**CME CREDIT**

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# Listeriosis: Recognizing it, treating it, preventing it

## ABSTRACT

*Listeria monocytogenes* has become a major pathogen in foodborne illness. It most often affects patients who are pregnant, at the extremes of life, or immunocompromised in some way. A variety of clinical manifestations are possible, but bacteremia and meningitis are most common. This article reviews the epidemiology, microbiology, populations at risk, clinical manifestations, treatment, and prevention of listeriosis.

## KEY POINTS

In suspected or proven cases of listerial infection, prompt treatment is crucial. The first-line treatment is the combination of either ampicillin or penicillin plus gentamicin. Patients allergic to penicillin can receive trimethoprim-sulfamethoxazole instead.

*L monocytogenes* can survive and even slowly proliferate at 4° to 10°C. Therefore, refrigerating food does not completely prevent listeriosis.

Groups at risk are pregnant women, neonates, immunocompromised people, and the very elderly.

Meningitis and bacteremia are the most common manifestations of listeriosis, and more than 20% of people affected die.

THE RECENT WIDESPREAD OUTBREAK of listeriosis associated with tainted processed meats from a food manufacturing plant in Michigan is responsible for 100 illnesses and 15 deaths thus far, refocusing attention on the potential menace of *Listeria monocytogenes* to public health. Although this organism has been recognized as a human pathogen for 70 years,[1] until recent foodborne outbreaks occurred it was an uncommon infection associated with sporadic disease and fostered only a passing interest.[2,3]

## SOURCES OF PAST OUTBREAKS

Epidemics of listeriosis have been linked to many foods. Some of the more publicized and larger outbreaks have been ascribed to soft cheese,[4] cole slaw,[5] deli meats,[6] hot dogs,[7] and pasteurized milk.[8,9] Other foods involved in outbreaks have included raw vegetables, raw milk, fish, pâté,[10] raw and undercooked poultry,[7] ice cream,[10] sausage,[11] raw eggs, and prepackaged mixed salads.[11] Any meat can harbor *L monocytogenes*, but chicken appears to support its growth best.[10]

## *LISTERIA*'S MICROBIOLOGIC PROFILE

Although there are at least seven species of *Listeria*, only *L monocytogenes* appears to cause disease in humans.

*L monocytogenes* is a gram-positive bacillus that displays tumbling motility and beta-hemolysis. In mixed cultures it is difficult to isolate and is often mistakenly identified as a contaminant diphtheroid or corynebacterium. In partially treated patients, culture isolates of *Listeria* may resemble *Hemophilus influenzae*, leading to further confusion.
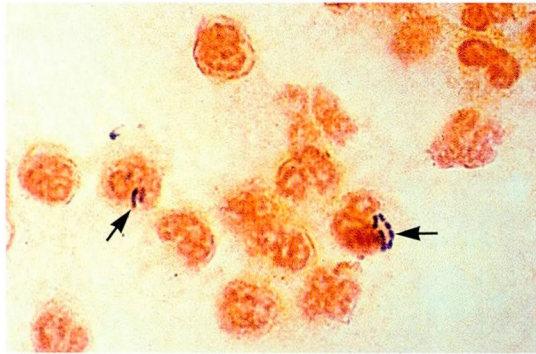
**FIGURE 1.** *Listeria monocytogenes* (arrows) inside macrophages in a cerebrospinal fluid sample from a patient with listerial meningitis. Oil, × 1,000.

SOURCE: COURTESY OF GERALDINE S. HALL, PHD

*L monocytogenes* is ubiquitous.[12] It prefers moist environments[13] and can be isolated from soil, decaying vegetation, sewage, manure, and silage.[9] It is also part of the fecal flora of birds, fish, and mammals. Five to ten percent of humans may carry it in their intestinal tracts.[9,12] It is responsible for epizootics in herd animals and causes abortions, stillbirths, and the "circling disease" (a form of basilar meningitis) in sheep.[14]

This organism has several capabilities that make it particularly dangerous:

**It can survive at low temperatures.** In fact, because *L monocytogenes* can proliferate at 4° to 10°C, cold is used in the laboratory to help isolate it.[12] Refrigeration therefore does not completely protect against listeriosis.

