Gastroenteritis Due to *Listeria monocytogenes*

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It has been known for a long time that many patients experience diarrhea antecedent to the development of bacteremia or meningoencephalitis due to *Listeria monocytogenes*, but it was only recently that convincing evidence was obtained that this organism can cause acute, self-limited, febrile gastroenteritis in healthy persons. At least 7 outbreaks of foodborne gastroenteritis due to *L. monocytogenes* have been reported. Illness typically occurs 24 h after ingestion of a large inoculum of bacteria and usually lasts 2 days. Common symptoms include fever, watery diarrhea, nausea, headache, and pains in joints and muscles. *L. monocytogenes* should be considered to be a possible etiology in outbreaks of febrile gastroenteritis when routine cultures fail to yield a pathogen.

*Listeria monocytogenes* is generally thought of as a foodborne pathogen that causes bacteremia and meningoencephalitis in individuals with impaired cell-mediated immunity, including neonates, pregnant women, elderly persons, and immunosuppressed recipients of transplants [1]. Although antecedent diarrhea has been reported in cases of invasive listeriosis (i.e., cases involving the presence of *L. monocytogenes* in a normally sterile site) [2], it was only recently that *L. monocytogenes* was established as a cause of acute, self-limited, febrile gastroenteritis in healthy persons. At least 7 outbreaks of foodborne gastroenteritis for which *L. monocytogenes* was the most likely etiology have been described. The present report reviews gastroenteritis caused by *L. monocytogenes*.

**OUTBREAKS OF GASTROENTERITIS DUE TO *L. MONOCYTOGENES***

The reported outbreaks of gastroenteritis due to *L. monocytogenes* are listed in table 1. In 1989, when Riedo et al. [3] isolated identical strains of *L. monocytogenes* from blood samples from 2 febrile pregnant women and from the stool samples of a person with diarrhea, they proposed the possibility that *L. monocytogenes* might cause gastroenteritis. The 3 people had attended the same party. A total of 47% of attendees of that party (17 of 36) reported at least 1 gastrointestinal symptom.

With the exception of the stool sample from the 1 person who reported diarrhea and had a positive result of culture 42 days after the party, all stool samples (which were collected 6 weeks after the party) had negative results of culture for *L. monocytogenes*, as did food samples and environmental specimens. In another report [4], 18 of 39 attendees of a private dinner developed acute febrile gastroenteritis, and 4 were hospitalized; 2 of the 4 who were hospitalized had *L. monocytogenes* bacteremia caused by a strain that was indistinguishable from the strain isolated from some left-over food. Although it is likely that *L. monocytogenes* was the pathogen responsible for this outbreak, many foods, including the one implicated as the vehicle for the outbreak, were contaminated with coliforms in numbers as high as 10^7 colony-forming units (cfu) per gram of food, and none of the cultures of stool samples from 39 guests grew *L. monocytogenes*.

Convincing evidence that *L. monocytogenes* could cause gastrointestinal illness came from an outbreak of febrile gastroenteritis that was associated with the consumption of contaminated chocolate milk [5]. Symptoms developed in 75% of persons (45 of 60) who drank chocolate milk that had been served at a picnic. Indistinguishable strains of *L. monocytogenes* were isolated from unopened cartons of chocolate milk, from environmental specimens from the dairy that supplied the milk, and from the stool samples of 14 symptomatic persons.

The largest documented outbreak [6] occurred in 1997, when 1566 students and staff members from 2 primary schools in northern Italy developed febrile gastrointestinal illness after eating cafeteria food that had been prepared by the same caterer. A total of 292 persons were hospitalized. Cultures of 1 blood sample and 123 stool samples from hospitalized patients yielded
L. monocytogenes strains that were identical to strains isolated from food and environmental specimens at the catering plant. In several subsequent outbreaks [7–10], investigators have shown identity between strains of L. monocytogenes isolated from stool samples of individuals with febrile gastroenteritis and strains cultured from the epidemiologically implicated food.

