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Epidemiology and Clinical Manifestations of *Listeria monocytogenes* Infection

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ABSTRACT Listeria monocytogenes is a Gram-positive pathogenic bacterium which can be found in soil or water. Infection with the organism can develop after ingestion of contaminated food products. Small and large outbreaks of listeriosis have been described. Listeria monocytogenes can cause a number of clinical syndromes, most frequently sepsis, meningitis, and rhombencephalitis, particularly in immunocompromised hosts. The latter syndrome mimics the veterinary infection in ruminants called "circling disease". Neonatal infection can occur as a result of maternal chorioamnionitis ("early onset" sepsis) or through passage through a birth canal colonized with Listeria from the gastrointestinal tract. ("late onset" meningitis). Treatment of listeriosis is usually with a combination of ampicillin and an aminoglycoside but other regimens have been used. The mortality rate is high, reflecting the combination of an immunocompromised host and an often delayed diagnosis.

EPIDEMIOLOGY

Listeria monocytogenes is a Gram-positive motile facultative anaerobe that inhabits a broad ecologic niche (1–3). With selective media it can be readily isolated from soil, water, and vegetation, including raw produce designated for human consumption without further processing (4, 5). Newer chromogenic media may offer some advantages in the detection of contaminated foodstuffs (6, 7). Surface contamination of meat and vegetables is relatively common, with up to 15% of these foods harboring the organism. In addition, the organism is a transient inhabitant of both animal and human gastrointestinal tracts (8–10), and intermittent carriage suggests frequent exposure. The gut is the source for the organism in invasive listeriosis when it occurs, and the virulence factor ActA may promote carriage (11). The organism is psychrophilic and enjoys a competitive advantage against other Gram-positive and Gram-negative microorganisms in cold environments, such as refrigerators. It may also be amplified in spoiled food products, particularly when spoilage leads to increased alkalinity. Feeding of spoiled silage with a high pH has resulted in epidemics of listeriosis in sheep and cattle (12).

Several large foodborne outbreaks of listeriosis in humans have parallels to epidemic listeriosis in animals. The first proven foodborne outbreak occurred in Canada in 1980 to 1981 and was caused by ingestion of contaminated coleslaw (13). Subsequently, many other foodstuffs have been implicated in both small and large outbreaks, including unpasteurized and pasteurized cheeses (14–22), pasteurized milk (23, 24), butter (25), various fruits and vegetables (26–30), and several meat products (31–35) (Table 1). A large outbreak of listeri-

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TABLE 1 Some foods implicated in published reports of foodborne listeriosis

Dairy products	Fruits and vegetables	Meat products	Fish products
Pasteurized whole milk	Coleslaw (cabbage)	Delicatessen foods (deli meats)	Tuna salad
Chocolate milk	Lettuce	Pâté	Smoked fish
Mexican-style cheese	Corn	Uncooked hot dogs	Shrimp salad
Soft cheese (different types)	Rice salad	Turkey franks	
Hard cheese	Strawberries	"Rillettes"	
Goat cheese	Cantaloupes	Pork tongue in aspic	
Ice cream	Nectarines	Pork pie	
Fresh cream	Salted mushrooms	Beef	
	Alfalfa tablets	Jellied pork	
	Apples	Cooked ham	
	Blueberries	Foie gras	
	Stone fruit	Ox tongue	
	Sprouts	Undercooked chicken	

osis with over 900 cases and 200 deaths was reported from South Africa in 2017-2018. The source was a contaminated processed meat called "polony" (36). Recent evidence suggests that hospitalized patients are also at risk of acquiring invasive listeriosis (37). Tracking listeriosis cases and creating linkages to food products is now dependent on typing isolates using pulsed field gel electrophoresis and whole-genome sequencing, which have largely replaced older methods such as serotyping (38, 39). Uncertainty exists as to why outbreaks of listeriosis occur in human populations, although the 50% infective dose in sporadic disease is probably high. Enhancement of organism-specific virulence factors may play a role in epidemic disease, although all isolates of *L. monocytogenes* have the ability to produce all the virulence factors characteristic of the species.

Recent evidence has suggested that sporadic cases of listeriosis are also foodborne. Case-control studies of sporadic listeriosis cases in the absence of epidemic disease have implicated food products, including cold meats, turkey franks, and delicatessen-type foods, as vehicles for the development of sporadic invasive listeriosis in humans (40).

