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Listeria monocytogenes infections: presentation, diagnosis and treatment

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Abstract

Listeriosis is an infective complication that primarily affects pregnant women, patients at extremes of age or those with weakened immune systems. Ingestion of food contaminated with *Listeria monocytogenes* is the most common source of infection, causing self-limiting illness in immunocompetent hosts but associated with invasive infection and high mortality in high-risk patient groups. Milder illness presents as gastroenteritis with fever, diarrhoea, nausea and vomiting common in the 7 days post exposure. Invasive infection, characterised by bacteraemia and encephalitis, can develop in high-risk patients. Fetal loss is a major complication of listeriosis during pregnancy. Penicillin-based therapy (high dose penicillin or amoxicillin) in combination with gentamicin is advised for invasive infection; co-trimoxazole may be considered for patients intolerant to penicillin. Vulnerable individuals, notably pregnant women, should be counseled on appropriate preventative strategies including avoiding foods commonly contaminated with *L. monocytogenes*, such as soft ripened cheeses, pate, cooked chilled meats, unpasteurised milk, and ready to eat poultry unless thoroughly cooked.

Key words: Fever of unknown origin; Listeriosis; Meningo-encephalitis; Neonatal sepsis; Pregnancy

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Introduction

Listeriosis is a rare infection that most commonly occurs after ingestion of contaminated food. While usually self-limiting in healthy adults, those who are immunosuppressed, at extremes of age or pregnant are at risk of serious complications of infection. The majority of cases of invasive listeriosis are caused by the species *Listeria monocytogenes*, and bacteraemia or meningitis carries a high mortality despite antibiotic treatment among non-pregnancy related cases. Identifying at-risk patients and giving appropriate empiric treatment are most important in reducing mortality.

Listeria species are short, Gram-positive rods (0.4–0.5 × 0.5–2.0 µm) that occur singly or in chains. Members of this genus are facultative anaerobes. The genus *Listeria* currently includes at least 20 recognised species (Orsi and Wiedmann, 2016; Nwaiwu, 2020), of which *L. monocytogenes* is the most clinically relevant human pathogen. Other species can cause disease, but this is rare. Infection with *L. monocytogenes* can cause a spectrum of illness ranging from non-invasive, self-limiting gastroenteritis to invasive bacteraemia and meningitis or meningo-encephalitis which carry a high and significant mortality rate (Cartwright et al, 2013; Orsi and Wiedmann, 2016). Early identification and empiric treatment of at-risk patients are most important in reducing mortality.

Epidemiology

The importance of *L. monocytogenes* as a pathogen is related to the potential for serious infection and associated high mortality. Public Health England (2018) reports on average 166 cases per year of listeriosis in England and Wales (annual case numbers from 2008 to 2018), giving an approximate incidence rate of between 0.2 and 0.5 cases per 100 000 population.

All *Listeria* species are widespread in the environment (soil, silage), domestic animal faeces and foods. Human listeriosis is predominantly caused by foodborne exposure to *L. monocytogenes* (Cartwright et al, 2013), particularly cold meats, dairy products, vegetables and pre-packed or processed food (Pagliano et al, 2017). Pre-prepared sandwiches served

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within NHS hospitals have resulted in some of the largest *Listeria* outbreaks in the UK in the last decade. This is a result of the ability of the bacteria to continue to replicate at low (ie refrigerator) temperatures. Most cases are not related to outbreaks. Transmission may also occur transplacentally or perinatally, or by direct contact with infected livestock. Cross infection in delivery suites has also been well documented (Nelson et al, 1985). There is approximately a 5% faecal carriage rate among healthy adults, which is transient following ingestion.

Individuals at highest risk

Most infections occur in well-defined at-risk groups: pregnant women, those at extremes of age and the immunocompromised, for example secondary to malignancy, diabetes, renal disease, excess alcohol intake, transplantation or corticosteroid use (Guevara et al, 2009; Friesema et al, 2015).

Immunosuppression of pregnancy greatly increases the incidence of listeriosis and infection is 18 times more common (12/100 000) than in non-pregnant peers (0.7/100 000) (Lamont et al, 2011). This accounts for approximately 16–27% of all infections reported. Invasive listeriosis in pregnancy is associated with high mortality of the fetus or newborn infant (Silk et al, 2013). A large prospective cohort study, MONALISA (Charlier et al, 2017), demonstrated that fetal loss occurred in 26 (24%) of 107 infected pregnant women, and premature delivery or a delivery with fever and fetal distress occurred in 70 (65%) of 107 women.

