Review

Clinical Findings of *Listeria monocytogenes* Infections with a Special Focus on Bone Localizations

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Review

Clinical Findings of *Listeria monocytogenes* Infections with a Special Focus on Bone Localizations

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Abstract: *Listeria monocytogenes* is a Gram-positive pathogenic bacterium which can be found in soil or water. Infection with the microorganism can occur after ingestion of contaminated food products. Small and large outbreaks of listeriosis have been described in the past. *L. monocytogenes* can cause a number of different clinical syndromes, most frequently sepsis, meningitis, and rhombencephalitis, particularly in immunocompromised hosts. *L. monocytogenes* systemic infections can develop following tissue penetration across the gastrointestinal tract or to hematogenous spread to sterile sites, possibly evolving towards bacteremia. *L. monocytogenes* only rarely causes bone or joint infections, usually in the context of prosthetic material that can provide a site for bacterial seeding. We describe here the clinical findings of invasive listeriosis, mainly focusing on diagnosis, clinical management and treatment of bone and vertebral infections occurring in the context of invasive listeriosis.

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1. Introduction

Listeria monocytogenes is a Gram-positive, motile facultative anaerobe bacteria that inhibits a broad ecologic niche [1,2]. The microorganism can be isolated from soil, water and vegetation, including raw designated also for human consumption without further processing [3,4]. Newer chromogenic media may offer advantages in the detection of contaminated food [5,6]. The surface contamination of meat and vegetables is common, with up to 15% of these foods harboring the microorganism. Furthermore, *L. monocytogenes* is a transient inhabitant of both animal and human gastrointestinal tracts; intermittent carriage suggests possible frequent exposure [7,8]. Usually, gut is the source for the microorganisms in case of invasive listeriosis; the virulence factor ActA is associated with carriage development [9]. The microorganism has a competitive advantage against other Gram-positive and Gram-negative bacteria in cold environments, such as refrigerators; it is also amplified in spoiled food products, possible leading to increased alkalinity. Feeding of spoiled silage with a high pH resulted in epidemics of listeriosis in sheep and cattle [10]. Several foodborne outbreaks of listeriosis derived from animal epidemics; the first one occurred in Canada and was associated with the ingestion of contaminated coleslaw [11]. Subsequently, many other foodstuffs have been implicated in different outbreaks, including unpasteurized and pasteurized cheeses and milk or milk derivates [12–23], meat products [24–29] and fruits and vegetables [30–34]. In addition, also hospitalized individuals seem at risk of acquiring *L. monocytogenes* infections [35]. To optimize the tracking of listeriosis cases, the whole-genome sequencing has been developed and then replaced older techniques as serotyping [36,37]. However, it remains not completely understood why outbreaks of listeriosis can occur in humans; a possible enhancement of organism-specific virulence factors may play a role in developing epidemic dissemination. Nevertheless, all isolates of *L. monocytogenes* are able to produce all the virulence factors characteristic of the species.

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Also sporadic cases of listeriosis can be foodborne related; reports of sporadic cases of *L. monocytogenes* infection in absence of documented outbreaks have been associated with different food products that could represent vehicles for the occurrence of sporadic invasive listeriosis in humans [38]. Consequently, *L. monocytogenes* can be considered a common contaminant of food products and the ingestion of small quantitative of this microorganism occurs frequently in humans [39]. *L. monocytogenes* usually grows in biofilms or in food products not undergoing to pasteurization and kept at cold temperature. Invasive diseases occur when the ingestion of a large number of microorganisms overwhelm the innate host-defense systems at gastrointestinal, liver or spleen level. Although the annual rate of sporadic listeriosis in Europe and North America is usually < 1/100000 population per year [40–42], the development of this infection is associated with a high burden of costs [43,44]. Sporadic listeriosis usually follows seasonal variations, being more common during spring- and summertime, mainly associated to the increased consumption of higher-risk products during the warmer period. In addition, the risk of developing invasive listeriosis could be associated with the presence of pre-existing damages on the gastrointestinal mucosa due to other microorganisms that usually induced viral gastroenteritis and that have seasonal patterns that may overlap with those of listeriosis. These damages may allow translocation of *L. monocytogenes* from the gastrointestinal tract with subsequent development of invasive diseases [45].

