

An Epidemic of Food-Borne Listeriosis in Western Switzerland: Description of 57 Cases Involving Adults

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This article describes 57 cases of listeriosis that occurred in adults in western Switzerland during an outbreak associated with the consumption of a soft cheese. Twenty-one percent of the cases were of bacteremia, 40% were of meningitis, and 39% were of meningoencephalitis. Overall, 42% of the patients had an underlying disease and 54% were >65 years of age. Patients with bacteremia were significantly older than those with meningitis or meningoencephalitis (median ages, 75, 69, and 55 years, respectively). The epidemic strain, defined by phage typing, was isolated in three-quarters of the listerial cases observed during the epidemic period and did not appear to differ significantly from the nonepidemic strains in terms of virulence. The overall mortality associated with the 57 cases was 32%. Among the patients' characteristics, age and type of clinical presentation were independent predictors of death in a multivariate logistic regression model (pseudo- r^2 [coefficient of determination], .26; both P values <.05), and a presentation of meningoencephalitis was associated with an increased death risk (odds ratio, 6.5; 95% confidence interval, 1.1–39.5; P < .05). Neurological sequelae developed in 30% of the survivors of CNS listeriosis.

From 1974 to 1982, 28 cases of human listeriosis (an equal number of maternofetal infections and cases involving nonpregnant adults) occurred in western Switzerland. During the winter of 1983–1984, the number of cases of listeriosis increased, and the disease occurred in a surprisingly large number of relatively young and previously healthy patients. A common origin was suspected [1] but could not be identified by a preliminary case-control study. A similar increase in cases of listeriosis occurred again the following winters. In 1987, a third case-control study established the association (odds ratio [OR], 8.0; 95% confidence interval [CI], 2.8–22.6; P < .05) with the consumption of a locally produced Swiss soft cheese (Vacherin Mont d'Or), which is eaten in winter months only. Two epidemic-associated strains of *Listeria monocytogenes* (serotype 4b) with particular phage types were isolated from the majority of patients, from the incriminated cheese, and from the factories' environments [2].

From 1983 to 1987 the annual incidence of human listeriosis increased from 5 to 50 cases per one million people. During this 5-year period, a total of 122 cases occurred. Sixty-five cases occurred in newborn infants and pregnant women, and 57 cases in nonpregnant adults. We describe the clinical presentation, laboratory findings, and outcome in those 57 cases.

Patients and Methods

Patients. All patients included in the study were >18 years of age, and *L. monocytogenes* was isolated from either their blood or their CSF at the Bacteriology Laboratory of the Centre Hospitalier Universitaire Vaudois (CHUV, Lausanne, Switzerland) between January 1983 and December 1987. Most patients (77%) were initially hospitalized in this facility, which is a 1,200-bed university-affiliated tertiary care center for the 500,000 residents of the canton of Vaud. The remaining patients were initially hospitalized and treated in smaller regional hospitals of the canton of Vaud.

L. monocytogenes was identified by standard microbiological methods [3]. Fifty-six of the 57 strains were available for serotyping (courtesy of H. Seeliger, Institut für Hygiene und Microbiologie, Würzburg University, Würzburg, Germany; and J. Bille, National Center for Listeria, CHUV) and for phage typing (courtesy of J. Rocourt, Unité d'Ecologie Bactérienne, Institut Pasteur, Paris). Two epidemic-associated strains were defined as *L. monocytogenes* serotype 4b and had the following particular phage-type configurations: (1) 47; 108; 340; 2,389; 2,425; 2,671; and 3,724; and (2) 47; 108; 340; and 2,389.

Methods. Medical records of all patients were available, and these were reviewed and abstracted by the same physician (C.J.B.) with use of a structured recording instrument. Data regarding the following factors were collected: demographic characteristics; underlying condition; prodromal period; clinical symptoms and signs; antibiotic therapy; results of biological, microbiological, and neuroradiological studies; neurological sequelae noted at discharge from the hospital and at follow-up visits and/or during a subsequent hospitalization (5 months to 3 years [median, 10 months] after the initial discharge).