Pathogenesis

Once ingested, *L. monocytes* can cross the intestinal epithelium barrier, invading the mesenteric lymph nodes and entering the blood (Goulet et al, 2013). Most of the bacteria are sequestered in the liver and are subsequently cleared from the circulatory system. Surviving bacteria replicate in hepatocytes. Early recruitment of polymorphonuclear cells leads to hepatocyte lysis resulting in release of the bacteria. If the infection is not controlled at this point, a secondary bacteraemia develops.

Circulating bacteria exhibit a tropism for the brain and gravid uterus (Goulet et al, 2013; Lowe et al, 2018). Fetal transmission is not invariable, but once the placenta is infected, it becomes a reservoir for re-infection and placental micro-abscesses may be present (Lamont et al, 2011).

Presentation and clinical syndrome

L. monocytogenes gastroenteritis is characterised by fever, diarrhoea, nausea and vomiting, and can have an incubation period of 11 hours to 1 week after exposure (Sim et al, 2002). Less commonly, infection can present with flu-like symptoms, muscle or joint pain, headache and sore throat, in the absence of any gastrointestinal symptoms (Salamina et al, 1996).

In bloodstream infections, patients present with symptoms and signs of illness such as fever, chills, tachycardia, abdominal pain, diarrhoea, vomiting, backache, headache, decompensated comorbidity and multiorgan failure (Charlier et al, 2017). The incubation period is usually 1–2 weeks but can vary between a few days and up to 90 days. However, patients may also have a positive blood culture result with no symptoms.

Neurolisteriosis is traditionally associated with symptoms of encephalitis but not exclusively so. Up to 13% of cases of neurolisteriosis have meningeal involvement without encephalitis, thus complicating the diagnosis (Charlier et al, 2017). Symptoms and signs seen in patients presenting with *L. monocytogenes* meningitis are similar to those found in patients with community-acquired bacterial meningitis. The CSF findings of patients with CNS disease can vary from showing only mild abnormalities to a pleocytosis similar to that of meningitis from viral causes with a predominance of mononuclear cells. Aside from mycobacterial infection, *Listeria* is the only other bacteria to cause a significant lymphocytosis of the CNS. Similar to other infective causes of meningitis, CSF protein concentration can be raised and CSF glucose concentration normal or reduced. The classic triad of fever, neck stiffness and altered mental status was present in 43% of patients with community-acquired *L. monocytogenes* meningitis (Brouwer et al, 2006). Almost all of these patients (97%) presented with at least two of the four symptoms and signs of headache, fever, neck stiffness and altered mental status.

The presentation of listeriosis in pregnancy may be mild or asymptomatic. In a large series of cases of listeriosis in pregnancy (Lamont et al, 2011), 32% of women had symptoms of a flu-like illness and most had a fever (65%). Other symptoms included backache (21.5%), headache (10.5%), vomiting or diarrhoea (7%), muscle pains (4%) and sore throat (4%). Approximately 29% of the women were asymptomatic. Invasive listeriosis in pregnant women can result in intrauterine infection, premature labour, stillbirth and neonatal infections.

Neonatal listeriosis caused by vertical transmission or de novo infection can be potentially fatal. Infections are divided into early neonatal infection, occurring hours to days after birth with a predominantly septicaemic illness or late neonatal infection, occurring more than 5–7 days after delivery with a predominantly meningitic presentation.

Diagnostic microbiology

Isolation of *L. monocytogenes* is most commonly from blood, CSF or less commonly other sterile sites such as joint fluid. Blood cultures are the most sensitive and specific test for all manifestations of infection but may be negative in late neonatal infection. Gram stains are positive in only approximately 30% of CSF specimens that subsequently grow *L. monocytogenes* (Figure 1). The bacteria will grow readily on a variety of standard bacteriological laboratory culture media, usually within 48 hours (Figure 2). Selective media, although not routinely available in clinical microbiology laboratories, can be useful for screening foods, for example during investigation of food-associated outbreaks of listeriosis. Stool cultures are generally not useful in diagnosing invasive disease, having a low sensitivity. High vaginal swabs may be of use in the diagnosis of missed abortion where products of conception are not available, since the bacterium would not usually be found in the absence of infection.