Our current understanding of the epidemiology of human listeriosis suggests that the organism is a common contaminant of food products and that ingestion of small numbers of *L. monocytogenes* occurs frequently in human populations. In one prospective study, a rate of 5 to 9 exposures per person-year was estimated (41). Amplification of the organism in biofilms or on food products undergoing processing but not pasteurization and kept at cold temperatures allows overgrowth of *L. monocytogenes*. Subsequent ingestion of large numbers of the organism may overwhelm innate host-defense systems in the gastrointestinal tract, liver, and spleen with subsequent development of invasive disease. The annual rate of sporadic listeriosis in Europe (42–44) and North America (45) is usually <1/100,000 population per year, and the disease is costly in both human (46) and economic terms (47). Sporadic listeriosis appears to be more common in the spring and summer months. This could be explained by seasonal variations in the types of food products eaten by human populations, with higher-risk products eaten in the warmer months. In addition, data suggest that preexisting damage to the gastrointestinal mucosa by other microorganisms, such as those that are associated with viral gastroenteritis, may allow translocation of *L. monocytogenes* from the gastrointestinal tract with subsequent development of invasive disease (48). These viral pathogens often have seasonal patterns that overlap with those of invasive listeriosis.

Demographic data from surveillance studies indirectly revealed several host-specific risk factors for invasive listeriosis (49, 50). Infection is most commonly seen in the first 30 days of life or in patients older than 60. In the first instance, the fetus is infected during maternal sepsis with *L. monocytogenes* or from perivaginal and perianal colonization of the mother by transition through the birth canal. Host defense against listeriosis is impaired in those infants with underdeveloped macrophage and cell-mediated immune function, and invasive listeriosis is more likely to occur if colonization of the liver, respiratory tract, or gastrointestinal tract has occurred.

The increased risk of invasive listeriosis in older patients reflects the increasing incidence of immunosuppressive conditions, such as solid tumors and hematologic malignancy, in this age group. Control of early infection in humans and in animal models is highly dependent on an intact gastrointestinal mucosa and effective macrophage function in the liver, spleen, and peritoneum following bacterial translocation from the gastrointestinal tract. Both these protective events can be

impaired by the primary disease or by chemotherapy or radiation-induced damage. In addition, treatment of malignancy and the use of immunosuppressive agents with a specific effect on cell-mediated immune function, such as corticosteroids or cyclosporin A (51), predispose to invasive infection by diminishing *L. monocytogenes*-specific host responses that occur after the initial phase of infection. The recent proliferation of biologic treatments with immune modulators such as tumor necrosis factor-alpha inhibitors has also contributed to increases in invasive listeriosis (52–54).

The cell-mediated immune response to *L. monocytogenes* is impaired in pregnant women (55) and, with the decreased gastrointestinal motility (56) seen in pregnancy, may predispose to invasive listeriosis and subsequent transplacental infection of the infant. This results in "early-onset" listeriosis characterized by the delivery of an often premature and severely ill infant. Spontaneous recovery of the mother from *Listeria* sepsis normally occurs following delivery of the infant, although if recognized prepartum, appropriate antibiotic therapy can save the infant.

In "late-onset" listeriosis, the infant is infected through maternal gastrointestinal carriage of *L. monocytogenes* without sepsis, and the infant is infected during transition through a colonized birth canal. In these cases, clinical disease in the infant develops 7 to 14 days later. Direct cutaneous invasion is unlikely, and it is believed that aspiration of the organism into the respiratory tract or swallowing of the organism by the infant may occur during the incubation period. A unique outbreak of neonatal listeriosis in Costa Rica has been described: the vehicle was *L. monocytogenes*-contaminated mineral oil used to clean infants after delivery from healthy mothers, with cross contaminations of shared mineral oil (57). The index case was infected through the placental route of maternal-fetal transmission. Pregnancy-associated listeriosis has been recently reviewed (58, 59).

Several large outbreaks of a febrile gastroenteritis syndrome have further highlighted the importance of *L. monocytogenes* as a foodborne pathogen. In these outbreaks, with an average incubation period of approximately 24 h, attack rates (up to 72%) were much higher than those reported for outbreaks of invasive listeriosis. The reported vehicles for these more typical foodborne infections have included shrimp (60), rice salad (61), chocolate milk (24), corn salad (62), ready-to-eat meats (63, 64), jellied pork (65), and fresh cheese (15). The foods implicated were usually heavily contaminated (>10^9 CFU/ml of *L. monocytogenes*), and the amount of food ingested appeared to correlate with infection, suggesting that the high attack rates are not related to enhanced intrinsic virulence of the particular infecting strain of *L. monocytogenes*. A hospital-acquired outbreak of gastroenteritis has also been described from contaminated meat jelly (66).