Host-specific conditions also contributed to increase the risk of invasive listeriosis [46,47]. In particular, cases of invasive listeriosis are most commonly described in the first month of life or in elderly individuals. The fetus is mainly infected during maternal sepsis or secondary to peri-vaginal or peri-anal colonization of the mother, with transmission occurs through the birth canal. Infants usually don't have adequate host defense, mainly in cases of impairment of macrophage and cell-mediated immune function; therefore, invasive listeriosis can easily develop in case of colonization of the liver, respiratory tract or gastrointestinal tract. Pregnant women have usually a decreased gastrointestinal motility and also a slight impairment of cell-mediated immune response to *L. monocytogenes*; both these conditions may predispose to invasive listeriosis with transplacental infection of the infant [48–51] that can finally lead to a delivery of a premature and often severely ill newborn. Spontaneous recovery of the mother from invasive listeriosis normally occurs after the delivery; the administration of specific and appropriate antibiotic therapy can improve the prognosis of the infant and also accelerate the clinical recovery of the mother. When the infant is infected through a colonized birth canal, clinical disease in the infant usually develop 7 to 14 days later. A direct cutaneous invasion is unlikely in this context; aspiration of *L. monocytogenes* into the respiratory tract or by swallowing of the microorganism can occur only during the incubation period. At the moment, a unique outbreak of neonatal listeriosis has been described. *L. monocytogenes* was spread through contaminated mineral oil used to clean infants after delivery from healthy mothers, with cross contaminations of shared mineral oil; the index case was infected through the placental route of maternal-fetal infection [52].

The increased risk of invasive listeriosis in elderly usually reflects the increasing incidence of other immunosuppressive conditions in this specific population, such as solid or hematological malignancies, chronic diseases leading to immunological impairment such as diabetes or renal failure, or immunosuppressive treatments. In particular, malignancies may lead to abnormalities of gastrointestinal mucosa and impairment of effective macrophage function in liver, spleen and peritoneum, both directly or secondary to chemotherapy or radiation-induced damages, finally favoring bacterial translocation from the gastrointestinal tract. The increasing use of immunosuppressive treatments with a specific effect on cell-mediated immune function as corticosteroids or cyclosporine A, as well as the use of biologic treatments with immune modulator effect as tumor necrosis factor-alpha inhibitors can also contribute to an augmented risk of invasive listeriosis [53–55].

Among the cause of immunosuppression, HIV infection has been linked to the occurrence sporadic invasive listeriosis [56]. In particular, earlier studies described a 500-1000-fold greater risk of developing invasive listeriosis in HIV-infected individuals compared to general population. Subsequently, a progressive reduction of reported cases has been observed, due to dietary

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recommendations to prevent foodborne illnesses and, above all, due to the wide use of trimethoprim-sulfamethoxazole as *Pneumocystis jirovecii* pneumonia prophylaxis to which *L. monocytogenes* is also susceptible; furthermore, a possible contribute to the reduction of cases may be secondary to the widespread use of more efficacy antiretroviral treatments that induce a restoration of immune system function [57].

L. monocytogenes is overall considered one of the most important foodborne pathogen associated with the occurrence of febrile gastroenteritis outbreaks. Several foods have been described as vehicles of these outbreaks, including fresh cheese, ready-to-eat meat, shrimps, rice or corn salad and chocolate milk [15,22,58–63]. In these outbreaks, symptoms developed soon after ingestion (approximately 24 hours) and attack rates were significantly greater when compared to invasive listeriosis. These high attack rates are not usually related to enhanced intrinsic virulence of the *L. monocytogenes* strain but to a heavily contamination of the ingested food.

