcomes [19–21], exhibits poor response to third-generation cephalosporins, and is associated with a high mortality rate, it has become an increasingly important emerging infectious disease [22].

In the United States, *L. monocytogenes* is the fourth causative microorganism of bacterial meningitis [23]. Among persons aged >65 years, *L. monocytogenes* is the third leading pathogen [24, 25]. Most listeriosis cases have been reported from industrialized Western countries. Reports from East Asia and developing countries are scarce [26, 27].

Our goal was to retrospectively review all culture-proven cases of listeriosis at Peking Union Medical College Hospital (PUMCH) since 1999 and describe the clinical characteristics and outcomes of the infected patients.

**METHODS**

PUMCH is an 1800-bed tertiary care hospital in Beijing, China. Founded in 1921 by the Rockefeller Foundation, PUMCH is the national medical technical support center for the diagnosis and treatment of severe and complicated diseases. In 2002, another hospital in Beijing merged with PUMCH and was renamed the Western campus of PUMCH. The latter housed several departments (general medicine, rheumatology, oncology, and breast surgery), and both campuses shared other departments (hematology, gastroenterology). PUMCH provides medical services to patients from surrounding areas (Beijing, and Hebei province) and to patients being referred from various outside institutions throughout China.

We retrospectively identified all patients with *L. monocytogenes* infections based on a list generated from an electronic database in the clinical microbiology laboratory at PUMCH. All positive culture results for *L. monocytogenes* diagnosed at PUMCH since 1999 are stored in the database. We included all cases from January 1999 to October 2011. Clinical data from the identified cases were abstracted from the medical records. These data included demographic characteristics, comorbidities, known risk factors (immunosuppressive therapy, dietary history, travel, and exposures), the sites from which the organism was isolated, clinical presentation, laboratory data, type of antimicrobial therapy, duration of hospitalization, and outcomes.

The diagnosis of listeriosis was based on one of the following: isolation of *L. monocytogenes* from normally sterile clinical specimens (eg, cerebrospinal fluid [CSF], blood, amniotic fluid, uterine swab); isolation of *L. monocytogenes* from nonsterile specimens (eg, rectal swab, tracheal swab); and histopathology compatible with listeriosis [22]. Cases were categorized as neonatal, maternal, or nonmaternal infections. All maternal cases were in pregnant women who had *L. monocytogenes* isolated from cultures of normal sterile body sites or vaginal swab [19]. Healthcare-associated cases were defined as onset of listeriosis symptoms >48 hours after admission for medical conditions other than listeriosis.

We used descriptive statistics. Where appropriate, we present point estimates with 95% confidence intervals (CIs). This study was reviewed and approved by the Institutional Review Board at PUMCH.

**RESULTS**

We identified 38 patients (cases) of listeriosis diagnosed between 1999 and 2011. The demographic characteristics of these cases are summarized in Table 1. There were 5 neonatal, 8 maternal, and 25 nonmaternal infections with *L. monocytogenes*.

**Neonatal Listerialisis**

Of 26,221 deliveries during this time period, there were 5 cases of neonatal listeriosis identified. Four of 5 cases of neonatal listeriosis were male. All 5 neonatal listeriosis cases were born to symptomatic mothers. All had positive cultures and presented with fetal distress (n = 5), sepsis (n = 4), meningitis (n = 4), Apgar score <5 (n = 3), low birth weight (n = 2), and meconium aspiration (n = 1), suggestive of intrauterine infection. The clinical characteristics and outcomes of these 5 cases are summarized in Table 2.

**Maternal Listeriosis**

There were 8 maternal cases of listeriosis identified. Six cases were confirmed by culture. Two other cases were suspected based on symptoms and positive cultures in their infants at the time of delivery. The median age was 30 years (range, 26–33 years). The median gestation was 29 weeks (range, 18.9–39.9 weeks). Maternal cases presented with a sudden onset (<1 week from presentation) of symptoms (n = 7), which included high fevers with a maximal temperature >39°C (n = 6), gastrointestinal symptoms (diarrhea, abdominal pain; n = 5), and various obstetrical manifestations (decreased fetal movement in 2 cases, intrauterine fetal death, vaginal bleeding, and acute pyelonephritis) (Table 3). Two maternal cases had *L. monocytogenes* cultured from blood; all 3 cases whose *L. monocytogenes* was detected on uterine swabs had histopathologic evidence of either acute chorioamnionitis or intrauterine fetal infection. In one case, *L. monocytogenes* was cultured from the vaginal swab, placental histopathology demonstrated chorioamnionitis, and the infant had culture-proven listeriosis. The other 2 cases had symptoms consistent with
listeriosis, positive listeria cultures in the newborns, and pathologic findings of acute chorioamnionitis (Table 2). None of the mothers had central nervous system (CNS) involvement and all recovered fully after delivery.

Obstetrical outcomes included 5 cases of listeriosis in the infants postpartum. All 5 cases were the result of listeria infections during the third trimester of gestation, and a single one of these cases was fatal. There were 2 induced/late abortions as a result of listeria infections during the second trimester of gestation, and a normal pregnancy outcome for a single second-trimester infection.