While a predisposition to invasive listeriosis is seen in patients with malignancy or organ transplant, human immunodeficiency virus (HIV) infection is also an important risk factor in sporadic listeriosis (67). Earlier studies have reported that attack rates for invasive listeriosis in HIV-positive patients that were 500- to 1,000-fold greater than those in the general population. However, reductions in invasive listeriosis cases in HIV infection has been brought about by widely promulgated dietary recommendations to prevent foodborne illness and by the use of prophylaxis for *Pneumocystis jiroveci* pneumonia, primarily trimethoprim-sulfamethoxazole, to which *L. monocytogenes* is susceptible. Further reductions in HIV-associated cases may be due to better and more widespread antiretroviral therapy (68). Reductions in the overall incidence of listeriosis in non-HIV-positive patients may also be attributed to distribution of dietary recommendations to populations at risk, including pregnant women, patients with malignancies, and organ transplant recipients (69). Perhaps more importantly, the decreased incidence of listeriosis may be due to the promotion of guidelines to promote universal awareness of the problem in the food-processing industry, which has undertaken hazard analysis at critical control point (HACCP) (70–72) and microbial risk assessment (73, 74, 141) programs to reduce contamination of foods with *L. monocytogenes* as well as with other foodborne pathogens such as *Salmonella* spp., *Campylobacter* spp., and *Escherichia coli*. These activities have provided increased protection in the face of increased public demand for fresh, unprocessed food products that may not have been cooked or pasteurized and that by definition present a greater degree of risk for foodborne illness.

In addition to hazard analysis at critical control point programs, regulatory agencies have aggressively pursued the control of *L. monocytogenes* contamination of food. The U.S. Food and Drug Administration has a zero-tolerance policy for *L. monocytogenes* in its industry sampling programs (75). Other countries have adopted less stringent guidelines, allowing a small amount of contamination (<10^2 CFU/g) to strike a balance between protection of public health and needless condemnation of otherwise edible food products. While invasive listeriosis may be more common in some countries in Europe than in the United States, it is not clear whether these

differences can be attributed to less stringent standards in Europe that allow more *L. monocytogenes* in the food supply. The debate continues between zero tolerance advocates and those supporting a risk-assessment approach to *Listeria* contamination of food (76). However, these measures have not led to decreases in the incidence of *L. monocytogenes* infections in the developed world (77).

CLINICAL DISEASE DUE TO *L. MONOCYTOGENES*

A wide variety of clinical syndromes have been associated with *L. monocytogenes* infection in both animals and humans (Table 2). The earliest descriptions of *L. monocytogenes* sepsis were described in an epizootic affecting South African rodents (78) and in laboratory colonies of rabbits (79). One distinguishing characteristic of infection in rabbits was the production of monocytosis in blood, which suggested the species name *monocytogenes*. A monocytosis-producing antigen has been described as a virulence factor of *L. monocytogenes* (80), but monocytosis in the peripheral blood is not a characteristic of infection in humans.

Many wild and domesticated animals are subject to invasive listeriosis. Animals acquire the organism from the environment through grazing, amplified by fecal contamination of soil and vegetation. Specific syndromes with parallels in human disease have been recognized in animals. In New Zealand in the 1930s, Gill (81) described "circling disease," a rhombencephalitis of sheep that may effect flocks fed spoiled silage. *L. monocytogenes* has also been implicated as a cause of abortion and prematurity in ruminants. Intravenous and oral models of *L. monocytogenes* infection in rodents can duplicate the illness seen in the natural state in animals, including maternal sepsis and abortion (82).