Preliminary identification of *Listeria* is based upon Gram stain of the culture, colonial morphology and appropriate biochemical tests. Confirmation and identification of *L. monocytogenes* can then be undertaken through a range of methods, commonly including

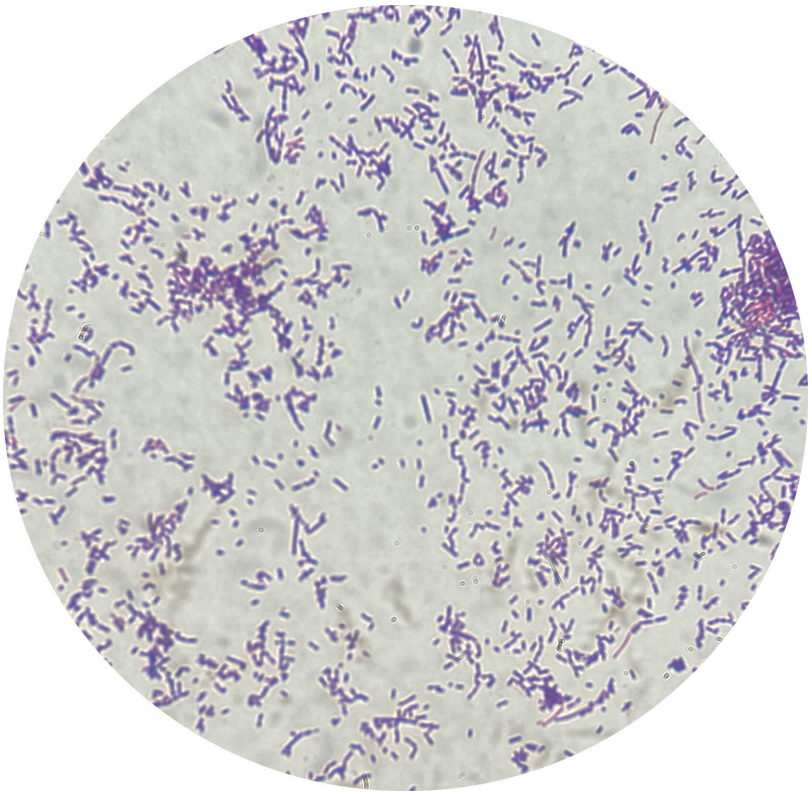

Figure 1. Gram stain of *Listeria monocytogenes* (at x100 oil immersion objective + x10 eyepiece).

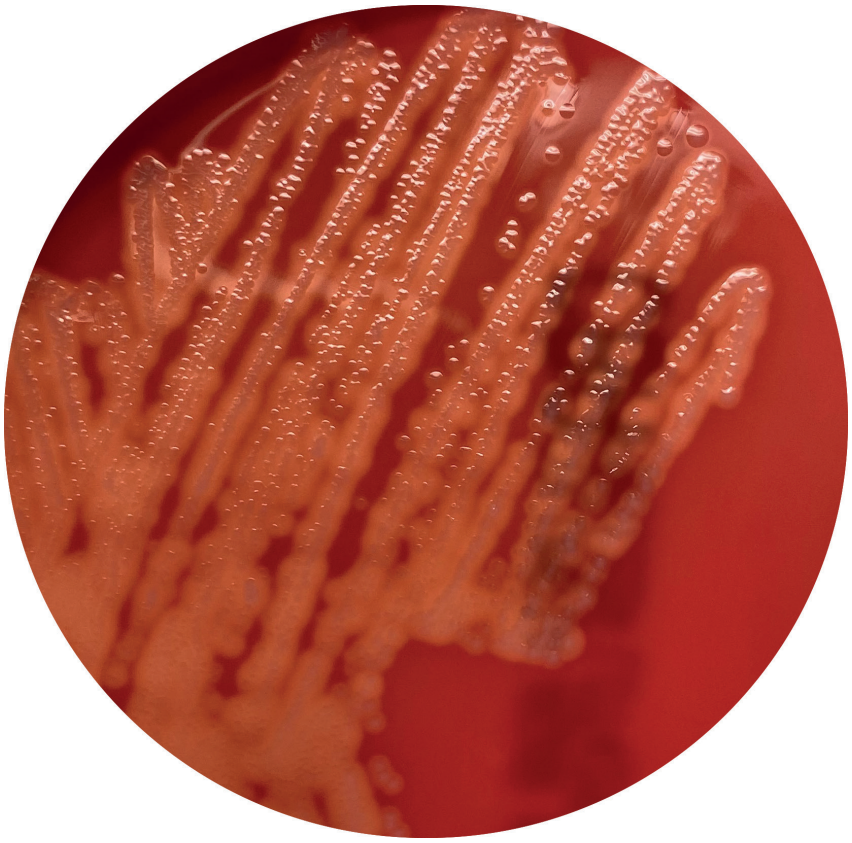

Figure 2. *Listeria monocytogenes* on blood agar incubated in oxygen at 37ºC for 48 hours.