In addition to the outbreaks mentioned above, small clusters of listeriosis cases manifesting gastrointestinal illness have been detected by surveillance during outbreak investigations [5, 8]. These clusters, identified by active surveillance in the geographic region surrounding the point-source outbreak, were related to the consumption of food from the same suppliers that had been implicated in the outbreaks. Additionally, reports of small outbreaks include one outbreak in a day-care facility that involved 3 children aged <3 years who had fever and diarrhea and whose stool cultures grew indistinguishable isolates [11] and an outbreak of 5 cases of febrile gastroenteritis associated with the consumption of cold smoked rainbow trout contaminated with L. monocytogenes [7].

### CLINICAL FEATURES

Commonly reported symptoms from outbreaks of gastroenteritis due to L. monocytogenes are listed in table 2. The symptoms most frequently reported are fever (in 60%–100% of patients), diarrhea (in 33%–88%), arthromyalgia (in 20%–100%), and headache (in 15%–88%). In most outbreaks, >70% of patients had at least 1 gastrointestinal symptom (e.g., diarrhea, vomiting, nausea, and/or abdominal pain). In the massive outbreak in Italy [6] that involved 1566 students and staff members, fever and vomiting were reported significantly more frequently among children than among adults, whereas diarrhea and arthromyalgia were more common among adults than among children. Diarrhea was typically nonbloody and watery [6, 11], with a median of 12 stools during the 24 h of maximal diarrhea (range, 3–50 stools) [5]. Bloody diarrhea was rare and was noted in 3% of cases [5]. Although chills and sore throat were not reported in every outbreak, they were present in >65% of patients in some reports [4, 5, 9]. It is also interesting to note that sleepiness (an unusual complaint in febrile gastroenteritis) was reported in 63% of cases described by Aureli et al. [6], and fatigue was noted in 74% and 83% of cases reported by Dalton et al. [5] and Frye et al. [9], respectively. Other, less frequently reported symptoms include rash, lymphadenopathy, retrobulbar pain, and dizziness.

The incubation period from the time of food ingestion to the onset of symptoms is usually 24 h or less, but it has ranged from 6 h to 10 days. In the outbreak described by Salamina et al. [4], patients who had gastrointestinal symptoms had a shorter incubation period (mean time, 18 h), compared with patients who had a flu-like illness without gastrointestinal symptoms (mean time, 43 h; P = .06). Listerial gastroenteritis is typically self-limited without serious complications in healthy individuals. The usual duration of symptoms is 1–3 days [5–7] but may be as long as 1 week [6, 8]. In most instances, only a small number of affected individuals required hospitalization because of illness—reportedly 2% [5] and 6.9% [10] in 2 studies; however, in the outbreak described by Aureli et al. [6], 19% of symptomatic persons were hospitalized. Almost all of those hospitalized have been children or elderly persons [5, 6, 10]. In another outbreak, 4 young adults aged 17–27 years were reported to require inpatient care because of their illness [4]. In 2 of these patients, L. monocytogenes was isolated from cultures of blood samples. The prevalence of bacteremia in patients with listerial gastroenteritis is unknown. In the largest outbreak, in which 292 children were hospitalized, only 1 of 40 blood cultures grew L. monocytogenes [6], suggesting a low rate of occurrence.
Table 2. Prevalence (%) of commonly reported symptoms in gastroenteritis due to *L. monocytogenes*.

<table>
<thead>
<tr>
<th>Reference</th>
<th>Fever</th>
<th>Headache</th>
<th>Diarrhea</th>
<th>Nausea</th>
<th>Vomiting</th>
<th>Abdominal pain</th>
<th>Arthromyalgia</th>
</tr>
</thead>
<tbody>
<tr>
<td>[4]</td>
<td>100</td>
<td>78</td>
<td>78</td>
<td>78</td>
<td>44</td>
<td>44</td>
<td>78</td>
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<td>[6]</td>
<td></td>
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<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adults</td>
<td>57</td>
<td>88</td>
<td>53</td>
<td>60</td>
<td>19</td>
<td>72</td>
<td>45/51</td>
</tr>
<tr>
<td>Children</td>
<td>76</td>
<td>86</td>
<td>40</td>
<td>54</td>
<td>40</td>
<td>72</td>
<td>24/20</td>
</tr>
<tr>
<td>[8]b</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cluster 1</td>
<td>78</td>
<td>67</td>
<td>33</td>
<td>11</td>
<td>11</td>
<td>NA</td>
<td>89</td>
</tr>
<tr>
<td>Cluster 2</td>
<td>76</td>
<td>81</td>
<td>67</td>
<td>76</td>
<td>29</td>
<td>57</td>
<td>NA</td>
</tr>
<tr>
<td>[9]c</td>
<td>83</td>
<td>NA</td>
<td>83</td>
<td>33</td>
<td>33</td>
<td>17</td>
<td>100</td>
</tr>
<tr>
<td>[10]</td>
<td>60</td>
<td>15</td>
<td>88</td>
<td>4</td>
<td>21</td>
<td>54</td>
<td>29</td>
</tr>
</tbody>
</table>