Nonmaternal Listeriosis

Among the 25 nonmaternal cases, the median age was 47 years (range, 18–79 years), and 72% (95% CI, 52.5%–85.7%) were female. Twenty-three (92%) infections occurred in patients with significant comorbidities (Table 4). Ten (40%) patients had concurrent neoplasms: 2 cases each of leukemia, multiple myeloma, liver cancer, and rectal cancer, and 1 case each of breast cancer and abdominal malignant metastases from an unknown primary. Ten nonmaternal infections occurred in patients with autoimmune diseases: 6 cases in patients with systemic lupus erythematosus (SLE), 2 cases in patients with dermatomyositis, 1 case in a patient with Still’s disease, and 1 in a patient with mixed connective tissue disease. Other comorbidities included diabetes mellitus and polycystic kidney disease with chronic renal failure. Ten (40%) nonmaternal adult listeriosis cases were receiving chronic corticosteroids at the onset of symptoms, and 6 (24%) had received chemotherapy within 2 months before the onset of listeriosis.

Fever (96%), CNS involvement (64%), and gastrointestinal symptoms (48%) were the most common presentations. Listeria monocytogenes was cultured from blood (n = 13), blood and CSF (n = 8), CSF (n = 3), and CSF and sputum (n = 1).

The 2 cases of L. monocytogenes that occurred in otherwise healthy hosts had early CNS involvement, manifested by coma. The first, a 20-year-old patient, experienced sudden onset of diarrhea, fever, and headache and deteriorated rapidly.

| Group                | Neonatal | Maternal | Nonmaternal |
|----------------------|----------|----------|-------------|
| Total                | 5 (13.2) | 8 (21.1) | 25 (65.8)   |
| Male                 | 4 (80)   | 0        | 9 (36)      |
| Median age (min, max), y | NA       | 30 (26, 33) | 47 (18, 79) |
| Median gestation (min, max), wk | 37 (27, 39.9) | 29 (18.9, 39.9) | NA |
| Underlying disease   |          |          |             |
| Autoimmune disease   |          |          | 23 (92)     |
| Neoplasm             |          |          | 10 (40)     |
| Diabetes             |          |          | 3 (12)      |
| Ulcerative colitis   |          |          | 2 (8)       |
| Polycystic kidney and hepatic disease |          |          | 1 (4)       |
| iatrogenic factors   |          |          |             |
| Chronic use of corticosteroids |      |          | 10 (40)     |
| Chemotherapy         |          |          | 5 (20)      |
| Clinical manifestations |        |          |             |
| Fever                | 4 (80)   | 6 (75)   | 24 (96)     |
| Gastrointestinal symptoms |      | 5 (62.5) | 12 (48)     |
| Neurological symptoms |        | 1 (12.5) | 16 (68)     |
| Laboratory findings  |          |          |             |
| Peripheral WBC, mean ± SD, 10⁹/L | 13.3 ± 5.1 | 17.6 ± 6.2 | 8.3 ± 5.1   |
| CSF WBC median (min, max), cells/µL | 1660 (16, 128 300) | 200 (36, 2590) |
| CSF neutrophils, %, median (min, max) | 65 (62, 97) | 40 (10, 96) |
| CSF mononuclear, %, median (min, max) | 35 (3, 38) | 60 (4, 90) |
| CSF neutrophils >50% | 3/3 (100) | 7/15 (46.7) |
| CSF protein median (min, max), g/L | 1.8 (0.94, 9.16) | 1.77 (0.65, 8.45) |
| Mortality            | 1 (20)   | 0        | 9 (36)      |

Data are presented as No. (%) unless otherwise specified. Abbreviations: CSF, cerebrospinal fluid; max, maximum; min, minimum; NA, not applicable; SD, standard deviation; WBC, white blood cell.

a On steroid of prednisone equivalent 30–40 mg/d in 4 of 10 cases, >50 mg/d in 6 of 10 cases; of those, 4 patients were on concurrent immunosuppressive therapies.
Table 2. Characteristics of 5 Neonatal Cases of Listeriosis

| No. | Sex | Presentation | Maternal Illness | Gestation (wk) | Culture Sites | Initial Antibiotic | Switch Antibiotic | Intubation | Complication | Outcome |
|-----|-----|--------------|------------------|----------------|---------------|-------------------|-------------------|------------|--------------|---------|
| 16  | F   | Fetal distress, Apgar 9, Tmax 37.5°C, low birth weight, WBC 18.3 x 10^9/L, SpO2 76% on ambient air | High fever; positive cultures | 37.1 | Blood, rectal swab, laryngeal swab | Meropenem + PNG | No | No | Sepsis, meningitis, aspiration pneumonia, bilateral IVH | Survived |
| 24  | M   | Fetal distress, C-section, SOB, Apgar 5, afebrile, WBC 15 x 10^9/L, increased ICP, turbid CSF, CSF WBC 1660/µL | Diarrhea, fevers; positive cultures | 31 | Blood, rectal swab | Meropenem | PNG | Yes | Sepsis, meningitis, pneumonia, low birth weight, ICH | Survived |
| 25  | M   | Fever (38°C), Apgar 1, SOB, cyanosis, rash, hypotension, WBC 16 x 10^9/L, bloody and turbid CSF, CSF WBC 128 300/µL | Headache, fevers, severe abdominal pain. No microbiologic data. | 32.7 | Blood, laryngeal swab, tracheal tube tip | Cefmetazole | Meropenem + PNG | Yes | Sepsis, meningitis, pneumonia NRDS, Bilateral IVH, SAH | Survived |
| 36  | M   | Fetal distress, Apgar 9, C-section, meconium aspiration, low fever (37.9°C), WBC 5.39 x 10^9/L, CSF WBC 0 | High fevers; positive cultures | 39.9 | Blood, laryngeal swab, tracheal tube tip | Meropenem | Ampicillin/ sulbactam + cefepime | Yes | Sepsis, IVH | Survived |
| 28  | M   | Extremely low birth weight (720 g), Apgar 5, WBC 11.4 x 10^9/L | SLE, prednisone 10 mg/d, abdominal pain, no cultures placental pathology: acute chorioamnionitis | 27 | Rectal swab | Ampicillin/ sulbactam | Meropenem | Yes | Intrauterine infection, pulmonary hemorrhage (NRDS), neonatal asphyxia, premature birth, extremely low birth weight, sclerema neonatorum | Deceased day 2 |