**It survives inside human phagocytic cells,** shielding itself from many of the host's humoral defenses (**FIGURE 1**).[10,15] Therefore, cell-mediated immunity is critical in fighting this pathogen.

**It expresses listerolysin O,** a hemolysin similar to streptolysin O.[10,12,15] This is the organism's major virulence factor. When the organism is engulfed by a macrophage, the macrophage encloses it in a vacuole called a phagosome. Listerolysin O dissolves the phagosome and allows the organism to escape into the macrophage's cytoplasm, evading destruction. (The presence of iron, particularly in iron-overload states, further adds to its virulence.[12,16])

> **Any meat can harbor *L monocytogenes*, but chicken supports its growth best**

## POPULATIONS AT RISK

Although *L monocytogenes* can infect healthy people,[11,17] the vast majority afflicted are either at the extremes of life (< 1 month or > 60 years old), pregnant, or immunocompromised in some way.

Pregnant women account for more than 25% of cases,[12] most commonly in the third trimester, although disease has been recorded throughout all trimesters.[2,14]

Patients with malignancy or some alteration of cell-mediated immunity account for approximately 70% of nonperinatal infections.[12] Chemotherapy, particularly with fludarabine plus prednisone to treat chronic lymphocytic leukemia, enhances the risk of infection with *L monocytogenes*.[18,19] Organ transplant recipients,[20] particularly renal transplant recipients, are at risk because of their immunosuppressed status.[2] HIV-positive patients have perhaps a 150 times higher risk of *L monocytogenes* infection than healthy persons.[21]

Other groups at risk are people with diabetes, renal failure, alcohol abuse,[14] intravenous drug abuse,[11] hypochlorhydria,[7,12] and iron overload states.[16]

## INCIDENCE AND MORTALITY

The estimated annual incidence of listeriosis is approximately 7.4 cases/million population—about 2,000 cases in the United States each year.[7,12,22] However, these figures may be low, due to under-recognition and under-reporting.

Of persons infected, 20% to 30% die—about 400 deaths per year.[7] This percentage is higher than in any other foodborne illness and reflects the host population[11]: the mortality rate is even higher in patients that are older and more seriously immunocompromised[14] and who have more serious underlying diseases.[23]

## ROUTES OF INFECTION

The usual route of infection is by eating contaminated food. Vertical transmission (ie, from mother to infant) also occurs, but other human-to-human transfer is very rare. Cutaneous infection by contact with infected

**Characteristics of central nervous system infections:**
***Listeria monocytogenes* vs other bacteria**

|  | *LISTERIA MONOCYTOGENES* | OTHER BACTERIA |
|---|---|---|
| **Cerebrospinal fluid analysis** | | |
| Glucose level | Normal in > 60% of cases | Typically depressed |
| White blood cell count | High | High |
|  | (50%–70% polymorphonuclear) | (≥ 80% polymorphonuclear) |
| Protein level | High | High |
| Gram stain | Negative in ≥ 60% of cases | Frequently positive |
| **Blood cultures** | Positive in about 75% of cases | Less commonly positive |
| **Clinical abnormalities** | | |
| Cranial nerve deficits | May occur | Rare |
| Ataxia and tremor | May occur | Rare |
| Altered mental status | Common | Less common |
| Nuchal rigidity | Absent in 15% to 20% of cases | Usually present |
| Cortical invasion | May occur | Uncommon |
| Seizures | May occur | Uncommon |

animals has been documented in poultry handlers, ranchers, and veterinarians. The amount of inoculum necessary to produce infection is not known. Experts have postulated the presence of coinfecting microorganisms not yet identified.[24]

### ■ CLINICAL MANIFESTATIONS

One to 2 days after exposure, some patients experience a self-limited gastrointestinal syndrome, which probably occurs more often than recognized.[9] Clinical signs and symptoms may include fever, abdominal cramps, diarrhea, fatigue, headache, and myalgia. A listerial infection should be considered in suspected foodborne gastroenteritis when other pathogens are not isolated.[12] However, most laboratories do not specifically culture stool specimens for *Listeria*.

