Review paper
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HUMAN LISTERIOSIS COMEBACK ODE

Biljana Curcic-Trajkovska[1*], Biljana Kakaraskoska - Boceska[1], Dzengis Jashar[2], Kornelija Trajkova[3]

[1]Microbiology Laboratory, Acibadem Sistina Hospital, Skupi 5a, 1000 Skopje, Macedonia
[2]Histopathology Laboratory, Acibadem Sistina Hospital, Skupi 5a, 1000 Skopje, Macedonia
[3]Gynecology and Obstetrics Department, Acibadem Sistina Hospital, Skupi 5a, 1000 Skopje, Macedonia

[*]e-mail: b.curcic@acibademsistina.mk

Abstract

Human listeriosis is a potentially fatal foodborne infection caused by *Listeria monocitogenes*. The first confirmed case was in 1929, while the first described large outbreaks occurred in the 1980s. *Listeria* is small, intracellular, non-capsulated, non-sporulating, beta-hemolytic, aerobic, and facultative anaerobic gram-positive, motile bacilli. *L. monocitogenes* is ubiquitous and part of the fecal flora in humans, mammals, birds, and crustaceans. The chances of food contamination during any food production process are numerous. This research aimed to raise awareness about invasive infections caused by *L. monocitogenes*, persistently present in foods and the environment despite up-to-date food safety measures.

Since *L. monocytogenes* multiply intracellularly, infection control requires cell-mediated immunity; therefore immunocompromised patients, neonates, older people, and pregnant women are vulnerable to invasive listeriosis. Infection occurs sporadically or in outbreaks. Primary bacteremia is unusual, with high fever without specific symptoms and signs, and it may become prolonged and asymptomatic. Focal infections such as pneumonia, pleuropneumonia, endocarditis, peritonitis, osteomyelitis, septic arthritis, meningitis, ophthalmitis, and cholecystitis infected prosthetic joints, localized internal abscesses, and granulomatous lesions in the liver and other organs have also been described. Febrile gastroenteritis may occur after ingestion of contaminated food. Listerial bacteremia during pregnancy can cause intrauterine infection, chorioamnionitis, premature labor, fetal death, or neonatal infections. In the past few years, an increasing rate of listeriosis has been reported in several European countries. The reported fatality rate has been around 30 percent in both risk and non-risk groups. The increased incidence of the disease could be associated with a higher presence of coexistent diseases, with treatments related to immunosuppression, and the increased survival of the population with serious health problems. The diagnosis is a challenge due to the incubation period and the different clinical manifestations. For proper diagnosis, *L. monocytogenes* should be isolated from blood, cerebrospinal fluid, placenta, meconium, fetal gastrointestinal contents, and other normally sterile sites. Antibiotic treatment is fundamental as early as possible because of the severity of the disease and the high associated mortality. Crucial recognition of the most efficient strategies based on risk assessment from the food production to consumption stage is required to prevent the comeback of human listeriosis.

The current reality is that listeriosis has a high mortality despite adequate and early treatment. In Europe, invasive listeriosis has been reported to be an infection of serious concern to public health considering its clinical severity (hospitalization rate > 90%) and high fatality rate (20% to 30%). The imperative is to reduce the incidence of human listeriosis. Focal and continuous education and a multidisciplinary approach are the key strategies to battle the human listeriosis comeback ode.

***Key words**: Listeriosis, Foodborne infection, Incidence, Mortality.*

1. Introduction

Listeriosis, caused by *Listeria monocytogenes*, is not just another foodborne illness; it is a deadly reminder of the vulnerabilities in our food safety systems and the ease with which nature's threats evolve to outpace our defenses [1, 2]. Despite being first identified in 1929, *Listeria* remained largely under the radar until large-scale outbreaks emerged in the 1980s [3]. Now, decades later, it has resurfaced as a public health nightmare, threatening global food security, particularly in the face of emerging food production practices and changing dietary habits [4]. Regardless of advances in food safety measures, *Listeria* has proven to be an exceedingly resilient adversary, constantly adapting to environmental changes and exploiting gaps in our regulatory frameworks.

The continued prevalence of listeriosis underscores a profound paradox: while we have become more adept at preventing a wide range of foodborne diseases, *Listeria* persists as an enigmatic and unpredictable killer [5]. It disproportionately affects vulnerable populations, including pregnant women, neonates, the elderly, and immunocompromised individuals, yet it continues to be underappreciated as a significant threat by both the public and policymakers [6].

To confront this challenge, we must reconsider not only the scientific and regulatory approaches to controlling *Listeria* but also the societal and behavioral factors that contribute to its spread [7]. This research goal was to raise awareness about invasive infections caused by *L. monocitogenes*, persistently present in foods and the environment despite up-to-date food safety measures.

2. Human listeriosis comeback ode

2.1 Listeria facts and taxonomy: a master of survival

Listeria monocytogenes is an unconventional pathogen. It does not rely on the traditional arsenal of virulence factors that most bacteria deploy to wreak havoc on the human body. Instead, it has perfected a stealthy intracellular lifestyle that allows it to elude the body's defenses [8]. A gram-positive, non-capsulated bacterium, *L. monocytogenes* can thrive in both aerobic and anaerobic environments, making it an ideal contaminant in diverse ecological niches. From the soil to animal feces and across the food production chain, Listeria has an unmatched ability to survive under adverse conditions that would otherwise deter most pathogens [9].