Abbreviations: C-section, cesarean section; CSF WBC, white blood cell count in cerebrospinal fluid; ICH, intracranial hemorrhage; ICP, intracranial pressure; IVH, intraventricular hemorrhage; NRDS, neonatal respiratory distress syndrome; PNG, penicillin; SAH, subarachnoid hemorrhage; SLE, systemic lupus erythematosus; SpO2, oxygen saturation from pulse oximetry; SOB, shortness of breath; Tmax, maximal temperature; WBC, peripheral white blood cell count.
| No. | Age (y) | Gestation (wks) | Symptom Duration | Presentation | Culture Sites | Initial Antibiotic | Switch Antibiotic | Maternal Complications | Maternal Outcome | Fetal Outcome |
|-----|---------|----------------|------------------|--------------|---------------|-------------------|-------------------|----------------------|-----------------|--------------|
| 19  | 32      | 18.9           | 1 wk             | Fever (T<sub>max</sub>, 39.5°C), chills, headache, dysuria, WBC 12 × 10<sup>9</sup>/L | Blood         | Ceftriaxone→ cefmetazole + clarithromycin | Amoxicillin/ clavulanate | Pyelonephritis       | Recovered       | C-section 5 mo later, healthy baby |
| 34  | 33      | 23             | 1 d              | Fever (T<sub>max</sub>, 39.6°C), diarrhea, WBC 24 × 10<sup>9</sup>/L | Blood         | Ceftriaxone + metronidazole | None               | None                 | Recovered       | Fetal death; placental pathology: acute chorioamnionitis |
| 6   | 30      | 26.7           | 2 d              | Fever (T<sub>max</sub>, 39.4°C), abdominal pain, vaginal bleeding, WBC 28 × 10<sup>9</sup>/L | Uterine swab | Cefuroxime + metronidazole | No change          | Late abortion        | Recovered       | Fetal death; placental pathology: chorioamnionitis |
| 23  | 31      | 31             | 3 d              | Ingestion of roasted lamb and rabbit in a Mongolian village 5 d before, decreased fetal movement 3 d, fever (T<sub>max</sub>, 39°C) 1 d, diarrhea, abdominal pain, WBC 19 × 10<sup>9</sup>/L | Uterine swab | NA                | NA                | None                 | Recovered, C-section (severe meconium stained amniotic fluid) | Infant listeriosis (case no. 24, Table 2); placental pathology: acute chorioamnionitis |
| 15  | 28      | 37.1           | 1 d              | Fever (T<sub>max</sub>, 39°C), WBC 15 × 10<sup>9</sup>/L | Uterine swab | Ceftriaxone + metronidazole | Amoxicillin + metronidazole | None                 | Recovered, C-section (meconium stained amniotic fluid) | Infant listeriosis (case no. 16, Table 2); placental pathology: acute chorioamnionitis |
| 35  | 29      | 39.9           | 4 h              | Fever (T<sub>max</sub>, 38.8°C) for 4 hours, decreased fetal movement for 1 d, WBC 9.29 × 10<sup>9</sup>/L | Vaginal swab | Ceftriaxone + metronidazole | No change          | Intrauterine fetal hypoxia | Recovered        | Infant listeriosis (case no. 36, Table 2); Placental pathology: chorioamnionitis |
| 37  | 26      | 32.7           | 2 wk             | Headache, fever (T<sub>max</sub>, 39.8°C) 2 wk, decreased fetal movement 1 wk, severe abdominal pain 1 d | NA          | NA                | NA                | Infan listeriosis | Recovered, postpartum uterine curettage for retention of fetal membranes | Infant listeriosis (case no. 25, Table 2); placental pathology: NA |
| 38  | 30      | 27             | 1 d              | Sudden onset of lower abdominal pain | NA          | NA                | NA                | Premature labor | Recovered       | Late abortion, fetal death (case no. 28, Table 2); placental pathology: acute chorioamnionitis |