biochemical strips such as ASP Listeria (bio-Merieux, Marcy-Etolie, France), automated liquid-culture systems, matrix-assisted laser-desorption/ionisation-time of flight (MALDI-ToF) mass spectroscopy or by targeted or 16s RNA polymerase chain reaction where available. Various typing methods are available to enable strain differentiation to help with outbreak investigation, but whole genome sequencing is becoming increasingly available and aids the tracing of outbreaks.

In the UK all cases of invasive listeriosis must be reported to public health organisations. Local infection prevention and control teams should also be informed of presumptive and confirmed isolates of *L. monocytogenes.*

Prevention

Prevention of listeriosis focusses on vulnerable individuals avoiding foods commonly contaminated with *L. monocytogenes,* such as soft ripened cheeses, pate, cooked chilled meats, unpasteurised milk, and ready to eat poultry unless thoroughly cooked. Food must also be appropriately stored and handled. Pregnant women are also advised to avoid contact with sheep at lambing time and should not handle silage. Patient information is available at https://www.nhs.uk/conditions/listeriosis/

Treatment

Treatment recommendations should be tailored to the anatomical site and severity of infection. Most immunocompetent non-pregnant patients who develop febrile gastroenteritis after consuming *L. monocytogenes*-contaminated foods have a self-limiting illness and do not require antimicrobial treatment.

For patients with invasive listeriosis, optimal therapy is an intravenous aminopenicillin (such as amoxicillin or ampicillin) or benzylpenicillin (Janakiraman, 2008; Thønnings et al, 2016). Synergy with aminoglycosides has been documented in in vitro studies, but

clinical studies have shown conflicting results with combination therapy. Retrospective analysis from Denmark (Thønnings et al, 2016) demonstrated no mortality benefit with the addition of gentamicin to aminopenicillins or benzylpenicillin. However, in a large prospective analysis from France (Charlier et al, 2017), gentamicin added to penicillin therapy was associated with a reduced mortality (odds ratio 0.6 (95% confidence interval 0.38–0.84); *P*=0.024). Gentamicin therapy was continued for up to 7 days in these studies. In the absence of prospective randomised control studies, a short course of gentamicin (≤7 days) should be considered in combination with penicillin for patients presenting with invasive listeriosis.

In vitro activity has been demonstrated for the carbapenem, meropenem; however, meropenem-based treatment of listeriosis causing bacteraemia or meningitis is associated with inferior clinical outcomes to aminopenicillins or benzylpenicillin-based therapies and is not recommended (Thønnings et al, 2016). Trimethoprim-sulfamethoxazole is an alternative if the patient has a penicillin allergy.

L. monocytogenes is inherently resistant to all cephalosporin antibacterials. Cephalosporins, such as ceftriaxone and cefotaxime, are typically used as first-line empirical treatment for meningitis and thus early targeted therapy for listeriosis may be delayed. The addition of amoxicillin or co-trimoxazole is advised in high-risk groups presenting with meningitis or patients presenting with concurrent confusion or other evidence of encephalitis. Delayed empiric treatment for listeriosis is associated with higher mortality and long-term neurology-related sequelae (Thønnings et al, 2016). Dexamethasone therapy prescribed for presumptive streptococcal meningitis may be associated with deleterious outcomes for patients with neurolisteriosis and should be stopped promptly once *L. monocytogenes* is isolated. *L. monocytogenes* bacteraemia should be treated be for a minimum of 14 days. A 21-day treatment plan is advised for patients with neurolisteriosis (Table 1).

Prognosis

Invasive *L. monocytogenes* infections have a high mortality rate despite antimicrobial treatment; this is most pronounced in patients at the extremes of age. The 90-day mortality rates range from 30–46% in patients presenting with neurolisteriosis and positive blood cultures respectively (Charlier et al, 2017). Neurolisteriosis patients with frank encephalitis had three times higher mortality than those without encephalitis (72 (33%) of 218 patients vs three (9%) of 34 patients, *P*=0·003) (Charlier et al, 2017). Delayed or inadequate empirical antibiotic therapy is associated with an increase in all-cause 30-day mortality for patients with invasive listeriosis (39.7% (46/116) compared with 13.3% (15/113) for patients treated with adequate empiric antibiotic therapy (Thønnings et al, 2016)). Patients treated with a penicillin-based antibacterial had a 3·3 times higher survival than those who