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Definitions. Patients were categorized according to clinical presentation. (1) Patients with bacteremia had positive blood cultures and no other clinically or microbiologically documented sites of infection. (2) Patients with meningitis had positive CSF cultures and clinical evidence of meningitis (fever, headache, photophobia, neck stiffness, and a positive Kernig's or Brudzinski's sign). Two patients included in this group had only positive blood cultures; one of these patients had a negative CSF culture, but the lumbar puncture was done 24 hours after the beginning of an effective antibiotic therapy, and the CSF values were consistent with meningitis. The other patient did not undergo lumbar puncture before death, but the autopsy disclosed purulent meningitis. (3) Patients with meningoencephalitis had positive CSF cultures and/or blood cultures and focal neurological signs (such as cranial nerve palsies and a cerebellar syndrome and/or hemiparesis), with or without meningitis. One patient, who became comatose and died, was included in this category because of evidence of a brainstem tumefaction on neuroimaging.

Statistical analysis. Differences of proportion in the three groups were compared with the Fisher's exact test. Differences between continuous variables were compared with the Kruskal-Wallis rank sum test, because the observed distributions were not normal. Univariate and multivariate logistic regression models were used to establish predictors of death and employed patient age and gender, the presence of an underlying condition, the type of clinical presentation, and the strain of *L. monocytogenes* as covariates. Analysis was done on a computer with use of Stata^R statistical software package (Computing Resource Center, Santa Monica, CA).

Results

Patients' characteristics. The main characteristics of the 57 patients are shown in table 1. Twelve cases of bacteremia (21%), 23 cases of meningitis (40%), and 22 cases of meningoencephalitis (39%) occurred. The median age was significantly different among patients in the three clinical presentation categories. Patients with bacteremia were older (median age, 75 years) than those with meningitis (69 years) and meningoencephalitis (55 years) ($P = .01$, Kruskal-Wallis rank sum test). Underlying conditions tended to be more frequent in cases of bacteremia (67%) than in cases of meningitis (39%) and meningoencephalitis (32%) ($P = .17$, Fisher's exact test). This trend becomes significant if an age of >65 years is included as an underlying condition. The other underlying conditions (table 2) were mainly malignancies (11 cases), for which some patients were receiving immunosuppressive therapy; chronic alcoholism, with or without liver cirrhosis (4 cases); and diabetes mellitus (4 cases).

Main features of the three presentations are also

described in table 1. Fever (rectal temperature, $>38^{\circ}\text{C}$) was almost universally present, although five patients with meningoencephalitis were afebrile at admission and up to 72 hours later. Overall, 46% of the patients had digestive symptoms (vomiting [43%] and diarrhea [3%]). Meningismus was present in 78% of patients with meningitis and in 64% of those with meningoencephalitis. An altered mental status was noted in 83% of the cases of meningitis but in only 59% of the cases of meningoencephalitis ($P = .11$, Fisher's exact test).

Neurological findings and outcomes in the meningoencephalitis group are described in table 3. Cranial nerve palsies were the most frequent presenting CNS sign in the meningoencephalitis group, occurring in 46% of the cases. Five of seven patients admitted because of isolated or multiple cranial nerve palsies did not have any other clinical abnormality; in particular, they remained afebrile during the first 72 hours of hospitalization. Additional deficits developed during the hospital stay, and overall 77% of the patients with meningoencephalitis had cranial nerve deficits at one point during their hospital course. Hemiparesis and ataxia occurred in 36% and 27% of these patients, respectively.

The delay between the appearance of the first symptoms of listeriosis and hospitalization ranged from several hours to 2 weeks both for patients with meningitis (median, 2 days) and for those with meningoencephalitis (median, 3 days). For patients with bacteremia, this delay ranged from a few hours to 6 days (median, 12 hours). There was no association between the length of the delay and type of clinical presentation or outcome.

Laboratory findings. Leukocytosis (leukocyte count, $>9.0 \times 10^9/\text{L}$) was noted in all but two patients, who were leukocytopenic secondary to immunosuppressive therapy. No difference was found among the three groups in terms of leukocyte count ($P = .16$, Kruskal-Wallis rank sum test). Polymorphonuclear cells were largely predominant in all groups. None of the blood values were significantly associated with outcome.