A reduction in the overall incidence of listeriosis could be due to a larger promotion of dietary recommendations to high-risk individuals, including pregnant women, patients with malignancies or underwent to transplantation [64]. More probably, this reduction could be due to the worldwide promotion of awareness in the food-processing industry, including hazard analysis at critical control point (HACCP) [65,66] and, above all, to programs to reduce food contamination with different microorganisms including *L. monocytogenes*, *Salmonella* spp., *Escherichia coli* and *Campylobacter* spp [67–69]. These activities provided an augmented protection for fresh, unprocessed food products that may not have been cooked or pasteurized and that are at higher risk of convey foodborne illnesses. In addition to hazard analysis, regulatory agencies significantly implemented the control of microorganisms with potential ability to contaminate food. The U.S. Food and Drug Administration developed strict recommendations for the control of *L. monocytogenes* in the food industry [70], mainly including the use of whole-genomic sequences (WGS) [71]. Recently, Conrad et al. [72] described how, starting from 5 cases of invasive listeriosis in Kansas, the use of WGS permitted to identify *L. monocytogenes* contamination of ice-cream products in three other states; the Company facilities where the ice-creams were produced were located in Texas and Oklahoma, suggesting long-standing contamination. Other countries have adopted less stringent guidelines, allowing a small amount of contamination ($<10^2$CFU/g) to balance the protection of public health and the needless condemnation of otherwise edible food products. While invasive listeriosis seems more common in some European countries than in United States, it is still unclear whether these differences can be attributed to the less stringent standards in Europe. It remains therefore debatable if a "zero tolerance" approach for *L. monocytogenes* contamination of food could be preferable to a risk assessment approach [73].

2. Clinical Findings Due to *Listeria monocytogenes*

L. monocytogenes infections are associated with a high variety of clinical findings in both humans and animals. Sepsis by *L. monocytogenes* was first described in epizootic affecting South African rodents and in laboratory colonies of rabbits [74,75]. The species name monocytogenes was suggested by the production of monocytosis in blood; though a monocytosis-producing antigen has been considered a virulence factor for *L. monocytogenes*, monocytosis in the peripheral blood is not considered a distinguish finding in human infections [76].

Many wild and domestic animals are susceptible to invasive listeriosis. Animals usually acquire *L. monocytogenes* through grazing, further amplified by fecal contamination of soil and vegetation. In ruminants, *L. monocytogenes* has been implicated as a possible cause of abortion and prematurity [77]. The clinical syndromes associated with listeriosis in humans were discovered later. Neonatal listeriosis was firstly described in Europe in premature septic newborns during the post-war period [78]; subsequently, other reports described neonatal meningitis as late-onset listeriosis occurring in the post-partum period. In the developed world, listeriosis is a frequent cause of neonatal meningitis, though the wide use of antibiotic prophylaxis to prevent group B streptococcal infection has reduced in parallel the cases of neonatal listeriosis [79,80].

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3. Bone and Vertebral Infections by *L. monocytogenes*

L. monocytogenes only rarely causes bone and joint infections, usually in the context of prosthetic material that can provide a site for bacterial seeding.

3.1. Imaging Techniques

When suspecting bone or vertebral infections, the use of imaging techniques, as radiography or CT scan could provide valuable information in terms of bone erosions and vertebral bony integrity mainly in the later stages of the disease; during the early stage of infection no significant finding is usually detected. Furthermore, spinal stability must be assessed for patients in whom surgical management is being considered. Indeed, vertebral collapse, kyphotic deformity and loss of normal lordosis can be found in advanced infections. CT also provides guidance for percutaneous aspirations in order to provide specimens for the bacteriologic analysis in the presence of a fluid collection. MRI is the gold standard and represents the diagnostic imaging modality of choice. It should be performed in all patients in which a spinal infection is suspected, unless contraindicated. Unenhanced T1-weighted images usually reveal a hypointense signal at the level of the end plates in the vertebral body and loss of normal hyperintense fat signal in the vertebral bone marrow. T2-weighted imaging reveals high signal corresponding to edema, in the disk space and occasionally in the bone and paravertebral soft tissues. Gadolinium-enhanced T1-weighted imaging can demonstrate contrast-enhancement of the vertebral body, end plates, the prevertebral and paravertebral soft tissues, and the epidural space. Whenever the MRI is contraindicated or non-diagnostic (e.g. due to the presence of metallic implants causing artifacts), other imaging modalities should be considered. CT myelography provides another way for visualizing spinal cord and rule out compression in the setting of suspected cauda equina syndrome. On the contrary, nuclear medicine scans with radionuclide studies offer a high degree of sensitivity in early stages of the disease. Spinal infections can occasionally be multifocal so the whole spine should be scanned if an infectious focus is detected.

