# Epidemiology and treatment of the commonest form of listeriosis: meningitis and bacteraemia

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## SUMMARY

*Listeria monocytogenes* is a Gram-positive bacillus and facultative intracellular bacterium whose transmission occurs mainly through the consumption of contaminated food. Listeriosis has an incidence estimated at around three-six cases per million per year and the most common forms of the infection are neurolisteriosis, bacteraemia, and maternal-neonatal infection. Those affected by listeriosis are at the extremes age of the life or report specific risk factors, such as malignancies, causing a defect of cellular immunity.

Patients with *L. monocytogenes* meningitis present with signs and symptoms similar to those reported in the general population with community-acquired bacterial meningitis, but can experience a longer prodromal phase. Instead, patients with bacteraemia present generally with a febrile illness without focal symptoms, or with influenza-like symptoms and diarrhoea. These aspecific findings make the diagnosis difficult in the population of patients at the highest risk such as cirrhotics or those receiving chemotherapy. Mortality rate is estimated around 20% with a significant increase among those reporting a delay in diagnosis and treatment and in those with severe comorbidity.

A number of antibiotics have been demonstrated to be active against *L. monocytogenes*, but penicillin, amoxicillin, and ampicillin are those used with the highest frequency and suggested by current guidelines and expert opinions. These antibiotics bind to PBP-3 with high affinity and are stored in the cytosol when taken up by cells. Although amoxicillin appears to have a better activity than ampicillin on the basis of studies, ampicillin is currently the drug of choice for the treatment of listeriosis. Cotrimoxazole could be administered as an alternative treatment; its use is associated with a favourable outcome probably due to the favourable penetration with brain. Quinolones have an excellent tissue and cell penetration and are rapidly bactericidal, but their clinical activity is not as high as we can predict on the basis of experimental model. Linezolid offers a number of advantages in the empiric treatment of meningitis due to its favourable penetration of CSF and the absence of bacteriolytic effect on *S. pneumoniae* as confirmed by a number of case-series highlighting its use as rescue therapy of pneumococcal meningitis, but data are currently limited particularly if we consider neurolisteriosis. Combination therapies have been proposed to enhance the activity of penicillins against Listeria in an attempt to achieve complete killing and decrease mortality. Steroids use is ineffective.

*Keywords*: *Listeria monocytogenes*, meningitis, treatment, immunocompromised, cirrhosis, infection.

## INTRODUCTION

*Listeria monocytogenes* is a Gram-positive intracellular pathogen causing listeriosis, a food borne infection causing severe and life threatening diseases. In the industrialized countries, listeriosis has an incidence estimated at around three-six cases per million population per year, if we consider the most common forms of the infection: neurolisteriosis, bacteraemia, and maternal-neonatal infection. Patients with listeriosis are at the extremes age of the life or report specific risk factors such as malignancies, diabetes, cirrhosis, alcoholism, or other diseases causing a defect of cellular immunity. Only a few prospective studies

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investigated the characteristic of patients affected by listeriosis and current therapeutic guidelines are based only on the analysis of case-series, lacking prospective studies on the treatment. No improvement has been reported over the past decades in term of prognosis [1-5].

*Epidemiology and clinical findings of listeriosis*

Listeriosis is a sporadic disease, but outbreaks can occur after the consumption of contaminated food (Table 1). *L. monocytogenes* exists in different conditions due to its ability to survive in extreme conditions, such as wide pH range, high salt concentrations and due to the ability to grow and persist at refrigeration temperatures. All these conditions can give an advantage in respect to other more common pathogens transmitted by contaminated food [6]. An idea of the ability of Listeria to persist in extreme condition can be given by the observation that *L. monocytogenes* can persist over12 months in the extreme condition of a milkshake machine causing cases of invasive disease [7]. Several listeriosis outbreaks occurred in United States recently, linked to dairy products and fresh produce [8-10].