The more serious syndromes of listerial meningitis and bacteremia do not arise until days to weeks later, often making it difficult to trace the source of infection. The incubation period for these syndromes ranges from 11 to 70 days (mean: approximately 21 days).[12,24] The amount of inoculum and host factors likely influence the duration between exposure and disease.

### Central nervous system infection

Central nervous system (CNS) infection is the most common manifestation of listerial infection.[2] The mortality rate is greater than 30%, the highest of all causes of meningitis.[12]

Blood cultures are positive in 60% to 75% of patients with listerial CNS infections.[14]

CNS infection may manifest as meningitis, meningoencephalitis (rhombencephalitis), or abscesses.

**Listerial meningitis.** *Listeria* is the most common cause of meningitis in patients with hematologic malignancies, in transplant recipients, and in those receiving corticosteroids.[12] It is the third most common cause of meningitis in newborns (after *Escherichia coli* and group B streptococci),[26] and the third most common cause of meningitis in adults (after *Streptococcus pneumoniae* and *Neisseria meningitidis*).[27] Overall, it is the fifth-leading cause of bacterial meningitis in all age groups.[12] Interestingly, listerial meningitis in pregnant women, one of the groups at high risk, is exceedingly rare.[2,12,28]

Listerial meningitis is similar in many ways to other forms of meningitis, except that meningismus occurs less often and mental status changes, movement disorders, and seizures are more common (**TABLE 1**).[12] The cere-

**Serologic testing is not reliable for diagnosing listeriosis**

brospinal fluid usually has an elevated protein level and an elevated white blood cell count with a neutrophilic predominance, but the glucose level may be normal in up to 60% of cases.[14] The Gram stain is negative in more than 60% of cases, possibly owing to the organism's intracellular life cycle.[15] In the uncommon scenario of an adult without underlying disease, listerial meningitis may present with lymphocytic pleocytosis (ie, an increased number of lymphocytes in the cerebrospinal fluid),[17] therefore increasing the possibility of incorrectly attributing the infection to a virus.

**Meningoencephalitis and rhombencephalitis** are very uncommon in adults[29,30] and are almost never seen in neonates. Frequently, the patient is not immunocompromised. Rhombencephalitis (ie, inflammation of the medulla, pons, and cerebellum) manifests as a biphasic process, beginning with fever, headache, nausea, and vomiting and followed by neurologic findings. Because *L monocytogenes* has an affinity for the brain stem, common neurologic findings include asymmetric cranial nerve deficits, cerebellar abnormalities, tremor,[14] hemiparesis, seizures, and respiratory impairment. Personality changes have also been noted.

The differential diagnosis for this type of syndrome is broad and should include many infectious and noninfectious diseases (TABLE 2). The mortality rate in patients with rhombencephalitis may reach 50%. Neurologic sequelae are common, occurring in approximately 60%. The cerebrospinal fluid findings are not as impressive as in listerial meningitis and often more closely resemble those found in brain abscess.[29]

### Isolated bacteremia

Isolated *L monocytogenes* bacteremia presents as a nonspecific flulike illness with fever, arthralgia, myalgia, and headache. It most commonly affects pregnant women, usually in the third trimester, but cases may occur throughout pregnancy. Because the organism has an affinity for the placenta, listerial bacteremia may result in premature labor, stillbirth, or miscarriage. Maternal death is rare, but fetal mortality may approach 40%.[31] If the disease is recognized, it is possible to treat the mother successfully and still allow the birth of a healthy infant.