Abbreviations: C-section, cesarean section; NA, not available; T<sub>max</sub>, maximal temperature; WBC, peripheral white blood cell count.
Table 4. Characteristics of 25 Cases of Nonmaternal Listeriosis

| No. | Sex | Age (y) | Comorbidities | Predisposing Factor | Healthcare-Associated Duration | Presentation | Culture Sites | Complications | Outcome |
|-----|-----|---------|---------------|--------------------|-------------------------------|--------------|---------------|---------------|---------|
| 31  | F   | 24      | Acute lymphoblastic leukemia (L2) | Chemotherapy, neutropenia | Yes 1 d | Abdominal pain x 2 wk before admission, sudden fever (T<sub>max</sub> 40.1°C) hospital day 12 | Blood, CSF | Sepsis (Listeria, E. coli), cerebral hemorrhage, coma | Death hospital day 25 |
| 3   | F   | 43      | Metastatic liver disease; unknown primary | Neoplasm | No 3 d | Intermittent abdominal pain for 1 mo, fever (T<sub>max</sub> 39.3°C), and headache 3 d | Blood, CSF | Meningitis, coma | Death hospital day 6 |
| 1   | M   | 53      | Multiple myeloma | Chemotherapy, chronic use of melphalan, thalidomide | No 2 d | Fever (T<sub>max</sub> 40.7°C), headache, loss of consciousness | Blood, CSF | Septic shock, ARF, GI perforation | Death hospital day 8 |
| 4   | M   | 20      | None | None | No 3 wk | Sudden onset fever (T<sub>max</sub> 40°C), headache, worsening mental status (delirium, coma), ventricular enlargement, placement of external CSF shunt, intubated | CSF, sputum | Meningo-encephalitis, pneumonia, MOF, coma, central diabetes insipidus | Death hospital day 12 |
| 18  | F   | 47      | Dermatomyositis | Prednisone 40 mg/d | No 3 d | Fever, dizziness, and dysphagia, sudden cyanosis and coma while in emergency room | Blood, CSF | Meningitis, HAP (MRSA, Enterobacter) brain stem stroke, brain death | Death hospital day 20 |
| 2   | F   | 56      | SLE and abdominal malignancy of unclear primary | Prednisone 30–40 mg/d, CTX 0.4/wk | Yes 3 d | Admitted with fatigue, edema, and jaundice. Fever (T<sub>max</sub> 39.8°C) started 3 d after admission. | Blood | Pneumonia, bacterial sepsis, MOF | Death hospital day 25 |
| 14  | F   | 23      | SLE | Prednisone 50–80 mg/d | No 1 d | Fever (T<sub>max</sub> 39.2°C), epigastric pain for 1 d, epistaxis | Blood | Acute liver failure hepatic encephalopathy, coma, GI bleed, respiratory failure | Death hospital day 7 |
| 21  | M   | 71      | Rectal cancer, hepatic metastases | Chemotherapy | No 1 d | Fever (T<sub>max</sub> 40°C) after chemotherapy, stool OB(+) | Blood | Coma, seizure, septic shock | Death hospital day 4 |
| 27  | F   | 33      | SLE with nephropathy | Prednisone 60 mg/d, 2 course of MP pulses | Yes 2 mo | Diarrhea and abdominal pain for 2 mo; sudden onset fever (T<sub>max</sub> 39.2°C) on day 26 after admission | Blood | Multiple hospital-acquired infections, septic shock | Death hospital day 30 |
| No. | Sex | Age (y) | Comorbidities | Predisposing Factor | Healthcare-Associated Duration | Presentation | Culture Sites | Complications | Outcome |
|-----|-----|---------|----------------|---------------------|------------------|--------------|---------------|---------------|---------|
| 5   | F   | 43      | Dermatomyositis, DM, HCC | Prednisone 80 mg/d, CTX 0.4/wk | Yes | 4 d | Fever (T<sub>max</sub> 39.7°C) started on day 20 after admission, with headache, left hemiplegia | Blood | Sepsis (meningitis) | Recovered |
| 8   | F   | 22      | SLE with nephropathy | Prednisone 50–60 mg/d, 2 courses of MP pulses + hydroxychloroquine 0.2 bid + CyA/ Dapsone/MMF | Yes | 2 wk | Fever (T<sub>max</sub> 40°C) and diarrhea started on day 40 after admission | Blood | Meningitis | Recovered |
| 10  | M   | 53      | Still’s disease | Prednisone 50–60 mg/d or dexamethasone 5 mg/d, methotrexate 15 mg/d | Yes | 1 d | Fever (T<sub>max</sub> 39.6°C) started on day 44 after admission, with headache, vomiting, change in mental status | Blood, CSF | Meningitis, respiratory failure, MRSA pneumonia | Recovered |
| 7   | F   | 18      | SLE | None | No | 2 wk | Fever (T<sub>max</sub> 39°C) headache and vomiting for 2 wk, and diplopia 1 d | Blood, CSF | Cryptococcus neoformans also grew from blood cultures | Recovered |
| 30  | M   | 74      | DM, chronic kidney disease | None | No | 2 d | Fever (T<sub>max</sub> 39.2°C), nausea, vomiting | Blood, CSF | Meningitis, HAP | Recovered |
| 17  | M   | 69      | None | None | No | 4 d | Fever (T<sub>max</sub> 39°C), change in mental status | CSF | Coma, ARF, pneumonia | Recovered |
| 13  | F   | 53      | SLE with nephropathy | Prednisone 30 mg/d, CTX 0.4/wk | No | 2 d | Fever (T<sub>max</sub> 39.4°C), headache, vomiting, loss of consciousness | CSF | Meningitis | Recovered |
| 12  | F   | 45      | Mixed connective tissue disease | Prednisone 60 mg/d | No | 6 d | Fever (38.5°C), headache and altered mental status | CSF | Meningitis, DVT | Recovered |
| 20  | F   | 60      | Non-Hodgkin lymphoma and lymphoblastic leukemia | Chemotherapy and neutropenia | Yes | 5 d | Fever (T<sub>max</sub> 40°C) started 5 d after chemotherapy on hospital day 9 | Blood | Perianal abscess | Recovered |
| 26  | F   | 42      | Breast cancer with metastases to bone, liver, and lungs | Neratinib (HKI-272), neutropenia | Yes | 3 d | Fever (T<sub>max</sub> 39.8°C), oral ulcers, diarrhea, after HKI-272 on hospital day 15 | Blood | None | Recovered |
| 11  | F   | 36      | Ulcerative colitis, hepatic cirrhosis, AIH | Prednisone 40 mg/d | Yes | 1 d | Fever (T<sub>max</sub> 39.7°C) and hepatitis on hospital day 21 | Blood | None | Recovered |
He was intubated and treated at a local outside hospital (where no \( \text{L. monocytogenes} \) was isolated from his cultures), and \( \text{L. monocytogenes} \) was isolated from sputum and CSF 4 weeks after the onset of gastrointestinal symptoms (Table 4, patient 4).