On the basis of a recent prospective study considering over 800 patient with listeriosis observed in 372 centre in France over a 4-year period, it was estimated that less than 15% of the cases report maternal-neonatal infections, 50% reports bacteraemia, and the remaining are cases of neurolisteriosis [5]. Current investigations and guidelines suggest that *L. monocytogenes* has to be considered among the causative agents of invasive infection and meningitis in all patients at the extremes ages of the life and in those reporting immunocompromission. Evaluating the whole population of patient with listeriosis enrolled in the MONALISA study, specific risk factors are considered maternal origin from Maghreb or sub-Saharan Africa for newborn; instead male sex, diabetes mellitus, treatment with steroids, and solid cancer are the condition reported with the highest frequency in those with neuroinvasive infection and bacteraemia. Only 4% of patients with neurolisteriosis were younger than 40 years, reported no comorbidity, and did not report any infection before listeriosis [5]. Moreover, less than 5% of the cases of bacteraemia and neurolisteriosis reported during a 15-year period in a Danish study and 14% of the cases with neurolisteriosis reported in the multinational retrospective study reported no specific risk factor. On the basis of cumulative data reported, we can establish that *L. monocytogenes* has to be strongly considered as the causative agents of neuroinvasive infection and sepsis mainly in particular subset of immunocompromised patients [3, 5, 11].

Patients with bacteraemia present generally with a febrile illness without focal symptoms, or with influenza-like symptoms and diarrhoea. These nonspesific findings make the diagnosis difficult in some patients at high risk such as cirrhotics or those receiving chemotherapy as they can acquire a wide range of infections with aspecific prodromal symptoms [12-15]. Alteration of consciousness and fever are frequently reported in neurolisteriosis cases. Nuchal rigidity can be observed in about 60% of these cases and the classic triad of nuchal rigidity, fever and impaired consciousness status was reported in about 50% of them [16, 17]. No conclusive data are reported regarding incidence of septic shock that is observed among 1% of the cases reported in the MONALISA prospective study, but appears to be more frequent on the basis of other retrospective studies considering patients with bacteraemia or meningitis. *L. monocytogenes* is not considered among the common causes of septic shock [18]. Moreover, focal neurologic deficit or seizure are reported in about 20% of the cases, less frequently than reported in those with pneumococcal meningitis considering studies comparing the findings of pneumococcal and listerial meningitis (Table 2). Respiratory failure within 48 hours from admission is reported less frequently in Listeria meningitis patients [16]. Patients with bacteraemia/meningitis sustained by *L. monocytogenes* report a mortality rate exceeding 20%. Lack of administration of an adequate therapy resulted in the patient's death within

**Table 1** - Food item with the highest risk of contamination with *Listeria monocytogenes*.

| |
|---|
| Sausages |
| Raw meat, in particular turkey and chicken |
| Sandwiches |
| Raw milk and products made from this ingredient |
| Any meat conserved after having been heated |
| Soft cheese |
| Sea food (salmon, mussels) |

**Table 2** - Antibiotics commonly administered to treat listeriosis.

| *Antibiotic* | *Daily dosage* | *Number of administrations* |
|---|---|---|
| Penicillin G | 24 MU | 4-6 |
| Ampicillin | 9-12 g | 4 |
| Amoxicillin | 8 g | 4 |
| Meropenem | 6 g | 3 |
| Vancomycin | 2 | 4 |
| Gentamicin | 5 mg x kg | 3 |
| Rifampin | 600-900 mg | 1-2 |
| Cotrimoxazole | 10-20 mg x kg | 2-4 |
| Levofloxacin | 1000 | 2 |
| Linezolid | 1200 mg | 2 |

3 days in all the untreated cases reported in the MONALISA study and any delay of initiation of an adequate treatment was associated to an increase of the risk of death [5].

*Treatment*

The intracellular nature of Listeria makes its effective treatment difficult. Many antibiotics have been demonstrated to be active *in vitro* against Listeria, but most of them have been demonstrated to be only bacteriostatic in the intracellular environment. Moreover, the findings deriving from studies *in vitro* do not directly correlate with *in vivo* efficacy [19].

An ideal antibiotic active against Listeria must penetrate within host cell, and must bind tightly to an intracellular target (Table 3). Ideally, antibiotic has to concentrate within host cell creating depots, ensuring a long-lasting optimal antibiotic concentration to avoid that bacteria can survive when antibiotic concentration becomes low. Moreover, an antibiotic active against Listeria must have the ability to bind to penicillin-binding protein 3 (PBP-3) of Listeria, which causes cell death [20, 21].