**NOTE.**  NA, not available.

* a Arthralgia/myalgia.

b For reference 8, data are given for 2 clusters at 2 different locations.

c Data are from confirmed cases only; presumptive cases were not included.

Although uncommon, the presence of bacteremia indicates that invasive disease can occur as a complication of gastrointestinal illness. During surveillance after the outbreak of gastroenteritis that was linked to contaminated chocolate milk [5], a case of bacteremia was identified in a 2-year-old girl, another case was identified in an 81-year-old man, and a case of cerebral abscess was detected in a 72-year-old man. All 3 individuals consumed chocolate milk from the implicated dairy before the onset of illness, and *L. monocytogenes* isolates from the individuals were indistinguishable from the strain identified in the outbreak. In another report [10], a 64-year-old woman who had been taking steroids for chronic arthritis developed diarrhea that was complicated by septic arthritis due to *L. monocytogenes*. No sepsis syndrome or death has been described in any reported outbreak.

**PATHOGENESIS**

The prevalence of asymptomatic stool carriage of *L. monocytogenes* in healthy adults is said to be 1%–5% [12, 13]. Hof [13] isolated *L. monocytogenes* from 2 of ~100 colon biopsy specimens from patients with colon cancer. Prevalences as high as 20%–25% have been found in certain groups, including household contacts of patients with invasive disease [14–16]. A markedly increased prevalence of *L. monocytogenes* has been found in the stool specimens of patients receiving long-term treatment with gastric acid-suppressive medications, compared with patients who have normal gastric acid secretion [17]. Grif et al. [12] studied the incidence of fecal carriage by examining 868 stool specimens obtained from 3 healthy volunteers during a 1-year period. Using culture and PCR, the researchers showed an incidence of 5–9 exposures (which were defined as a negative culture result followed by a positive culture result followed by a negative culture result) to *L. monocytogenes* per person per year and an average of 2 episodes of asymptomatic fecal carriage (at least 2 positive results of cultures performed on consecutive days) per person per year; no episode of fecal shedding lasted >4 days, and shedding was not associated with any symptoms. In rare instances, promoting events may turn colonizing listeriae into invasive pathogens, as is suggested by instances in which the development of listeriosis followed shigella infection or colonoscopy [1].

Contaminated food appears to be the source of listerial infection in sporadic cases as well as in outbreaks. In what has become known as the “refrigerator study” [18], *L. monocytogenes* was grown from at least 1 food specimen from the refrigerators of 79 (64%) of 123 patients with invasive listeriosis; 11% of >2000 food specimens collected in the study contained *L. monocytogenes*. Twenty-six (33%) of 79 refrigerators with foods that grew *L. monocytogenes* were found to have at least 1 isolate of the same strain as that in the corresponding patient—a frequency that is much higher than would be expected to occur by chance (P < .001) [18]. Similar findings were also noted in cases of asymptomatic fecal carriage and febrile gastroenteritis, in which the strains of *L. monocytogenes* isolated from the patient were indistinguishable from the strains isolated from the food source [5, 6, 12]. A wide variety of food types have been implicated as the source of gastroenteritis outbreaks due to *L. monocytogenes*. Food-based vehicles of infection have included rice salad, cold corn-and-tuna salad, chocolate milk, cold smoked rainbow trout, corned beef and ham, cheese, and ready-to-eat delicatessen meat (table 1). There is no evidence of waterborne infection.
Although ingestion of food contaminated with *L. monocytogenes* is the usual mode of transmission, multiple factors likely play a role in the spectrum of presentations, from asymptomatic presentation to mild gastroenteritis to life-threatening invasive listeriosis. These variables likely include bacterial virulence factors, size of ingested inocula, and underlying host defenses.