The second, a 69-year-old previously healthy man, developed sudden fever and convulsions (Table 4, patient 17) rapidly progressing to coma complicated by acute renal failure and pneumonia. His condition improved after an extensive hospital stay and he was transferred to an outside institution for further rehabilitation. No long-term follow-up was available.

Seventy-two percent of adults were treated empirically with cephalosporins and all were switched to ampicillin after the positive culture results became known. Among the 9 (36%; 95% CI, 20.25%–55.48%) fatal cases, 8 had severe underlying diseases and developed complications after being infected with \( \text{L. monocytogenes} \). All died of multiple severe complications within 30 days after the onset of infection. The fatal cases were more likely to have sepsis (n = 9), rapid onset of coma (n = 6), and multiorgan failure (n = 3).

Healthcare-Associated Listeriosis

Eleven (44%; 95% CI, 26.67%–62.93%) nonmaternal adult cases were healthcare-associated. The patients were admitted for treatment of rheumatologic diseases (n = 6), malignancy (n = 4), and malignancy with ulcerative colitis (n = 1). The admitting department and its location, timing of infection, and duration are illustrated in Figure 1. The onset of symptoms related to listeriosis occurred after a median of 20 days (range, 3–44 days) following admission. The mortality among healthcare-associated cases was 27.2% (95% CI, 9.74%–56.56%).

These infections were first detected in 2006, and there were 1, 3, 3, 1, and 3 infections detected per year from 2006 to 2010, consecutively. These infections were scattered in 6 different wards, both in the eastern and western campuses of PUMCH. There were 2 cases each in the rheumatologic and hematology wards and 3 cases in the general medicine ward. Only 2 cases appeared to be clustered in space and time. Nine of these 11 cases did not appear to be clustered. There was no consistent pattern (location, seasonality, and timing) that emerged for the 9 nonclustered cases. The source of their infection could not be determined.

**Table 4 continued.**

| No. | Sex | Age (y) | Comorbidities | Predisposing Factor | Healthcare-Associated | Duration | Presentation | Culture Sites | Complications | Outcome |
|-----|-----|---------|---------------|--------------------|-----------------------|----------|--------------|---------------|---------------|---------|
| 9   | F   | 49      | DM            | None               | No                    | 5 d      | Fever (\( T_{\text{max}} \) 40.5°C), abdominal bloating, headaches | Blood | Urosepsis | Recovered  |
| 22  | M   | 79      | Polycystic kidney disease, CRF | None | No | 4 d | Fever (\( T_{\text{max}} \) 39°C), left upper quadrant abdominal pain | Blood | None | Recovered  |
| 32  | M   | 59      | Ulcerative colitis, rectal cancer with diffuse metastases | Chemotherapy | Yes | 1 d | Fever (\( T_{\text{max}} \) 40°C) on hospital day 24 | Blood | Candidiasis | Recovered  |
| 33  | F   | 36      | Multiple myeloma | None | Yes | 1 d | Fever (\( T_{\text{max}} \) 38°C), on hospital day 3 | Blood | HAP | Recovered  |
| 29  | M   | 59      | DM            | None               | No | 2 d | Fever (\( T_{\text{max}} \) 39.9°C), diarrhea, abdominal pain, mental status change | Blood, CSF | None | Recovered  |

Abbreviations: AIH, autoimmune hepatitis; ARF, acute renal failure; bid, twice daily; CRF, chronic renal failure; CSF, cerebrospinal fluid; CTX, cyclophosphamide; CYA, cyclosporine A; DM, diabetes mellitus; DVT, deep vein thrombosis; E. coli, Escherichia coli; GI, gastrointestinal tract; HAP, hospital-acquired pneumonia; HCC, hepatocellular carcinoma; MMF, mycophenolate mofetil; MOF, multiple organ failure; MP, methylprednisolone; MRSA, methicillin-resistant Staphylococcus aureus; OB, occult blood; SLE, systemic lupus erythematosus; \( T_{\text{max}} \), maximal temperature.