TABLE 2 Some clinical syndromes associated with *L. monocytogenes* infection

Neonatal meningitis
Meningoencephalitis in adults
Rhombencephalitis
Sepsis (bacteremia) in infants or adults
Native or prosthetic valve endocarditis
Spontaneous bacterial peritonitis
Septic arthritis
Biliary tract disease
Hepatitis
Liver abscess
Cutaneous infections (in animal workers)
Endophthalmitis
Febrile gastroenteritis
Continuous ambulatory peritoneal dialysis peritonitis
Osteomyelitis

The clinical syndromes associated with listeriosis in humans were discovered later. Neonatal listeriosis was initially described in postwar Europe in premature septic newborns in East Germany (83). This description of early-onset listeriosis was followed by reports of neonatal meningitis (late-onset listeriosis) occurring later in the postpartum period. *L. monocytogenes* as a cause of meningitis in neonates is third to group B streptococci and *E. coli* in the developed world (84, 85). The use of antibiotic prophylaxis to prevent group B streptococcal infection may also have reduced cases of neonatal listeriosis (86). In less-developed countries, Gram-negative meningitis with *E. coli* or *Salmonella* spp. is more common, but *Listeria* meningitis still occurs.

PREGNANCY-ASSOCIATED LISTERIOSIS

Pregnant women are at high risk of infection, and occult or overt bacteremia can result in chorioamnionitis producing early-onset neonatal listeriosis (58). These infants have characteristic clinical features, including prematurity, sepsis at birth, fever, a diffuse maculopapular cutaneous eruption, and evidence of significant hepatic involvement with jaundice (87). The mortality rate of early-onset listeriosis, even with treatment, is very high, and stillbirth is also common in this setting. Autopsy findings in cases of early-onset listeriosis show significant chorioamnionitis in placental remnants and granulomas in multiple organs, particularly the liver and spleen, in infected infants. The original descriptions from East Germany characterized the entire syndrome as "granulomatosis infantiseptica." (83).

The mothers of these septic infants may be asymptomatic but commonly have flu-like or pyelonephritis symptoms before the early onset of labor, and their blood cultures are frequently positive for *L. monocytogenes*. Symptoms in the mother include fever, chills, and malaise, which resolve spontaneously following delivery of the infected infant and placenta (87). Anecdotal case reports suggest that early treatment of the mother who has *Listeria* sepsis can prevent transplacental infection or treat the fetus *in utero*, with subsequent delivery of a normal uninfected infant (88). Unfortunately, this usually only happens when a community-based outbreak of *L. monocytogenes* has been identified and physicians are aware of the problem in a particular geographic region through public health alerts.

Late-onset neonatal meningitis due to *L. monocytogenes* has the typical features of the same syndrome caused by other organisms in this setting, including fever, irritability, bulging fontanelle, and meningismus (89). These symptoms usually develop 1 to 2 weeks following delivery. The mother has usually had an uncomplicated pregnancy, delivery, and postpartum course with no signs of sepsis. The clinical syndrome usually dictates a lumbar puncture, and the cerebrospinal fluid (CSF) in 50% of the cases reveals the organism by Gram's stain. CSF cultures are usually positive, although the organism may be isolated simultaneously or only from the blood in some cases. The CSF shows other characteristics of bacterial meningitis, including a high polymorphonuclear leukocyte count, elevated protein, and low glucose with a decrease in the CSF-serum glucose ratio.

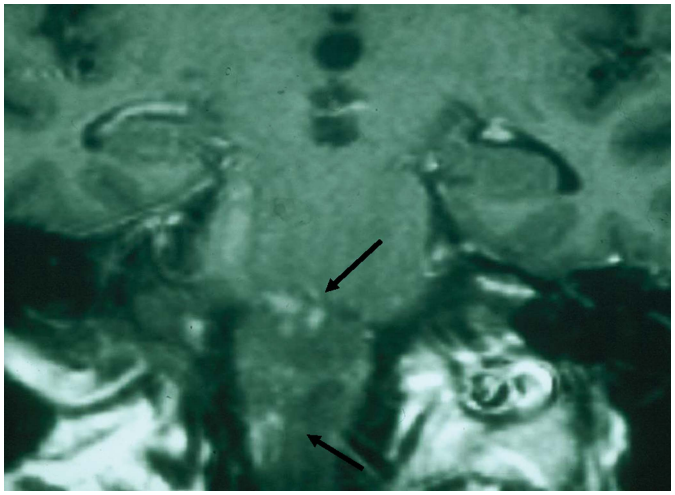

FIGURE 1 Computed tomography scan from a 72-year-old male with *Listeria* rhombencephalitis. The arrows point to multiple microabscesses.