There are at least 13 serotypes of *L. monocytogenes*; however, only serotypes 4b, 1/2a, and 1/2b are known to commonly cause human infection. Serotype 4b has been the type most commonly responsible for invasive listeriosis [19], whereas serotypes 1/2a and 1/2b have been the dominant isolates in outbreaks of gastroenteritis. These serotype differences may reflect virulence differences between serotypes. Heterogeneity of virulence with different strains of *L. monocytogenes* has been demonstrated in vitro and in animal studies [20, 21]. Recently, Jacquet et al. [19] identified variations in internalin, a cell surface protein that mediates the entry of *L. monocytogenes* into enterocytes in clinical strains and strains from food products. The expression of full-length internalin was strongly associated with clinical strains—found in 288 (96%) of 300 clinical strains versus 98 (65%) of 150 food strains—whereas the expression of a truncated internalin was strongly associated with food strains (*P < .001*).

*L. monocytogenes* is found commonly in food, and recovery rates ranging from 2.2% to 92% have been reported in dairy and meat products during routine sampling [22]. The ingestion of listeriae must be a common event; however, clinical disease due to listeriae is rare, especially in healthy individuals. In reported gastroenteritis outbreaks, and in contradistinction to invasive listerial infection, the vast majority of people affected have been healthy, without obvious underlying disease. Attack rates have been high (range, 52%–90%) [4–6, 8–10].

Ingestion of a large inoculum of *L. monocytogenes* has been postulated as one of the factors in the pathogenesis of clinical illness. Farber [23] studied healthy nonhuman primates that received doses of various concentrations of *L. monocytogenes* suspended in sterile whole milk. Only animals that received 10⁷ cells became noticeably ill; those that received 10⁶ or 10⁵ cells of *L. monocytogenes* did not become ill, which suggests that there is a dose-dependent response to *L. monocytogenes*. It is unclear what the minimum infecting dose is for either healthy or high-risk individuals. The concentration of *L. monocytogenes* found in food during microbiologic surveillance has been as high as 10⁷ cfu/g of food but is most often <10⁶ cfu/g of food; on the other hand, in outbreaks of invasive listeriosis, counts have been >10⁴ cfu/g of food in most cases, even though colony counts from implicated food sources have ranged from 10⁶ cfu/g to 10⁷ cfu/g of food [22]. Similarly, in outbreaks of gastroenteritis, the degree of bacterial contamination in the implicated food source has varied from 3 × 10⁶ cfu/g of food to 1.6 × 10⁷ cfu/g of food, but is most typically >10⁵ cfu/g of food. It should be remembered that, because a considerable amount of time may pass from the initial recognition of human disease to the sampling of potential food sources, the number of organisms found in food samples at the time of the outbreak investigation may not necessarily reflect the infecting dose. A retrospective calculation taking into consideration the growth rate of *L. monocytogenes* has estimated high-grade contamination with ~1.0 × 10⁷ cfu/g of food during an outbreak of acute febrile gastroenteritis that involved 16 of 44 healthy attendees of a catered party [9]. Carrigue-Mas et al. [10] demonstrated a dose-dependent response in an outbreak of gastroenteritis related to consumption of contaminated cheese; illness developed in 36.3% of persons who had eaten 1–2 servings of cheese, 46.1% of those who had eaten 3–6 servings, and 77.8% of those who had eaten >6 servings.