CSF was analyzed in 43 of the 45 cases of CNS listeriosis (CSF data were missing for one patient with meningitis and one with meningoencephalitis). Lumbar puncture was performed at admission in all meningitis cases but was delayed in four meningoencephalitis cases in which the patients were afebrile at admission. Overall, pleocytosis (>5 cells/ mm^3) was noted in all CSF specimens, and values of <100 leukocytes/ mm^3 were recorded in only 3 cases (1 meningitis case and 2 meningoencephalitis cases). Pleocytosis was higher in cases of meningitis than in cases of meningoencephalitis (cells/ mm^3 , 790 ± 170 vs. 437 ± 101 ; $P = .008$, Kruskal-Wallis rank sum test). Similarly, mean percentages of polymorphonuclear cells were higher in patients with meningitis than in those with meningoencephalitis ($76\% \pm 4\%$ vs. $59\% \pm 6\%$; $P = .008$, Kruskal-Wallis rank sum test). No other signifi-

Table 1. Characteristics of 57 adults with listeriosis, as related to clinical presentation.

Characteristic	Data for indicated patient group				P value
	Entire group (n = 57)	Bacteremia (n = 12)	Meningitis (n = 23)	Meningoencephalitis (n = 22)	
Age (y)					
Median	66	75	69	55	.01*
Range	31-96	44-85	31-96	37-79	
>65	31 (54)	10 (83)	15 (65)	6 (27)	.003
No. (%) of males	33 (58)	9 (75)	12 (52)	12 (55)	.43
No. (%) with underlying condition					
Not including age >65 y	24 (42)	8 (67)	9 (39)	7 (32)	.17
Including age >65 y	40 (70)	12 (100)	18 (78)	10 (45)	.002
No. (%) with following signs:					
Fever	50 (88)	12 (100)	21 (91)	17 (77)	.11
Digestive manifestation	26 (46)	4 (33)	11 (48)	11 (50)	.70
Meningismus	32 (56)	...	18 (78)	14 (64)	.34†
Altered mental status	32 (56)	...	19 (83)	13 (59)	.11†

* Kruskal-Wallis rank sum test; all other P values are per Fisher's exact test.

† Comparison is between meningitis and meningoencephalitis only.

cant difference was found between the two types of CNS listeriosis.

The CSF protein level was abnormal (>410 mg/L) in all but 4 CSF specimens (from 1 patient with meningitis and 3 with meningoencephalitis, all of whom had marked pleocytosis). The CSF-blood glucose level ratio was normal (>0.5) for only 6 patients (3 in each CNS listeriosis group). It is of interest that in 2 of these cases (both of meningoencephalitis) the protein level also was normal or slightly elevated. Lactic acid values were determined in 29 cases (15 meningitis and 14 meningoencephalitis cases). Values were abnor-

mal (>2.4 mmol/L) in all but 4 cases, all in the meningoencephalitis group. Lactic acid levels tended to be higher in patients who died ($P = .09$, Kruskal-Wallis rank sum test), but no significant association was found between other CSF values and outcome.

Direct gram stain examinations were positive in only 10 (23%) of the 43 tested cases; these positive results were equally distributed over the entire epidemic period and among meningitis and meningoencephalitis cases. CSF cultures were positive in 21 of the 22 meningitis cases and 18 of the 21 meningoencephalitis cases. Blood cultures were performed for all but one patient and were positive for all bacteremia patients but for only 52% and 43% of the meningitis and meningoencephalitis patients, respectively ($P = .002$, Fisher's exact test).

Computerized tomographic scans of the brain showed abnormalities (hypodense lesions) in 8 of the 21 meningoencephalitis cases; these lesions were multiple in 3 cases and located in the brain stem in 3 cases. In contrast, the studies showed an abnormality in only 1 of 7 tested patients with meningitis; that patient had a dilatation of the ventricular system, attributed to the infectious process.

Strain characteristics. As mentioned above, 56 of the 57 strains were available for serotyping and phage typing. Two epidemic strains with two particular phage type configurations were defined. Overall, 75% of the cases were due to the epidemic strains, and more cases of CNS listeriosis tended to be associated with the epidemic strain (77% of meningitis and 80% of meningoencephalitis cases vs. 58% of the bacteremia cases; $P = .3$, Fisher's exact test). Epidemic and nonepidemic cases did not differ in terms of the age and gender of patients, presence of an underlying condition, clinical and laboratory findings, and outcome.

Table 2. Underlying conditions of 57 adults with listeriosis, as related to clinical presentation.