ADULT MENINGOENCEPHALITIS

L. monocytogenes is an uncommon cause of bacterial meningitis in adults. There are two major clinical presentations. The first is a typical subacute bacterial meningitis characterized by fever, headache, and neck stiffness (90). Because the organism is not commonly seen on Gram's stain of CSF, and because the cell counts are lower than in other forms of bacterial meningitis, an initial diagnosis of viral meningitis is commonly made before culture of the organism from CSF or blood. The onset of the syndrome can occur over several days, unlike meningococcal or pneumococcal meningitis, which have more abrupt onsets. During epidemics of foodborne listeriosis, *Listeria* meningitis can occur in apparently healthy individuals of all ages. In sporadic disease, patients more commonly have obvious defects in cell-mediated immune function that predispose them to listeriosis.

The second form of central nervous system listeriosis in adults is a rhombencephalitis that has features characteristic of the same illness in animals, described as circling disease (91). Fever, headache, nausea, and vomiting occur early, with signs of meningeal irritation less commonly present. Subsequently, patients develop multiple cranial nerve abnormalities accompanied by cerebellar dysfunction, including ataxia. Fever may not be present in up to 15% of patients, which makes the diagnosis more difficult and more suggestive of noninfectious disorders. CSF pleocytosis may be minimal, and the organism is rarely seen on Gram's stain. The diagnosis is established by culture of CSF or blood. Magnetic resonance imaging is the best diagnostic study and frequently demonstrates typical multiple microabscesses of the cerebellum and diencephalon (Fig. 1). The mortality rate in this condition approaches 50%, and despite treatment, residual morbidity, including permanent cranial nerve palsies and ataxia, may persist.

L. monocytogenes can also be responsible for cerebritis or typical brain abscess in the supratentorial region (92). In these cases the typical rhombencephalitic symptoms due to microabscesses are absent. Host risk factors reflecting immune deficiency are commonly seen in these cases as they are in *Listeria* sepsis.

LISTERIA SEPSIS

Listeria sepsis, or bacteremia without central nervous system involvement, represents one-third of adult cases of invasive listeriosis. The symptoms are nonspecific but usually include fever and chills. As noted above, in pregnant women *Listeria* sepsis often masquerades as pyelonephritis or "flu" (87). The diagnosis is often established in retrospect following delivery of an infected infant. In nonpregnant adults, *Listeria* sepsis almost always occurs in patients with malignancy, organ transplant, or other immunocompromised states (93–95). In these settings, the presentation is also nonspecific and mimics sepsis with other Gram-positive and Gram-negative pathogens. The mortality rate for *Listeria* sepsis in these series is 25 to 30%.

OTHER CLINICAL SYNDROMES

Cutaneous Listeriosis

Cutaneous listeriosis is an occupational hazard of veterinary workers exposed to infected amniotic fluid or

placental remnants that are removed from the birth canal of animals (96–98). Occasionally, cutaneous infection, including conjunctivitis, has been seen in laboratory workers (99). Cutaneous listeriosis is characterized by low-grade fever and multiple papulopustular lesions of the skin from which the organism can be isolated. Its appearance is similar to the rash seen in infants with early-onset disseminated listeriosis. In adults, the condition may resolve spontaneously without treatment, but the infection itself should be entirely preventable with appropriate gloving and other protective wear.

Bacterial Endocarditis Caused by *L. monocytogenes*

Bacterial endocarditis presumably follows transient bacteremia from a gastrointestinal source, with subsequent establishment of endovascular infection on an abnormal heart valve. *L. monocytogenes* is an uncommon cause of native valve endocarditis, and over 50% of cases that have been described involve prosthetic valves (100–102). Infection with *L. monocytogenes* is usually found as part of the late prosthetic valve endocarditis syndrome. Diagnostic criteria for *Listeria* endocarditis include the presence of a prosthetic valve with or without vegetation and continuous bacteremia with *L. monocytogenes*. Septic emboli and abscess formations in other organs are relatively frequent. In native valve endocarditis, *L. monocytogenes* can sometimes follow previous episodes of streptococcal bacterial endocarditis or other valvular heart disease. Patients with malignancy, diabetes, steroid therapy, and renal and liver transplantation have been described with *Listeria* endocarditis. Their presentation is nonspecific for *L. monocytogenes* and includes prolonged fever, chills, and ultimately, signs of congestive heart failure. Septic embolization occurs in two-thirds of patients, and aortic and mitral valve involvement are most common. *L. monocytogenes* can also cause arterial infections that involve prosthetic abdominal and aortic grafts or native abdominal aortic aneurysms (103). The mortality of this condition approached 40% before 1985 but has been reduced to 12% with better recognition and surgical management.