Spontaneous resolution of primary bacteremia in pregnancy has been reported.[2] When bacteremia results in amnionitis, the baby must be delivered immediately, and maternal recovery usually follows. Infection during pregnancy does not predispose to a carrier state.[10]

### Neonatal listerial bacteremia

In neonates, listerial bacteremia usually occurs during the first 2 days of life. It may manifest as granulomatosis infantisepticum, a severe disseminated form of bacteremia with widespread microabscesses and granulomas and hepatosplenomegaly. This is believed to represent in utero infection and is associated with a poor prognosis and a mortality rate of up to 50%.[10,14] Although late-onset neonatal disease (10–14 days of age or older) most commonly presents as meningitis, bacteremia does occur in this age group as well.[31]

### Listerial endocarditis

Listerial endocarditis is uncommon and usually has a subacute presentation.[2,32] Often, the host is not immunocompromised but has underlying cardiac valvular abnormalities.

There appears to be a left-sided predominance of the affected valves.

## Localized listerial infection

Localized listerial infections are rare.[14] Lymph node abscesses, osteomyelitis, septic arthritis, pneumonia, empyema, and peritonitis have been described.[33] Cutaneous infections occur as occupational hazards for ranchers, veterinarians, and poultry workers. Myocarditis has been described in heart transplant recipients.[34]

## ■ DIAGNOSIS AND TREATMENT

In suspected or proven cases of listeriosis, prompt initiation of antibiotic therapy is crucial. Diagnosis is established by culture, growth, isolation, and characterization of L monocytogenes from the blood and cerebrospinal fluid. Serologic testing is not reliable for diagnosis.

## Antibiotic regimens

**Ampicillin** in maximal doses (2 g every 4 hours for adults, or 200–400 mg/kg/day for children) is the preferred agent to treat listeriosis, often in synergistic combination with gentamicin.[12,14] Penicillin G may be as effective as ampicillin. However, ampicillin and penicillin are only bacteriostatic for L monocytogenes.

**Trimethoprim and sulfamethoxazole** are synergistic,[35] and the combination is accepted as a second-line therapy for patients allergic to penicillin. Trimethoprim-sulfamethoxazole is bactericidal and penetrates the cerebrospinal fluid well.[14]

**Erythromycin** as monotherapy demonstrates good antilisterial activity[36] but is considered a third-line therapy at present. It may be a suitable alternative for penicillin-allergic pregnant patients, in whom trimethoprim-sulfamethoxazole would be contraindicated. Erythromycin penetrates the meninges very poorly, even when the meninges are inflamed, and therefore would be a poor choice in treating meningitis or rhombencephalitis.

**Vancomycin** has some activity against L monocytogenes. Most authorities do not recommend using it for this purpose however, because of limited efficacy and because of the desire to limit the use of vancomycin in general.

## Bacterial resistance

An isolate of L monocytogenes that is resistant to trimethoprim-sulfamethoxazole has been reported,[37] but overall resistance to first-line, second-line, or third-line therapy is rare. Cephalosporins, chloramphenicol, tetracycline, and quinolones are probably ineffective.

## Treatment duration

Bacteremia should be treated for 2 weeks, meningitis for 3 weeks, endocarditis for 4 to 6 weeks, and rhombencephalitis or brain abscess for 6 weeks[2,12] or until the patient has improved and the symptoms have resolved.

## ■ PREVENTION

Government agencies have launched programs to improve and ensure the safety of our foods.[38,39] In addition, new methods of sterilizing foods are under investigation. Irradiation was recently approved as one such method. Unfortunately, this technology has a bad pub-

lic image, and it changes the appearance and taste of food. If these obstacles can be overcome, irradiation may hold promise.

Persons at high risk for listeriosis must exercise caution in their dietary choices, and common sense must prevail for the rest of the population. **TABLE 3** provides some useful guidelines. Persons at risk should avoid raw vegetables unless they are known to be carefully washed. All dairy products should be pasteur-ized, and soft cheeses should be avoided. Meats should be cooked until the internal temperature is 160 to 180°F, ie, medium-well to well done. Refrigerated leftover foods need to be thoroughly reheated to destroy *L mono-cytogenes*, which can proliferate at low temperatures. Although deli foods usually carry a low risk for listerial infection, they either should be well heated before eating or should be avoided.

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