DISCUSSION

The most striking finding from this case series is the prevalence of nonclustered healthcare-associated cases of listeriosis. Eleven of 25 nonmaternal listeriosis cases were healthcare-associated. These infections did not appear to be clustered in time and space. There are rare reports of healthcare-associated transmission of \( \text{L. monocytogenes} \) via contaminated foods, healthcare workers, and infected patients, but most of these cases were clustered in time and space.
MacGowan et al found that without causing symptoms [32]. Using repeated sampling, stool of 1%−10% of the population, where it can persist [33]. Fecal, cervicovaginal, and oropharyngeal carriage of L. monocytogenes has been reported as a possible predisposing factor for perinatal listeriosis [34, 35]. In one study conducted by Schuchat et al [36], asymptomatic carriage of the illness-associated strain of L. monocytogenes was identified in nearly one-fifth of household contacts of patients with sporadic listeriosis, and no cases of secondary disease were detected within households in this study. Their findings suggest that gastrointestinal carriage of pathogenic strains of L. monocytogenes is not uncommon in contacts of cases, underscoring the critical role that host susceptibility plays in determining whether illness occurs following exposure to this organism. All of our cases of healthcare-associated listeriosis had severe underlying immunosuppression. Besides immunosuppression, many of our patients had underlying diseases involving the gastrointestinal tract, or their therapy could impact the integrity of the intestinal mucosa. So, the role that gastrointestinal colonization of Listeria played in the pathogenesis of these healthcare-associated infections warrants further study.

After the discovery of these nonclustered healthcare-associated cases, we have implemented a more aggressive approach: all healthcare-associated cases will be thoroughly investigated for both prehospital and in-hospital exposures. We are also saving all bacterial isolates for DNA fingerprinting. This more aggressive approach may help us better define the source of these infections.

Among the healthcare-associated listeriosis cases, one patient with diffuse metastatic breast cancer experienced sudden onset of fever, oral ulcers, and diarrhea after 3 days of HKI-272 treatment (Table 4, patient 26). Blood culture yielded L. monocytogenes. The HKI-272 therapy was discontinued and antibiotic treatment was initiated, and the patient fully recovered. HKI-272, also known as neratinib [37], is an oral, irreversible dual EGFR/HER2 inhibitor for breast and non-small-cell lung cancer. Phase 1 and 2 studies reported gastrointestinal adverse events, including diarrhea (89%), nausea (29%–64%), and vomiting (23%–50%). Approximately 30% of patients required discontinuation or dose reduction due to severe diarrhea. Cases of listeriosis were reported among patients undergoing therapy with other biologic agents such as infliximab (antitumor necrosis factor agents) [38–41], etanercept (a tumor necrosis factor antagonist) [42], and trastuzumab (a monoclonal antibody against the HER2 receptor) [43].

Forty percent of our cases had underlying rheumatologic diseases. This proportion is higher than what was previously reported in the literature [38]. Although PUMCH does not specifically specialize in the treatment of rheumatic diseases, we do have a large population of such patients. Persons of Asian descent have a higher incidence of SLE, compared with...
other races [44–46]. Given the paucity of published reports on *L. monocytogenes* from East Asia, this may explain the higher incidence among patients with rheumatic diseases in our report. This may also have impacted the sex distribution of cases. Traditionally, *L. monocytogenes* has been reported more often among men than women. The male to female ratio in our study was 1:1.8. This may reflect the increased predisposition of rheumatic diseases among women [47–49].

Comorbidity plays a very important role in the prognosis of listeriosis [18]. Eighty-one percent of 225 patients with listeriosis studied in France had a predisposing immunocompromising condition, whose severity was the major prognostic factor [17]. In our population, 92% of nonmaternal listeriosis cases were immunosuppressed.

Our cases of infant listeriosis mirrored the cases reported in the literature, as did their outcomes. We did not observe any late-onset cases of infant listeriosis, as reported by other authors [9, 22, 50–52]. Similarly, the characteristics of our maternal listeriosis were similar to those reported in the literature.

This study has several limitations. First, it is a retrospective assessment over a protracted timespan. As such, we were unable to obtain specimens for molecular testing, and we were unable to clarify additional issues relating to certain in-hospital epidemiological exposures. Second, it consists of a relatively small sample size, and our findings may not be necessarily generalizable to other populations or settings. Third, cases of listeriosis in China are not routinely reported to public health authorities. As such, the epidemiology of listeria is not well defined. Our case series reflects a selection bias toward hospitalized (ie, sicker) patients and may not reflect the overall epidemiology of listeria.

Nonclustered healthcare-associated cases of *L. monocytogenes* occurred at a large tertiary care hospital in Beijing, China. The source of these infections is unclear. Although rare, in the setting of immunosuppression, *Listeria* should be considered in the differential diagnosis of healthcare-associated infections—even in the absence of a point-source outbreak.