Its resistance to refrigeration, cleaning protocols, and even some antimicrobial agents renders it a constant and insidious threat to public health [10]. The bacteria's ability to grow in foods stored at refrigerator temperatures, often found in ready-to-eat products like deli meats and soft cheeses, highlights a significant gap in the food safety paradigm [11]. While modern food processing has made great strides in reducing contamination, Listeria is remarkably adept at surviving even the most stringent food safety practices [12, 13]. This poses a critical question: have we, as a global society, truly accounted for all the risk factors and failed to identify the potential weak points in our food production systems [14]?

2.2 Epidemiology: a global threat in disguise

In terms of incidence, listeriosis remains relatively rare compared to other foodborne diseases, but its consequences are disproportionately severe [15 - 17]. According to the 2020 reports from the European Centre for Disease Prevention and Control, Listeria has a low incidence rate of 0.7 cases per 100,000 in Europe, yet its devastating potential is evident in its fatality rate of approximately 30%. What is more concerning, however, is the fact that the true burden of disease may be far greater than official statistics suggest, particularly in countries with less robust food safety reporting systems [18 - 21].

High-risk populations, such as the elderly, neonates, pregnant women, and those with compromised immune systems, bear the brunt of this pathogen's insidious reach [22, 23]. The fatality rate in these groups, particularly among neonates and pregnant women, highlights the potential for catastrophic outcomes from what would be an otherwise mild illness in healthy adults [24, 25]. The fact that the disease is often undiagnosed or misdiagnosed due to its diverse and overlapping clinical manifestations further complicates efforts to understand its true impact on public health [26]. Can we afford to remain complacent while listeriosis continues to silently claim lives, or is it time to radically rethink our approach to its prevention and management [27, 28]?

2.3 Pathophysiology and pathogenesis: the silent invader

Listeria monocytogenes is an intracellular master of subversion [29]. Unlike most pathogens, which rely on extracellular factors to cause disease, Listeria thrives within host cells, effectively evading many aspects of the immune response [30 - 33]. Its ability to cross multiple host barriers-intestinal, placental, and even the blood-brain barrier - underlines the pathogen's versatility and ruthlessness [34, 35]. Upon ingestion, the bacteria penetrate the intestinal mucosa and gain access to the bloodstream, where they disseminate to critical organs such as the liver, spleen, and central nervous system (CNS) [36 - 39]. In pregnant

women, Listeria can invade the placenta, resulting in devastating outcomes like miscarriage or stillbirth [40, 41].

The pathogen's intracellular lifestyle is enabled by two key factors: ActA, a protein that induces actin polymerization to propel the bacterium through host cells, and Listeriolysin O, which facilitates escape from phagosomal vacuoles into the cytosol, where Listeria can replicate unchallenged [42 - 44]. These strategies allow the bacterium to remain hidden from immune surveillance, turning the host's cellular machinery into a haven for replication [45]. But this raises a troubling question: if Listeria is so adept at evading the immune system, are we focusing enough on the inherent limitations of our immune response in combating such infections [46]?

2.4 Clinical features and diagnosis: the diagnostic dilemma

The clinical presentation of listeriosis is highly variable, making diagnosis challenging [47, 48]. In its non-invasive form, the infection may present as a mild gastroenteritis or flu-like illness, including fever, diarrhea, and abdominal pain [49]. However, the hallmark of invasive listeriosis is its rapid progression to severe systemic manifestations, including meningitis, septicemia, and encephalitis [49, 50]. For pregnant women, the risk of intrauterine infection is particularly concerning, with the potential for fetal death or premature labor. Neonates infected with Listeria may develop septicemia or meningitis, with high mortality rates [51, 52].

Diagnosis of listeriosis requires isolation of *Listeria monocytogenes* from sterile body fluids such as blood or cerebrospinal fluid. Despite this, the diagnosis is often delayed due to the non-specific nature of early symptoms and the lengthy incubation period [53]. This diagnostic challenge is compounded by the fact that Listeria can easily be overlooked in the differential diagnosis, as its clinical presentation overlaps with other more common pathogens [47, 53 - 56]. Should we be questioning whether the current diagnostic approach is sufficient to deal with the growing threat of Listeria infections, especially as outbreaks in immunocompromised populations continue to rise?

2.5 Treatment, antibiotic resistance, and duration of therapy: a three-pronged challenge

Early treatment of listeriosis is critical due to its rapid progression and high mortality rate, yet the therapeutic landscape is fraught with challenges [57, 58]. First-line treatments typically involve beta-lactam antibiotics like ampicillin or amoxicillin, often in combination with gentamicin. Cephalosporins, however, are less effective, and alternative treatments like trimethoprim-sulfamethoxazole may be needed in specific situations [59]. Fortunately, *Listeria* remains largely susceptible to antibiotics, but this is not a guarantee that it will always be the case. Reports of antibiotic resistance to agents such as tetracyclines and ciprofloxacin are on the rise, suggesting that we may soon be dealing with strains that could outpace our current therapeutic arsenal [60 - 64].