3.2. Microbiological Diagnosis

The determination of a microbiological diagnosis of *L. monocytogenes* bone or vertebral infection is challenging especially in absence of referred exposures or negative blood tests. In this context, aspiration biopsy or surgical sampling represent the optimal method to provide a valid microbiological diagnosis. As a consequences, empiric antibiotic therapy should be delayed if the patient is hemodynamically stable and has no neurological signs, in order to obtain valid samples for cultures; postponing antimicrobial administration can improve microbiological yield, so it could be preferably deferred in absence of life-threatening conditions or spinal cord involvement [81]. However, initiation of antibiotic treatment does not always preclude undertaking a biopsy [82]; in those cases where antibiotic treatment has already been started, it was demonstrated that interrupting and withholding antibiotics for 2 weeks had a better yield compared to holding for only 3 days pre-biopsy [83]. These data can vary according to the pharmacokinetics, dose, duration and bone penetration of the selected antibiotic. Nevertheless, a short duration of empiric antibiotic exposure does not negatively impact pathogen recovery and therefore is not an absolute contraindication for biopsy [84]. Therefore, all these diagnostic and therapeutic issues should be taken in consideration when managing vertebral infections by *L. monocytogenes*.

3.3. Surgical Approach

In the absence of neurological deficits or sepsis, medical management with adequate intravenous antibiotics and immobilization of the affected spinal segment represent the optimal therapeutic approach. Antibiotic therapy should be started as soon as the microorganism has been isolated in order to achieve sterilization of the infected bone or vertebral disc and prevent the occurrence of a neurological deficit or painful deformity. The duration of antibiotic therapy varies depending on the extent of bone involvement and the status of the patient's immune system. Neurosurgical intervention should be considered only after taking into account patient's neurological

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status as well as the extent of bone erosions and the specific vertebral level involved. The principles of surgical treatment include debridement of infected tissue, decompression of neural elements as well as restoration of spinal alignment and/or correction of spinal instability. The presence of a neurological deficits is considered the most important factor in the decision-making process. Regardless of the duration of the weakness, emergency surgical intervention is offered unless the motor deficit is minimal. Patients for which a non-surgical management is considered should be carefully monitored as early progression with neurological deterioration may rapidly occur. Surgical approaches for spinal infections are usually dictated by the site of compression (ventrally vs dorsally-located lesions) and tailored to the vertebral level involved. The nature of the compressive lesion is also relevant as liquid collection of pus can be drained whereas a mass of granulation tissue or retro pulsed bone are better addressed with an open surgical approach. In addition, the optimal surgical approach is selected after consideration of the intrinsic features of each anatomic region of the spine and the likelihood of postoperative instability. In light of the degree of kyphotic deformity, the number of vertebral elements involved, as well as the bone and posterior tension band integrity, the extent of spinal instrumentation required to restore stability is determined. Surgical intervention is also indicated after failure of medical management or patients with chronic pain, significant deformity or spine instability in the setting of spinal infection or its sequelae.

3.4. Antibiotic Treatment

Reports of bone infections by *L. monocytogenes* are usually described in patients with predisposing factors as diabetes, leukemia or receiving long-term corticosteroids or immune-modulant treatments [85–89]. Usually, native vertebral infections by *L. monocytogenes* have an insidious course, with symptoms, especially back pain, that could be present for over a year, as described in previous reports [90,91]. In the review by Charlier et al. more than 70% of cases of listeriosis involving bone and joint infections were subacute or chronic at the onset. Furthermore, most of these cases occurred in the hip (60%) and in prosthetic joints [85]. In this review, patients with osteomyelitis by *L. monocytogenes* had only mild increased of inflammatory markers compared with those with other bacterial osteomyelitis. Vertebral osteomyelitis represents an even less frequent localization of invasive listeriosis. To date, eight other cases [90–97] have been reported in literature and all of them had significant risk factors for developing invasive listeriosis. All these patients were treated with ampicillin or amoxicillin or benzyl penicillin; 5 patients received combination with aminoglycosides; treatment duration was highly heterogeneous among these reports, ranging from 6 to 28 weeks, accordingly to possible delayed clinical responses. Only 1 report [94] used trimetoprim/sulphametoxazole as oral maintenance treatment but in no study it was combined with amoxicillin. Oral use of amoxicillin was described in two other reports and was administered for a total of 12 and 18 weeks, respectively [95,96]. The antibiotic treatment should often be associated with surgical intervention in case of spinal infections by *L. monocytogenes*, especially in those patients experiencing neurological deficit, cord compression, destruction of the vertebrae with instability, large epidural abscesses or inadequate response to antimicrobials [98].