Clinical presentation	Underlying conditions (no. of patients)
Bacteremia	Lung cancer (2) Chronic hemodialysis (1) Schwannoma (1) Renal transplant (1) Esophageal cancer (1) Evans's syndrome (1) Chronic granulocytic leukemia (1)
Meningitis	Diabetes mellitus (4) Chronic alcoholism (1) Hairy-cell leukemia (1) AIDS (1) Gastric cancer (1) Chronic lymphocytic leukemia (1)
Meningoencephalitis	Chronic alcoholism (3) Radiotherapy (1) Colonic cancer (1) Breast cancer (1) Acute lymphoblastic leukemia (1)

Table 3. Neurological manifestations in and outcome for patients with listerial meningoencephalitis.

Year diagnosed	Patient		Cranial nerves involved		Other neurological manifestations		Outcome
	No.	Sex/age (y)	On admission	During hospital stay	On admission	During hospital stay	
1983	1	M/57	IX, X	Sequelae (IX, X)
	2	F/37	V, IX, X	VI, VII, XI	...	"Locked-in" syndrome, ataxia, hemiparesis	Death
	4	M/42	Hemiparesis	...	Sequelae (hemiparesis)
	6	M/42	...	III, V, VII	Ataxia, hemiparesis	...	Sequelae (III, V, VII; ataxia)
1984	8	M/60	V, VII	Cure
	1	F/63	...	V, VI, VII, IX	...	Coma, hemiplegia, ataxia	Death
	5	M/51	...	III, VII, X	Coma	...	Sequelae
	7	F/53	Ataxia	...	Cure
1985	10	M/45	...	VI	...	Ataxia	Cure
	3	F/41	VI	Sequelae (VI)
	7	M/70	Coma	Seizures	Death
1986	2	F/79	...	VII	...	Hemiparesis	Death
	3	M/52	V, VII	VI, IX, X	Death
	5	M/76	Hemiparesis	...	Death
	6	M/38	...	VI, VII, X	Cure
1987	7	F/75	III, VI	Hemiparesis	Death
	5	M/77	...	VI, X	Delirium	...	Cure
	14	M/79	VI, VII	...	Hemiparesis	Coma	Death
	17	F/59	III, VII	VI	Delirium	Paraparesis	Sequelae (paraparesis)
	19	F/64	VI	III, IV	...	Tetraparesis	Sequelae (III, IV, VI; tetraparesis)
	20	M/54	Ataxia	Cure
	22	M/53	V, VII	III, VI	Sequelae (III, VI)

Treatment. An aminopenicillin alone (amoxicillin, 2 g 6 times a day) or in combination with an aminoglycoside (dosage was adjusted on the basis of levels of the drug in blood) was most frequently used in cases of bacteremia and meningoencephalitis, respectively. Seven patients with CNS listeriosis received trimethoprim-sulfamethoxazole (TMP-SMZ; 160 mg of TMP and 800 mg of SMZ twice a day) parenterally for 7 days and then enterally for 2 weeks. None of these patients died of the listerial infection, and no side effects necessitated discontinuation of the treatment. Four patients did not receive antibiotics because of an extremely poor prognosis; they all died within hours of hospital admission. Another untreated patient had bacteremia and was asymptomatic upon reception of blood culture results. Efficacy of treatment cannot be analyzed because the treatment regimens were nonrandomly assigned.

Outcome. The case-fatality rate was 32% overall (table 4) and was not statistically different for cases of bacteremia (25%), meningitis (30%), and meningoencephalitis (36%). Age was the only variable significantly associated with a risk of death in univariate logistic regression. The direction of the association indicates an increased risk of death with advanc-

ing age (pseudo- r^2 [coefficient of determination], .15; β [regression coefficient], .079; $P = .007$; 95% CI, .025-.136). Patient gender, presence of an underlying condition, type of clinical presentation, and the *L. monocytogenes* strain type were not predictors. In a multivariate model with use of the same covariates, age remained a significant independent predictor (pseudo- r^2 , .26; β , .114; $P = .003$; 95% CI, .040-.189), while type of clinical presentation became an independent predictor ($\beta = 1.257$, $P = .03$, 95% CI, .136-2.378). More specifically, the presentation of meningoencephalitis was associated with an increased risk of death (OR, 6.5; 95% CI, 1.1-39.5; $P = .04$) in comparison with the other two clinical presentations. Controlling for age and the presence of an underlying condition in the multivariate model reveals a higher mortality rate in association with meningoencephalitis.