Hepatitis and Liver Abscess Due to *L. monocytogenes*

L. monocytogenes has been described as a cause of acute hepatitis in several case reports (104). It occurs as acute onset of fever and jaundice accompanied by positive blood cultures for *L. monocytogenes*. The diagnosis is usually unsuspected. Severe disease with death has been described, and autopsy or liver biopsy generally reveals microabscesses and occasionally granulomas similar to those seen in severe early onset neonatal disease. Predisposing factors include cirrhosis and liver transplantation (105), although *Listeria* hepatitis can occur in a normal host.

Solitary and multiple liver abscesses with fever are also described (106, 107). Bacteremia occurs in half of these patients. Predisposing factors include diabetes mellitus, transplantation, cirrhosis, and alcoholism. Aspiration of the abscess demonstrates the organism. The mortality rate is 50%, and postmortem examination often reveals abscesses in other organs as well. Patients with multiple abscesses appear to do worse than those with a solitary abscess.

Listeria Peritonitis

L. monocytogenes can also cause isolated episodes of peritonitis (108, 109). It is most commonly seen in patients undergoing continuous ambulatory peritoneal dialysis (110), and the organisms are isolated from the dialysate or from blood culture. The organisms presumably cause infection through translocation from the gastrointestinal tract in patients who have ingested the organism with food. This complication is extremely rare and represents <1% of all cases of continuous ambulatory peritoneal dialysis peritonitis. It can also cause spontaneous bacterial peritonitis in advanced liver disease with ascites (111–113). The mortality rate is low, and laboratory and clinical features are typical of spontaneous bacterial peritonitis due to other organisms. The organism can rarely cause this disease in patients who have undergone liver transplantation.

Biliary Tract Infections

Recent reports have seen *L. monocytogenes* emerge as a biliary tract pathogen (114, 115, 142). Retrograde infection from contaminated food is the likely source. The organism is resistant to bile, and this may play some role in the pathogenesis of biliary disease. Most cases also have medical comorbidities, including immunosuppression from corticosteroid use or newer biologic agents to treat the underlying conditions. A number of deaths have been reported, often due to inappropriate antibiotic therapy.

Musculoskeletal Infection

L. monocytogenes is a very uncommon cause of osteomyelitis (116–118). Reports of *Listeria* osteomyelitis emphasize the role of diabetes mellitus or leukemia as predisposing factors, particularly when long-term corticosteroids are administered. Relapses have been described despite effective antibiotic therapy. Septic arthritis due to

L. monocytogenes appears to be more common than bone infection, and rheumatoid arthritis appears to be a frequently associated condition. Low-dose methotrexate therapy may predispose to this infection. Infection may follow joint injection with corticosteroids. Infection has been described in prosthetic hips and knees as well as in native joints (119, 120). The organism can also cause vertebral osteomyelitis with epidural abscess (121). With prolonged antibiotic therapy, medical treatment alone, as opposed to removal of the prosthetic joint, may be successful. Deaths are rare and are normally due to the underlying disease.

Gastroenteritis

A febrile gastroenteritis syndrome has been described for listeriosis (15, 24, 25, 60–64, 143). Gastrointestinal prodromal symptoms, such as diarrhea or abdominal pain, have been common in large outbreaks of foodborne adult listeriosis, but sepsis and meningoencephalitis have been the usual presenting syndromes. Population-based attack rates for invasive listeriosis have been low in this setting. In *Listeria* gastroenteritis, a more typical foodborne illness occurs with high attack rates (up to 72%) among the individuals exposed to the vehicle of infection. Large numbers of organisms in the contaminated food may be responsible.

Most patients are well before development of the infection. While bacteremia has occurred in some patients, primary symptoms are diarrhea, fever, fatigue, chills, and myalgias occurring 24 h following exposure. This incubation period is considerably shorter than the 3- to 4-week period for more usual forms of invasive listeriosis.

Pregnant women appear to be more likely to have sepsis in these outbreaks. Isolation of *L. monocytogenes* with selective media from stool has been rare, but serologic tests have been used to help define the extent of the outbreaks. In the outbreaks reported to date, rice salad, shrimp salad, chocolate milk, corn, deli meats, and fresh cheese have been the reported vehicles, and high colony counts of the organism (up to 10^9 CFU/g) appear to be present in the contaminated food. Invasive listeriosis can also be a result of loss of gastrointestinal integrity due to other gastrointestinal tract pathogens such as *Shigella* spp. (122) or to presumed viral gastroenteritis (48). This may account for some sporadic and epidemic cases of *Listeria* sepsis and meningoencephalitis.