**Note**

**Acknowledgments.** We thank all healthcare providers who had participated in taking care of our patients. We are grateful to all the medical record staff for their support.

**Potential conflicts of interest.** All authors: No reported conflicts.

All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

**References**

1. Allerberger F, Wagner M. Listeriosis. A resurgent foodborne infection. Clin Microbiol Infect 2010; 16:16–23.
2. Winter CH, Brockmann SO, Sonnentag SR, et al. Prolonged hospital and community-based listeriosis outbreak caused by ready-to-eat scalded sausages. J Hosp Infect 2009; 73:121–8.
3. Pichler J, Much P, Kasper S, et al. An outbreak of febrile gastroenteritis associated with jellied pork contaminated with *Listeria monocytogenes*. Wien Klin Wochenschr 2009; 121:149–56.
4. Little CL, Amar CF, Awofisayo A, Grant KA. Hospital-acquired listeriosis associated with sandwiches in the UK: a cause for concern. J Hosp Infect 2012; 82:13–8.
5. Cokes C, France AM, Reddy V, et al. Serving high-risk foods in a high-risk setting: survey of hospital food service practices after an outbreak of listeriosis in a hospital. Infect Control Hosp Epidemiol 2011; 32:380–6.
6. Centers for Disease Control and Prevention. Multistate outbreak of listeriosis associated with Jensen Farms cantaloupe—United States, August–September 2011. MMWR Morb Mortal Wkly Rep 2011; 60:1357–8.
7. Mead PS, Dunne EF, Graves L, et al. Nationwide outbreak of listeriosis due to contaminated meat. Epidemiol Infect 2006; 134:744–51.
8. Linnan MJ, Mascola L, Lou XD, et al. Epidemic listeriosis associated with Mexican-style cheese. N Engl J Med 1988; 319:823–8.
9. McLauchlin J. Human listeriosis in Britain, 1967–85, a summary of 722 cases. 1. Listeriosis during pregnancy and in the newborn. Epidemiol Infect 1990; 104:181–9.
10. Green HT, Macaulay MB. Hospital outbreak of *Listeria monocytogenes* septicemia: a problem of cross infection? Lancet 1978; 2:1039–40.
11. Schuchat A, Lizzo C, Broome CV, et al. W. Listeriosis during pregnancy in the United States, 1998–2007. N Engl J Med 2011; 364:2016–25.
12. Albritton WL, Cochi SL, Feeley JC. Overview of neonatal listeriosis. Clin Microbiol Infect 2009; –85, a summary of 722 cases. 1. Listeriosis during pregnancy and in the newborn. Epidemiol Infect 1990; 104:181–9.
13. Graham JC, Lanser S, Bignardi G, Pedler S, Hollyoak V. Hospital-acquired listeriosis. J Hosp Infect 2002; 51:136–9.
14. Larsson S, Cederberg A, Ivansson S, Svanberg L, Cronberg S. *Listeria monocytogenes* causing hospital-acquired enterocolitis and meningitis in newborn infants. Br Med J 1978; 1:1083–9.
15. Nelson KE, Warren D, Tomasi AM, Raju TN, Vidyasagar D. Transmission of neonatal listeriosis in a delivery room. Am J Dis Child 1985; 139:903–5.
16. Graham JC, Lanser S, Bignardi G, Pedler S, Hollyoak V. Hospital-acquired listeriosis. J Hosp Infect 2002; 51:136–9.
17. Larsson S, Cederberg A, Ivansson S, Svanberg L, Cronberg S. *Listeria monocytogenes* causing hospital-acquired enterocolitis and meningitis in newborn infants. Br Med J 1978; 1:1083–9.
18. Ooi ST, Lorber B. Gastroenteritis due to *Listeria monocytogenes*. Clin Infect Dis 2005; 40:1327–32.
19. Mook P, O’Brien SJ, Gillespie IA. Concurrent conditions and human listeriosis, England, 1999–2009. Emerg Infect Dis 2011; 17:38–43.
20. Iwarson S, Larsson S. Outcome of *Listeria monocytogenes* infection in compromised and non-compromised adults; a comparative study of seventy-two cases. Infectious 1979; 7:54–6.
21. Ooi ST, Lorber B. Gastroenteritis due to *Listeria monocytogenes*. Clin Infect Dis 2005; 40:1327–32.
22. Albritton WL, Cochi SL, Feeley JC. Overview of neonatal listeriosis. Clin Microbiol Infect 2009; 138:38
23. Thigpen MC, Whitney CG, Messonnier NE, et al. Bacterial meningitis in the United States, 1998–2007. N Engl J Med 2011; 364:2016–25.
24. Weisfelt M, van de Beek D, Spanjaard L, Reitsma JB, de Gans J, Community-acquired bacterial meningitis in older people. J Am Geriatr Soc 2006; 54:1500–7.
25. Cabellos C, Verdaguer R, Olmo M, et al. Community-acquired bacterial meningitis in elderly patients: experience over 30 years. Medicine (Baltimore) 2009; 88:115–9.
26. Hsieh WS, Tsai LY, Jeng SF, et al. Neonatal listeriosis in Taiwan, 1990–2007. Int J Infect Dis 2009; 13:193–5.