4. Other Clinical Features

4.1. Listeriosis and Pregnancy

Pregnant women have an increased risk of *L. monocytogenes* infections that can lead to chorioamnionitis and finally to early-onset neonatal listeriosis [48]. Infants with listeriosis have a peculiar constellation of clinical features, including prematurity sepsis at birth, fever, cutaneous maculo-papular exanthema and jaundice [99]. In this context, the mortality rate is very high, even when a prompt, specific antibiotic treatment is started. Autopsy findings showed chorioamnionitis in placental remnants and multiple granulomas in the spleen and liver of the infants; the syndrome, when firstly described, was therefore called “granulomatosis infantispetica” [78]. Though the infants have usually dramatic findings, mothers may be asymptomatic or may commonly have only mild symptoms, like flu-like or urinary or gastrointestinal symptoms, before their blood cultures got

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positive for *L. monocytogens*. The rapid administration of antibiotic treatment to mothers with *L. monocytogenes* bacteremia can prevent transplacental infection, with a delivery of an uninfected infant [100]. However, this is a very unusual condition and can only happen when a community-based outbreak of *L. monocytogenes* is identified in specific geographical areas by public health alerts. Symptoms of last-onset neonatal meningitis due to *L. monocytogenes* usually occur 1-2 weeks after delivering and included fever, irritability, bulging fontanelle and meningismus [101]. In this context, the mother does not develop any septic complication during pregnancy, delivery and in the post-partum period.

4.2. Meningoencephalitis

L. monocytogenes invasive infections have been associated with meningitis in adults. Usually, the clinical symptoms are those of a subacute bacterial meningitis with fever, headache and neck stiffness that can develop over several days [102]. During epidemics of foodborne listeriosis, meningitis by *L. monocytogenes* can occur also in apparently healthy individuals of all ages; on the contrary, in sporadic diseases a defect in cell-mediated immune function can predispose subjects to this finding of invasive listeriosis. In addition, *L. monocytogenes* can induce rhomboencephalitis in humans and in animals, describing mainly as circling disease [103]. When these features appear, fever, headache, nausea and vomiting occur early and signs of meningeal irritation are less commonly observed. Subsequently, multiple abnormalities of cranial nerves develop with associated cerebellar dysfunction, mainly ataxia. Fever is not present in up to 15% of patients, leading to a more difficult diagnosis. However, the presence of micro abscesses of cerebellum and diencephalon could help the diagnostic workout. This variant has a mortality of 50% and a high risk of neurological sequelae despite prompt administration of antibiotic treatment.

4.3. Listeria monocytogenes Sepsis

Bacteremia by *L. monocytogenes* without central nervous system involvement represents approximately one-third of adult case of invasive listeriosis. Symptoms are usually aspecific, but fever and chills are often presents. The occurrence of *L. monocytogenes* sepsis is often associated with pre-existing cancers, organ transplant or other causes of immune-depression and has a mortality up to 30%. In this context, symptoms are nonspecific and can mimic sepsis by other Gram-positive or Gram-negative bacteria [104,105].

4.4. Gastroenteritis

L. monocytogenes can cause a febrile gastroenteritis with diarrhea and abdominal pain, especially during large outbreaks of foodborne adult listeriosis, with high burden of microorganisms in the contaminated food [15,22,23,58–62,106]. Most of patients are well before the development of the infection; bacteremia is an unusual finding in this setting and most patients develop symptoms within 24 hours following exposure; a large amount of microorganisms (up to 10^9 CFU/g) is usually found in the contaminated food. During these outbreaks, pregnant women have a particularly high risk of developing sepsis and invasive listeriosis; isolation of *L. monocytogenes* from stool is unusual, but serological tests have been widely used to better define the extent of the outbreaks. Reported vehicles in the outbreaks reported to date have been identified in shrimp salad, chocolate milk, corn, deli meats and fresh cheese. Invasive listeriosis with meningoencephalitis could finally occur in this context when the gastrointestinal mucosa lost his integrity for other bacterial or viral concomitant gastroenteritis [45,107].