In the outbreak that was associated with chocolate milk [5], there was no apparent difference in the amount of milk consumed by the 42 persons who became ill and the amount consumed by 15 persons who consumed milk but did not become ill, thereby raising the question of the role of the host in clinical illness. Although impaired cell-mediated immunity is an important factor in invasive listeriosis, it is unlikely to play a role in gastroenteritis due to *L. monocytogenes*, because most of the persons affected have had no known underlying illness. Humoral immunity could potentially provide protection against infection. In feeding trials using goats, Miettinen et al. [24] demonstrated that the presence of preexisting IgG antibody to *L. monocytogenes* was associated with an absence of clinical symptoms and shortened duration of fecal carriage. Farber et al. [23] showed similar results in monkeys, demonstrating that rechallenge with a second infecting dose produced fewer cases of clinical illness than did the first dose. However, in the outbreaks of human gastroenteritis due to *L. monocytogenes*, there was no evidence to suggest preexisting immunity in persons who did not develop illness after exposure.

Gastric acidity is an important protective mechanism against many foodborne infections. Its role in listerial infection is unclear. Cobb et al. [17] showed a markedly increased prevalence of *Listeria* in stool samples from patients who were receiving long-term treatment with H₂ antagonists, compared with patients with normal gastric secretion. In animal models, rats that were pre-treated with cimetidine could be infected with a significantly lower dose of virulent *L. monocytogenes* than could untreated rats [25]. However, in a nonhuman primate model, there was no substantial difference in infecting dose between animals that were treated with antacids and control animals [23].

The mechanism by which *L. monocytogenes* causes diarrhea is unknown, but diarrhea is likely the result of direct invasion. The organism is not known to produce any enterotoxins, and invasion is suggested by fever, as well as by occasional bloody diarrhea and bacteremia.
DIAGNOSIS

Gastroenteritis due to *L. monocytogenes* should be considered in outbreaks of febrile gastroenteritis when routine stool cultures fail to yield a pathogen. The laboratory should be alerted so that selective media and other isolation techniques can be employed to optimize the isolation of listeriae. In clear-cut outbreaks of listerial gastroenteritis, the organism was isolated in >75% of stool samples for culture collected within 2 weeks of the onset of symptoms [7, 9–11], but no stool culture was positive 1 month after ingestion of the contaminated food [4]. Individuals with severe illness are more likely than others to have positive results of stool cultures. In the outbreak associated with chocolate milk [5], none of the asymptomatic individuals had *L. monocytogenes* isolated from stool; however, *L. monocytogenes* was present in 37% of the individuals who were symptomatic and 75% of the individuals who required hospitalization. Because the prevalence of stool carriage of *L. monocytogenes* in normal adults is 1%–5%, the isolation of the organism from stool culture in a single sporadic case is suggestive, but not diagnostic, of listerial infection.

Two reports [4, 5] have suggested that, in cases of gastroenteritis, high titers of antibodies to listeriolysin O, the major listerial virulence factor, may distinguish infected individuals from uninfected individuals. Antibody titers might be of greatest use to retrospectively implicate *L. monocytogenes* as a cause of an outbreak when enough time has passed to make stool cultures useless.

TREATMENT

Febrile gastroenteritis due to *L. monocytogenes* is self-limited, with a typical duration of ≤2 days. No data exist regarding the efficacy of treatment with antimicrobials in this illness, and it is our belief that antimicrobial treatment is not warranted in most instances. Recovery is generally complete, and complicating invasive disease has been rare. The utility, or even the feasibility, of treating acute illness or of eradicating gastrointestinal colonization as a means to prevent invasive disease is unknown. However, it could be argued that, in both symptomatic and asymptomatic persons known to have ingested a food implicated in an outbreak and who have a high risk of invasive disease because of underlying illness, pregnancy, or therapy, it might be prudent to administer oral ampicillin or trimethoprim-sulfamethoxazole for several days.

CONCLUSIONS

As reported by FoodNet [26], an active surveillance program coordinated by the US Centers for Disease Control and Prevention (CDC), *L. monocytogenes* is a rare human pathogen that accounts for 1% of culture-confirmed foodborne infections that occurred from 1996–1998, most of which were cases of invasive disease. *Listeria monocytogenes* has been well documented as a cause of gastroenteritis outbreaks, but its role in sporadic disease is unknown. It should be considered to be a potential cause of febrile gastroenteritis when routine stool cultures fail to identify a pathogen. Gastroenteritis outbreaks due to any foodborne pathogen serve as a reminder that all possible efforts need to be made to ensure the safety of the food supply.

Acknowledgments

Potential conflicts of interest. All authors: no conflicts.

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