A number of antibiotics have been demonstrated to be active against *L. monocytogenes*, penicillin, amoxicillin, and ampicillin are those used with the highest frequency and suggested on the basis of guidelines or expert opinions. These antibiotics, as expected, bind to PBP-3 with high affinity and are stored in the cytosol when taken up by cells, but have been demonstrated to be only slowly bactericidal in a model of intracellular infection *in vitro*. Although amoxicillin appears to have a better activity than ampicillin on the basis of *in vitro* studies, ampicillin is currently the drug of choice for the treatment of listeriosis. Current investigations suggest that the adult dose of ampicillin has to be over 9*g* per day and that the treatment has to be administered for at least 21 days when meningitis has to be treated [22].

Listeriosis is observed with the highest frequency in immunocompromised whose immune mechanisms can be inadequate to complete the bacterial killing after antibiotic treatment [23]. On the basis of pharmacokinetic considerations, encapsulation of antibiotics within liposomes has been proposed because of the favourable effect observed in a mouse model of meningitis, no similar study in humans has been reported [24].

Cotrimoxazole could be administered as an alternative treatment for listeriosis. However, it was not as effective as quinolones or ampicillin in an experimental model of meningitis, raising some doubt on its efficacy when administered as mono-

**Table 3** - Clinical and neurological findings of 131 ageing patients with bacterial meningitis (Adapted from Pagliano P. et al [16]).

| | *Streptococcus pneumoniae* (109 cases) | *Listeria monocytogenes* (22 cases) | P |
|---|---|---|---|
| Extrameningeal infection (%) | 72 (66) | 1 (5) | <0.0001 |
| Respiratory failure within 48 hours from admission (%) | 55 (50) | 2 (10) | <0.001 |
| Fever (%) | 96 (88) | 22 (100) | 0.12 |
| Neck stiffness (%) | 86 (79) | 15 (68) | 0.45 |
| GCS <11 (%) | 77 (71) | 21 (95) | <0.05 |
| Motor deficit | 9 (8) | 1 (5) | 0.99 |
| Seizure before admission | 9 (8) | 2 (9) | 0.99 |

therapy. Cotrimoxazole had the same effects on intracellular and extracellular *L. monocytogenes*, probably due to the ability of trimethoprim to inhibit cell wall synthesis and cell separation. An advantage in term of survival after cotrimoxazole administration in respect to the other antibiotic treatments (excluding ampicillin) was demonstrated in the French study [5, 25, 26].

Quinolones are valuable drugs in the treatment of listeriosis as they have an excellent tissue and cell penetration and are rapidly bactericidal. On the basis of an intracellular model of listerial infection, it was demonstrated that intracellular activity of quinolones against *L. monocytogenes* is only a fraction of what could be anticipated if their apparent accumulation in cells is taken into account. Thus, whereas quinolones show higher concentrations in cells compared with medium, they are also characterized by somewhat weaker activity against intracellular *L. monocytogenes* [27]. Levofloxacin has been proposed as empiric therapy of bacterial meningitis to ensure Listeria coverage, but its use has to be evaluated in larger series [28]. In using quinolones as empiric therapy of meningitis, we have to remember that their administration can increase teichoic acid release if *Streptococcus pneumoniae* is the causative agent boostering host immunity and contributing to brain damage [29].

Linezolid is an oxazolidinone reporting *in vitro* activity against *L. monocytogenes*. Its elevated CSF and intracellular concentrations seem adequate for the treatment of neurolisteriosis, as extrapolated by reliable animal models [30]. When allergy to both penicillin and cotrimoxazole became of concern, a linezolid-rifampin combination was successful administered to a patient with brain abscess sustained by *L. monocytogenes* without any hematological toxicity after 107 consecutive days of treatment [31]. Overall, linezolid offers a number of advantages in the empiric treatment of meningitis due to its favourable penetration of CSF and the absence of bacteriolytic effect on *S. pneumonia,* as confirmed by a number of case-series highlighting its use as rescue therapy of pneumococcal meningitis, but data are currently limited if we consider neurolisteriosis. Only 6 cases receiving linezolid are reported in the MONALISA study.

Meropenem, a broad-spectrum antibiotic of the carbapenem class of beta-lactam agents, displays a remarkably low minimum inhibitory concentration (even lower than that of ampicillin) against *L. monocytogenes* [32]. However clinical data are not conclusive and failure after treatment was suspected on the basis of case-reports. A Danish retrospective study highlights that patients receiving meropenem report a higher mortality, as assessed by multivariate analysis, compared to those receiving aminopenicillins and benzylpenicillin [11, 33]. The reason for this difference remains unclear, and we could speculate that some difference in the intracellular activity of the drug justifies the changes in the cure rate. Overall, these findings may be of some concern in some populations such as cirrhotics that report an increase of the risk of both Listeria and *Escherichia coli* meningitis and receive frequently treatment with carbapenems to cover the risk of multiresistant *E. coli*.