4.5. Endocarditis

Endocarditis by *L. monocytogenes* usually follows transient bacteremia from a gastrointestinal focus with subsequent endovascular infection on an abnormal heart valve; over 50% of cases of endocarditis by *L. monocytogenes* involved prosthetic valves, whereas cases on native valves are sporadic [108,109]. Diagnostic criteria included the presence of a prosthetic valve with or without

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vegetation and a continuous bacteremia by *L. monocytogenes*; septic emboli and abscesses in other organs are relatively frequent and can occur in approximately two-thirds of patients. Aortic and mitral valve are most commonly involved. In native valve endocarditis, *L. monocytogenes* infection can sporadically follows previous episodes of streptococcal bacterial endocarditis or other valvular heart disease. Reports of patients with malignancy, diabetes, prolonged steroid therapy, and renal and liver transplantation with *L. monocytogenes* endocarditis have been published to date [110]. The clinical presentation is usually nonspecific for *L. monocytogenes* and includes prolonged fever, chills, and, ultimately, signs of congestive heart failure. In these cases, diagnosis can be obtained only by performing systematically blood cultures. *L. monocytogenes* can also cause arterial infections that involve prosthetic abdominal and aortic grafts or native abdominal aortic aneurysms [111]. The mortality of this condition approached 40% before 1985 but has been reduced to 12% with better recognition and surgical management. In this context, a multidisciplinary approach is mandatory to better manage both the antibiotic treatment, the surgical intervention and the increased risk of systemic complications.

4.6. Abdominal Infections

L. monocytogenes associated hepatitis has been described in several case reports [112]. Though the diagnosis is often unsuspected, severe diseases can occur; autopsy findings showed micro abscesses and occasionally granulomas similar to those observed in neonatal disease [113]. Solitary and multiple liver abscesses with fever have also been reported [114,115]. Predisposing factors for liver complications by *L. monocytogenes* included cirrhosis, liver-transplantation, diabetes mellitus and alcoholism.

Recently, *L. monocytogenes* has been described as a possible cause of biliary tract infections, mainly by retrograde infection from contaminated food and because the microorganisms are resistant to bile [116,117]. Immunosuppression due to corticosteroid and use of biologic agents to treat underlying conditions are well established risk factors for this infection; mortality is high, mainly due to inappropriate antibiotic therapy for misleading diagnosis.

L. monocytogenes can also cause isolated episodes of peritonitis, especially in patients receiving peritoneal dyalisis with isolation of the microorganism from dialysate or blood cultures or in those with advanced liver diseases [118–122]. Infections are usually secondary to translocation of the microorganism from the gastrointestinal tract in patients who have ingested *L. monocytogenes* with food. The mortality is low, comparable to spontaneous bacterial peritonitis due to other microorganisms.

4.7. Cutaneous Infections

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 [123,124]. Also conjunctivitis has been reported in laboratory workers [125]. In these conditions, *L. monocytogenes* is usually isolated by the multiple papulo-pustular lesions of the skin; findings are similar to those observed in infants with early-onset disseminated listeriosis. In adults, the infection is usually self-limited and recover spontaneously without antibiotic treatment; however, its occurrence is easily preventable with the appropriate use of gloves and other protective wears.

5. Conclusions

In this paper we present a comprehensive description of *L. monocytogenes* clinical findings. We mainly focused on bone and vertebral infections by *L. monocytogenes*, because these localizations are usually under-estimate except in case of outbreaks. In fact, in the literature very few data are currently reported on this specific localization and most of them are extrapolated by case reports. We described the diagnostic and the clinical management of patients with bone infections due to *L. monocytogenes*, as well as the surgical and the optimal antibiotic treatment for this condition. Despite the limited number of reports, consideration for *L. monocytogenes* associated osteomyelitis should be taken in

account as part of the differential diagnosis, even in the absence of prosthetic material, especially in the context of epidemiologic risk factors. However, this diagnosis should also be considered in those individuals living in areas with relatively low incidences of *L. monocytogenes* infections, because sporadic outbreaks can occur everywhere.

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