After 5 months to 3 years of follow-up, neurological sequelae persisted in 9 (30%) of the 27 survivors of CNS listeriosis; 8 of the 9 had meningoencephalitis, and 1 had meningitis. The sequelae were cranial nerves palsies, principally of ocular motility (4 patients). It is not surprising that meningoencephalitis was associated with an increased risk of se-

Table 4. Outcome for 57 adult patients with listeriosis who were studied, as related to patient characteristics.

Characteristic	No. (%) of patients		
	Total	With sequelae (% of survivors)	Died
Clinical presentation			
Bacteremia	12 (21)	0 (0)*	3 (25)
Meningitis	23 (40)	1 (6)	7 (30)
Meningoencephalitis	22 (39)	8 (57)	8 (36)
Age			
>65 y	31 (54)	0 (0)*	14 (45)†
<65 y	26 (46)	9 (41)	4 (21)
Presence of underlying condition			
Not including age >65 y			
Yes	24 (42)	3 (21)	10 (42)
No	33 (58)	6 (24)	8 (24)
Including age >65 y			
Yes	40 (70)	3 (12)*	15 (38)
No	17 (30)	6 (43)	3 (18)
Type of strain			
Epidemic	43 (75)	6 (21)	14 (33)
Nonepidemic	14 (25)	3 (30)	4 (21)
Type of treatment†			
AP	16 (28)	...	6 (38)
AP + AG	28 (49)	9 (39)	5 (18)
TMP-SMZ	7 (12)	...	2 (29)
Erythromycin	1 (2)	...	1 (100)
No antibiotic	5 (9)	...	4 (80)
Total	57 (100)	9 (23)	18 (32)

* $P < .01$, Fisher's exact test.† $P < .05$, Fisher's exact test.

‡ AP = aminopenicillin; AG = aminoglycoside; TMP-SMZ = trimethoprim-sulfamethoxazole (see text for dosages of antibiotics).

quela (OR, 14.1; 95% CI, 1.5–132.0; $P = .02$), while other patient characteristics, the blood and CSF values, and the *L. monocytogenes* strain type were not.

Discussion

The 57 adults whose cases we have described were infected with *L. monocytogenes* during an outbreak of food-borne listeriosis in Switzerland. The importance of this outbreak is inherent in its size, the proof of its food-borne origin [2], and the careful microbiological documentation of the cases. Several findings are worth emphasizing.

First, we found a significant age difference among patients in the three clinical presentation groups. This finding is consistent with that of previous case reports, in which patients with bacteremia usually are noted as being older than those with CNS listeriosis [4–9]; this is especially true for those with listerial rhombencephalitis [10]. Several explanations for the age difference in our study were hypothesized, but neither a particular virulence factor of the epidemic strains

nor a difference in inoculum size could be proven retrospectively to be associated with this finding.

Second, an unusually high proportion of cases of CNS listeriosis (79%), especially meningoencephalitis (39%) occurred in this outbreak. In previous outbreaks [11–13], CNS listeriosis accounted for 28%, 31%, and 86% of the cases, respectively, and there was a majority of meningitis cases. Variation in case definition may explain the higher proportion of cases of meningoencephalitis but cannot explain the lower number of bacteremia cases. The epidemic strains may have had a particular tropism for the CNS, a theory suggested by the higher proportion of CNS infections with the epidemic strains, although this trend was not significant. Alternatively, immunocompromise is also considered a major predisposing condition for listeriosis, especially meningitis [14–19]. However, immunocompromise seems an unlikely explanation in this outbreak because underlying conditions were more frequent in the bacteremia group. Considering age >65 years as an underlying condition makes this explanation even less plausible, as all patients with bacteremia would then be considered compromised.

Third, underlying conditions were present in only 42% of the patients, a proportion close to the 50% observed in a cluster of 20 cases in Boston [20] but much lower than that reported in association with two previous outbreaks (98% and 100%) [11, 12]. However, in another outbreak [13], none of seven nonpregnant adults had an underlying condition. These differences may result from variations in case definitions. In particular, consideration of age >65 years as an underlying condition increases the overall proportion from 42% to 70%. However, the proportion of patients with meningoencephalitis with an underlying condition only marginally increases, from 32% to 45%. In addition, proportions of bacteremia and meningitis cases involving an underlying disease in this outbreak (67% and 39%, respectively) are in the range described in the literature (68%–77% for bacteremia and 25%–50% for meningitis) [5, 7]. Thus, the higher proportion of patients with meningoencephalitis in this outbreak seems a more likely explanation for the overall low proportion of underlying conditions. Patients with meningoencephalitis were relatively young and free of preexistent illness, as previously reported in regard to patients with CNS listeriosis, especially those with pure rhombencephalitis [10, 14–19]. Finally, whether a difference in virulence of the epidemic strains could have played a role remains speculative.