The duration of therapy can vary significantly depending on the clinical presentation and site of infection. The recommended duration of antibiotic therapy is guided by the severity and site of the infection, though this is a subject of ongoing discussion due to the variability in patient outcomes and resistance patterns. According to the Johns Hopkins ABX Guide for *Listeria monocytogenes*, a standard 2-week course of therapy is typically sufficient for bacteremia, where the infection is confined to the bloodstream. However, in severe cases such as meningitis, treatment should be extended to 3 weeks due to the complexities of the central nervous system and the need for thorough pathogen eradication. For brain abscesses or encephalitis, an even more aggressive regimen lasting 6 to 8 weeks is often required to ensure complete resolution and prevent relapse. Similarly, in the case of endocarditis, which is particularly challenging due to its association with high morbidity, a treatment duration of 4 to 6 weeks is generally recommended, and bone infections require the longest course of therapy at around 12 weeks, as the pathogen's persistence in bone tissue necessitates prolonged antibiotic exposure [65 - 67].

These duration guidelines, however, are not without their controversies [68 - 71]. Critics argue that the effectiveness of extended therapy regimens may be overstated, and more individualized treatment plans could offer better patient outcomes, especially given the growing concerns over antibiotic resistance and the risks of prolonged antibiotic use, such as adverse effects or complications from overly long courses. The evolving landscape of antimicrobial stewardship further complicates this issue, urging healthcare professionals to balance optimal treatment duration with the broader risks of over-prescription.

This brings into sharp focus the need for more research into novel treatments and the development of broader-spectrum antibiotics, as well as improved surveillance systems to monitor emerging resistance patterns [72]. Could the future of listeriosis treatment lie in a more targeted approach that combines conventional antibiotics with emerging therapies, such as bacteriophage therapy or the use of engineered probiotics [73]?

2.6 New approaches in prevention and treatment: innovative strategies for a persistent threat

The persistence of Listeria in food processing environments and its ability to adapt to various stressors has led to a surge in research on innovative prevention strategies. One promising avenue is the use of bioengineered probiotics, specifically Lactobacillus strains engineered to express Listeria adhesion proteins. These probiotics can potentially block Listeria's ability to adhere to and invade intestinal cells, providing a novel layer of defense against infection. This concept, though still in its infancy, offers hope that we may one day be able to prevent infection at the earliest point of the gastrointestinal tract entry [74 - 77].

Similarly, the European ListAdapt project, which aims to understand how *Listeria* adapts to the food production environment, holds promise for revolutionizing how we approach food safety. By identifying the genetic and environmental factors that contribute to *Listeria's* survival, we can develop more effective control measures at every stage of the food production process [78 - 80]. Are we truly utilizing all available tools to control Listeria, or are we simply reacting to outbreaks rather than proactively addressing the root causes?

3. Conclusions

- The resurgence of listeriosis is not just a public health concern-it is a clarion call to rethink our strategies for managing foodborne pathogens. *Listeria monocytogenes* remains a complex and adaptable threat that continuously evolves to exploit weaknesses in our food safety systems. To effectively reduce the burden of listeriosis, we must adopt a multifaceted approach that integrates new scientific discoveries, such as bioengineered probiotics, with a renewed focus on food safety measures, diagnostics, and antibiotic stewardship. As we move forward, we must ask ourselves whether our current strategies are enough to contain the growing risk of *Listeria* or if we need a radical rethinking of how we approach the prevention and treatment of this deadly infection. The emergence of new strains, coupled with the increasing ability of Listeria to adapt to varying environments, challenges the effectiveness of traditional control measures. This reality calls for a more proactive, integrated strategy that not only focuses on improving food safety standards at all stages of the food supply chain but also encourages the development of novel therapeutic interventions.
- Furthermore, the global nature of food distribution and the growing complexity of human behaviors, including consumption patterns and antibiotic usage, underline the need for a broader, more coordinated response. Cross-disciplinary collaboration, international partnerships, and a commitment to continuous surveillance will be crucial in staying ahead of this evolving pathogen. Ultimately, reducing the incidence of listeriosis and mitigating its devastating effects requires a combined effort that involves not just the scientific community but also policymakers, food industry stakeholders, and the public.
- In this regard, raising awareness and improving public health education on listeriosis will be instrumental in empowering individuals to make informed decisions about food safety. By fostering greater vigilance, embracing innovation, and ensuring that our public health systems are equipped to handle emerging threats, we can mitigate the dangers posed by Listeria monocytogenes and protect the most vulnerable populations from its potentially fatal consequences. Only through these concerted efforts can we hope to reduce the burden of listeriosis and safeguard global health in the face of an ever-changing microbial landscape.
- This publication serves to raise awareness about the persistence of *Listeria monocytogenes* and the need for continuous efforts to reduce its impact on public health. The integration of advanced research, food safety measures, and innovative prevention strategies is crucial to mitigating the threat of this lethal pathogen.

4. References

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