Table 1. Treatment options for *Listeria* spp. infections

Infection	Treatment	Duration
Uncomplicated gastroenteritis in immunocompetent patient	No antibacterial treatment advised	n/a
Listeriosis in pregnancy	First line: amoxicillin intravenous 2 g every 6–8 hours	7–14 days; longer if fetus survives
Meningitis or brain abscess	First line: amoxicillin intravenous 2 g every 4 hours Alternatively: benzylpenicillin intravenous 2.4 g every 4 hours or co-trimoxazole intravenous 30 mg/kg every 6 hours	21 days (42 days if brain abscess)
Bacteraemia	First line: amoxicillin intravenous 2 g every 6 – 8 hours Alternatively: benzylpenicillin intravenous 2.4 g every 6 hours or co-trimoxazole intravenous 30 mg/kg every 6 hours	14 days minimum
Neonatal listeriosis	First line: amoxicillin intravenous adjusted for age and weight Alternatively: benzylpenicillin intravenous adjusted for age and weight	14–21 days

Key points

- Listeriosis is predominantly caused by foodborne exposure to *Listeria monocytogenes*.
- Non-invasive *Listeria* spp gastroenteritis is typically characterised by fever, diarrhoea, nausea and vomiting, but patients may present without gastrointestinal symptoms. Most immunocompetent patients will have a self-limiting illness and do not require antimicrobial treatment.
- Bacteraemia and meningitis/meningo-encephalitis infections occur in well-defined at-risk groups: pregnant women, people at the extremes of age and the immunocompromised.
- Symptoms and signs of *L. monocytogenes* meningitis are similar to those of community-acquired bacterial meningitis.
- The presentation in pregnancy may be mild or asymptomatic. Invasive listeriosis can cause intrauterine infection, premature labour, stillbirth and neonatal infections.
- Neonatal listeriosis may occur hours to days after birth with a predominantly septicaemic illness or as a late neonatal infection more than 5–7 days after delivery with a predominantly meningitic presentation.
- *L. monocytogenes* is most commonly isolated from blood, CSF or less commonly other sterile sites such as joint fluid. Blood cultures are the most sensitive and specific test for all manifestations of infection but may be negative in late neonatal infection.
- Optimal therapy in invasive listeriosis is an intravenous or benzylpenicillin. Delayed or inadequate empiric antibiotic therapy is associated with an increase in all cause 30-day mortality.
- In the UK all cases of invasive listeriosis must be reported to local public health services, and local infection prevention and control teams should be informed of presumptive and confirmed isolates of *L. monocytogenes*.

did not (66% vs 20%, $P<0.0001$). Adding an aminoglycoside to treatment also improved survival (69% vs 52%, $P<0.0001$) (Charlier et al, 2017).

Post neurolisteriosis, long-term sequelae of neurological impairment (altered consciousness or focal signs) was reported in 44% of surviving patients and 52% of patients with encephalitis symptoms. Limb motor deficiency, cerebellar symptoms and eighth cranial nerve palsy are the most commonly persisting defects reported in surviving patients.

Conclusions

Listeriosis, a rare but serious infection, typically results from foodborne contamination. Most cases of *Listeria* infection are self-limiting, but among patients who are immunocompromised, pregnant or at extremes of age, it can cause invasive infection with a high associated mortality. Prevention of *L. monocytogenes* infection through appropriate food storage and hand hygiene can help high-risk group developing listeriosis. Where invasive infection is identified, it is critical to initiate appropriate antibacterial therapy to minimise mortality and morbidity.

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Conflicts of interest

LSP Moore has consulted for/received speak fees from bioMerieux (2013–2021), DNAelectronics (2015), Dairy Crest (2017–18), Pfizer (2018–21), Eumedica (2016–2021), Profile Pharma (2018), Shionogi (2021), and Umovis Labs (2020–21), and received research grants from the UK National Institute for Health Research (NIHR; 2013–19), and CW+

Curriculum checklist

This article covers the following areas from the general internal medicine curriculum:

- Managing an acute unselected take
- Managing an acute specialty-related take
- Managing medical problems in patients in other specialties and special cases.

Charity (2018–21). S Hughes has consulted for/received speak fees for Pfizer (2020–21), Eumedica (2020), Bowmed (2021) and Shionogi (2020–21). M Valenti and N Ranganathan declare that they have no conflicts of interest.

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