Several epidemiological and clinical observations warrant discussion. First, a preponderance of male patients is widely described in reports of outbreaks as well as in literature reviews, especially those pertaining to CNS listeriosis [5–8, 12–14, 21–25], but was only marginal in this outbreak. In particular, CNS listeriosis was almost equally frequent among men and women. Second, listerial meningoencephalitis may be especially difficult to diagnose, as shown by the absence of any infectious symptoms or signs in five patients

who presented only with isolated cranial nerve palsy. Although such a delay in diagnosis may in turn delay treatment of the infection, we did not find an association between delay and outcome. Third, none of the blood or CSF values were helpful in differentiating the type of clinical presentation or in predicting outcome. However, levels of lactic acid in CSF were abnormal for 25 of 29 patients, and higher levels tended to be associated with poorer outcome, although not significantly. Further work is needed to investigate this relationship.

In addition, pleocytosis and a predominance of polymorphonuclear leukocytes were both significantly more marked in cases of meningitis than in those of meningoencephalitis. These differences probably reflect variations in underlying pathophysiological processes and clearly support the need for distinguishing these two clinical presentations in reports of CNS listeriosis. Fourth, early microbiological diagnosis is difficult; few (23%) of the gram stain results in our study were positive, despite a high index of suspicion during the epidemic period. Other investigators have previously described this phenomenon [5, 6, 10, 23, 25]. In addition, the percentage of positive blood cultures we observed (52% of meningitis cases and 46% of meningoencephalitis cases) was lower than described in the literature (60%–75%) [5, 20, 23, 24]. In contrast, CSF cultures were positive in the great majority of patients with CNS listeriosis (96% of those with meningitis and 86% of those with meningoencephalitis), and positive results were all obtained within 48 hours. Fifth, it appears that treatment of CNS meningitis with TMP-SMZ was safe, effective, and well tolerated, as has been reported by other investigators [26, 27].

Two additional comments on outcome should be made. First, the overall mortality observed in this outbreak (32%) was similar to mortality rates reported in regard to other outbreaks (29%–37%) [11, 12]. The higher meningoencephalitis-associated case-fatality rate in this outbreak (36%) was counterbalanced by a lower bacteremia-associated case-fatality rate (25% vs. 44%–68% in previous descriptions) [7, 28]. The case-fatality rate associated with meningitis (30%) was similar to that noted in another outbreak (33%) [13] and in review articles [5, 6, 23, 24, 29, 30]. Older age and a presentation of meningoencephalitis were significantly and independently associated with an increased risk of death in a multivariate logistic regression model. In contrast, gender, presence of an underlying condition, or type of strain did not predict outcome; however, this lack of significant association may be the result of insufficient power.

Finally, a high proportion (30%) of survivors of CNS listeriosis suffered neurological sequelae. The figure for meningoencephalitis survivors was 60%, similar to the 61% noted for survivors of pure brain-stem encephalitis [10]. Meningoencephalitis was associated with the risk of sequelae, but one patient with meningitis also suffered sequelae (hydroce-

phaly with seizures). No other characteristics predicted the occurrence of sequelae.

Some limitations to the generalizability of this description must be mentioned. First, some unreported cases may have occurred during the outbreak period, because listeriosis was not on the list of reportable diseases at that time. However, the number of missed cases is probably small, because CNS listeriosis would unlikely be unnoticed. Second, this analysis was retrospective and thus depended on the data available in the charts. This bias was limited, however, because most cases were recorded at the same facility and standardized chart documentation was used.

In summary, this outbreak of infection due to food-borne *L. monocytogenes* resulted in a high proportion of CNS infections (79%) occurring in relatively young, previously healthy individuals. The unusual virulence of epidemic strains may account for the atypical features observed, but this hypothesis was not supported by our data. The mortality rate was 32% and was positively associated with age and a clinical presentation of meningoencephalitis. Neurological sequelae developed in 30% of the survivors of CNS infection.

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