27. Furyk JS, Swann O, Molyneux E. Systemic review: neonatal meningitis in the developing world. Trop Med Int Health 2011; 16:672–9.
28. Martins IS, Faria FC, Miguel MA, et al. A cluster of Listeria monocytogenes infections in hospitalized adults. Am J Infect Control 2010; 38: e31–6.
29. Kampelmacher EH, van Noorle Jansen LM. Isolation of Listeria monocytogenes from faeces of clinically healthy humans and animals. Zentralbl Bakteriol Orig 1969; 211:353–9.
30. Bojsen-Moller J. Human listeriosis. Diagnostic, epidemiological and clinical studies. Acta Pathol Microbiol Scand B Microbiol Immunol 1972 (suppl 229):1–157.
31. Kampelmacher EH, Huysinga WT, van Noorle Jansen LM. The presence of Listeria monocytogenes in feces of pregnant women and neonates. Zentralbl Bakteriol Orig A 1972; 222:258–62.
32. Ramaswamy V, Crescence VM, Rejitha JS, et al. Listeria—review of epidemiology and pathogenesis. J Microbiol Immunol Infect 2007; 40:4–13.
33. MacGowan AP, Marshall RJ, MacKay IM, Reeves DS. Listeria faecal carriage by renal transplant recipients, haemodialysis patients and patients in general practice: Its relation to season, drug therapy, foreign travel, animal exposure and diet. Epidemiol Infect 1991; 106:157–66.
34. Lamont RJ, Postlethwaite R. Carriage of Listeria monocytogenes and related species in pregnant and non-pregnant women in Aberdeen, Scotland. J Infect 1986; 13:187–93.
35. Gray JW, Barrett JF, Pedler SJ, Lind T. Faecal carriage of listeria during pregnancy. Br J Obstet Gynaecol 1993; 100:873–4.
36. Schuchat A, Deaver K, Hayes PS, Graves L, Mascola L, Wenger JD. Gastrointestinal carriage of Listeria monocytogenes in household contacts of patients with listeriosis. J Infect Dis 1993; 167:1261–2.
37. Bose P, Ozer H. Neratinib: an oral, irreversible dual EGFR/HER2 inhibitor for breast and non-small cell lung cancer. Expert Opin Investig Drugs 2009; 18:1735–51.
38. Chuang MH, Singh J, Ashouri N, Katz MH, Arrieta AC. Listeria meningitis after infliximab treatment of ulcerative colitis. J Pediatr Gastroenterol Nutr 2010; 50:337–9.
39. Burke JP, Kelleher B, Ramadan S, Quinlan M, Sugrue D, O’Donovan MA. Pericarditis as a complication of infliximab therapy in Crohn’s disease. Inflamm Bowel Dis 2008; 14:428–9.
40. Tweezer-Zaks N, Shiloach E, Spivak A, Rapsoprt M, Novis B, Langevitz P. Listeria monocytogenes sepsis in patients treated with anti-tumor necrosis factor-alpha. Isr Med Assoc J 2003; 5:829–30.
41. Kelesidis T, Salhotra A, Fleisher J, Uslan DZ. Listeria endocarditis in a patient with psoriatic arthritis on infliximab: are biologic agents as treatment for inflammatory arthritis increasing the incidence of Listeria infections? J Infect 2010; 60:386–96.
42. Schett G, Herak P, Graninger W, Smolen JS, Aringer M. Listeria-associated arthritis in a patient undergoing etanercept therapy: case report and review of the literature. J Clin Microbiol 2005; 43:2537–41.
43. Oliveira M, Braga S, Passos-Coelho JL, Fonseca R, Oliveira J. Complete response in HER2+ leptomeningeal carcinomatosis from breast cancer with intrathecal trastuzumab. Breast Cancer Res Treat 2011; 127:841–4.
44. Serdula MK, Rhoads GG. Frequency of systemic lupus erythematosus in different ethnic groups in Hawaii. Arthritis Rheum 1979; 22:328–33.
45. Namjou B, Sestak AL, Armstrong DL, et al. High-density genotyping of STAT4 reveals multiple haplotypic associations with systemic lupus erythematosus in different racial groups. Arthritis Rheum 2009; 60:1085–95.
46. Danchenko N, Satia JA, Anthony MS. Epidemiology of systemic lupus erythematosus: a comparison of worldwide disease burden. Lupus 2006; 15:308–18.
47. Lahita RG. The role of sex hormones in systemic lupus erythematosus. Curr Opin Rheumatol 1999; 11:352–6.
48. Amur S, Parekh A, Mummaneni P. Sex differences and genomics in autoimmune diseases. J Autoimmun 2012; 38:354–65.
49. Pennell LM, Galligan CL, Fish EN. Sex affects immunity. J Autoimmun 2012; 38:282–91.
50. Albritton WL, Wiggins GL, Feeley JC. Neonatal listeriosis: distribution of serotypes in relation to age at onset of disease. J Pediatr 1976; 88:481–3.
51. Posfay-Barke KM, Wald ER. Listeriosis. Pediatr Rev 2004; 25:151–9.
52. Skidmore AG. Listeriosis at Vancouver General Hospital, 1965–79. Can Med Assoc J 1981; 125:1217–21.