Rifampin has demonstrated excellent intracellular and extracellular bacteriostatic activity that is not dose dependent against *L. monocytogenes in vitro*. Rifampin is capable of excellent penetration into the CSF and cells. However, recent *in vitro* testing using time-kill studies indicated an antagonistic effect when combined with penicillins or cotrimoxazole. Therefore, rifampin use has to receive careful evaluation in the treatment of listeriosis [34].

Vancomycin shows variable activity against Listeria strains. It is bactericidal within six hours; however, its use is limited in cases of meningitis due to its inability to cross the blood-brain barrier reaching therapeutic concentration. *L. monocytogenes* meningitis was reported during treatment with vancomycin in a neutropenic patient receiving the drug due to staphylococcal infection, demonstrating that the drug has not sufficient activity against Listeria, at least in severely immunodepressed patients [35].

Combination therapies have been proposed to enhance the activity of penicillins against Listeria in an attempt to achieve complete killing and decrease mortality. Addition of gentamicin to ampicillin reports the best killing rate on the basis of *in vitro* studies, but activity of gentamicin within intracellular bacteria is quite irrelevant and we have to remember that *L. monocytogenes* reports the ability to penetrate rapidly within host cells [36]. Animal models fail to demonstrate significant advantages by this combined therapy

administration, but the large MONALISA study demonstrated that those receiving amoxicillin/aminoglycoside combination therapy reported a lower risk of death [5]. However, in reporting the results of this study, we have to consider that the effect of this combination therapy was reported for the whole population of patients including those with bacteraemia and neurolisteriosis and no separate analysis was reported.
Other drug combination has been tested against *L. monocytogenes*, in a small retrospective series of 22 cases with Listeria meningitis published over 20 years ago combination of cotrimoxazole and ampicillin was the most effective treatment, but the small size of the study cannot give definitive indication on the most effective treatment [37].
On the basis of the MONALISA study in the subset of patients with neurolisteriosis, the administration of steroids reported an increase of the risk of an unfavourable outcome. This finding was quite surprising as, on the basis of the randomized study by de Gans, dexamethasone administration in patients with non-pneumococcal meningitis did not worsen outcome [38]. No relevant information is reported in the French study about the dosage of steroids, but we can suppose that some impairment in immunity enhanced by steroids could justify this evidence [5]. Similar findings were not reported by other authors in other case-series analysis suggesting that steroids administration has no harm or benefit in patients with Listeria meningitis [39]. On the basis of current evidence, it is reasonable to stop dexamethasone when *L. monocytogenes* is identified in patients with meningoencephalitis.

## CONCLUSIONS

On the basis of current evaluations, treatments of listeriosis remains challenging, mainly because patients affected are immunocompromised due to relevant comorbidity or report an impairment of immunity related to age.
MONALISA study provides a lot of useful information, confirming the findings retrieved in smaller retrospective studies. First of all it underlines that *L. monocytogenes* must be suspected in immunocompromised host or in those patients at the extreme age of the life presenting with bacteraemia or meningitis: in these patients, an empirical treatment containing a drug active against Listeria is associate with a reduced mortality. Second, treatment cannot exclude aminopenicillin, as the other drugs currently proposed have limited data supporting their use and do not demonstrate a significant increase in term of *in vitro* activity or cure rate. Patients with invasive listeriosis can receive a combined therapy considering the administration of ampicillin and amynoglocosides if blood cultures are positive or ampicillin and cotrimoxazole if neurologic involvement is evident. Data supporting the use of other drugs in combination therapy has to receive careful evaluation, considering that the clinical experience is limited and that experimental data itself cannot be conclusive. Among the drugs proposed for the treatment, we believe that linezolid could be promising due to its activity against penicillin-tolerant strains of *S. pneumoniae* and due to the efficacy reported in case-reports, but the small number of cases treated makes difficult every conclusion. Third, steroids administration cannot be currently proposed to patients with listeriosis.

**Conflict of interest**
The authors declare no conflict of interest

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