DIAGNOSIS OF LISTERIOSIS

Diagnosis of all forms of *L. monocytogenes* infection depends on isolation of the organism from a normally sterile site, usually blood or cerebrospinal fluid. Gram's stain of specimens of sterile spinal fluid, peritoneal fluid, or joint aspirates occasionally, but unpredictably, reveals Gram-positive coccobacilli, characteristic of *L. monocytogenes*. In some forms of central nervous system infection, particularly rhombencephalitis, several samples may have to be obtained to isolate the organism. Focal neurologic findings that are characteristic of rhombencephalitis should prompt computed tomography or magnetic resonance imaging scanning. The finding of multiple microabscesses in the hindbrain is highly suspicious for *Listeria* rhombencephalitis, and empiric treatment for listeriosis should be started.

In situations where antibiotic therapy has already been administered, isolation of the organism from a nonsterile site may support a diagnosis of listeriosis. In pregnant women, stool or vaginal cultures may be positive when selective media for *L. monocytogenes* are used for culture. In febrile gastroenteritis syndromes, where traditional pathogens have not been isolated using standard media, culture of the stool with selective media for *L. monocytogenes* may also demonstrate the organism.

Direct detection of PCR products such as the HlyA from *L. monocytogenes* in CSF and other fluids has been studied. Sensitivity appears to be low but might be useful in patients already on treatment for listeriosis where cultures are negative (123, 124).

TREATMENT OF LISTERIOSIS

L. monocytogenes remains susceptible to most β-lactam antibiotics, with the exception of cephalosporins, to which the organism is usually resistant (125–127). Because newer cephalosporins are commonly used for the treatment of nonspecific sepsis syndromes or for the empiric treatment of bacterial meningitis, specific therapy for listeriosis may be delayed for some patients. Empiric therapy for bacterial meningitis with ampicillin is recommended for older adults but may not be necessary for children beyond the neonatal period (128). When listeriosis is a likely diagnosis, the use of ampicillin or, in penicillin-allergic patients, vancomycin provides empiric coverage for *L. monocytogenes* until the diagnosis is made by culture.

A combination of ampicillin and gentamicin is the current therapy of choice for all forms of listeriosis (129, 130). However, some data suggest that this combination is not useful and could be harmful (131). There has been a trend toward increasing resistance to penicillins (127). Ampicillin is not bactericidal for *L. monocytogenes*, and *in vitro* and *in vivo* data suggest that an additive or

synergistic effect with gentamicin may improve the outcome (132). No randomized, controlled clinical trials of therapy in humans have been carried out, however.

Trimethoprim-sulfamethoxazole, with or without the addition of rifampin, is an alternative treatment regimen that has been recommended. Early "step-down" to oral trimethoprim-sulfamethoxazole has been successful in several cases (133). In one retrospective study, the combination of amoxicillin and cotrimoxazole was found to be more effective than ampicillin and gentamicin (134). High-level resistance to trimethoprim has been recognized, however (127, 135). New quinolones may also be effective, but data are limited to *in vitro* studies (136, 137). Rifampin is active against *Listeria*, but resistance has been found in cases of prosthetic joint infection (138, 139). For central nervous system infection, dexamethasone and phenytoin have been suggested as possible treatment adjuncts (140).

Trimethoprim-sulfamethoxazole has also been used as a prophylactic agent against a number of microorganisms, including *P. jiroveci*, in patients with HIV infection and in patients undergoing chemotherapy for leukemia or lymphoma. This drug would be effective in protecting against *L. monocytogenes* infections. The use of prophylaxis has been temporally associated with a decrease in the incidence of listeriosis in these compromised hosts in combination with dietary guidelines that have been issued for these patients in recent years (68).

The duration of treatment for invasive listeriosis has not been studied. Relapses appear to be uncommon, and 2 to 3 weeks of therapy with ampicillin and gentamicin is sufficient for most forms of listeriosis. Rhombencephalitis with abscess formation in the central nervous system may require more prolonged therapy, but data are not available that support treatment beyond 4 weeks (129, 130).

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