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Clinical features and prognostic factors of listeriosis: the MONALISA national prospective cohort study

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Clinical features and prognostic factors of listeriosis: the MONALISA national prospective cohort study

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RESEARCH IN CONTEXT

Evidence before this study
We searched PubMed on June 30, 2016, for English-language cohort studies published since Jan 1, 1980, of patients with invasive listeriosis worldwide with the keywords "listeria", "listeriosis", "maternal", and "neurolisteriosis". Studies had to include epidemiological or clinical data on listeriosis. All clinical forms of infection were included (bacteraemia, neurolisteriosis, and maternal–neonatal infection). Host risk factors for listeriosis have been well identified, but the clinical features and prognostic factors of the disease are based on retrospective studies compiling heterogeneous data or random collected cases. Furthermore, no clinical trial has ever been done and medical management is not evidence based.
Added value of the study
Our study is the first prospective clinical study focusing on all forms of invasive listeriosis. The study is based on a national mandatory system that allowed the nearly complete capture of microbiologically proven cases. The study shows a higher burden of listeriosis than reported before: more than 80% of infected mothers experienced major fetal or neonatal
complications (fetal loss, very high prematurity, early or late onset disease); only 39% of patients with neurolisteriosis survived and fully recovered. The study provides important new data to improve management and predict outcome in listeriosis, such as determination of the time window for fetal losses (<29 weeks of gestation and <3 days of adequate management) and new factors independently associated with mortality. Our data show the deleterious effect of adjunctive dexamethasone in neurolisteriosis, and argue for the use of beta-lactam and gentamicin or co-trimoxazole over other antimicrobials for bacteraemia and neurolisteriosis.
Implications of all the available evidence
Given the practical difficulties in completing clinical trials in listeriosis, these results could guide clinical practice and suggest that combined amoxicillin and gentamicin should be considered the first-line combination in invasive listeriosis, and that adjunctive dexamethasone should be avoided in cases of confirmed listeriosis.

ABSTRACT

Background: Listeriosis is a severe foodborne infection and a notifiable disease in France. We did a nationwide prospective study to characterise its clinical features and prognostic factors.

Methods: MONALISA was a national prospective observational cohort study. We enrolled eligible cases declared to the National Reference Center for Listeria (all microbiologically proven) between Nov 3, 2009, and July 31, 2013, in the context of mandatory reporting. The outcomes were analysis of clinical features, characterisation of Listeria isolates, and determination of predictors of 3-month mortality or persisting impairment using logistic regression. A hierarchical clustering on principal components was also done for neurological and bacteraemic cases. The study is registered at ClinicalTrials.gov, number NCT01520597.

Findings: We enrolled 818 cases from 372 centres, including 107 maternal–neonatal infections, 427 cases of bacteraemia, and 252 cases of neurolisteriosis. Only five (5%) of 107 pregnant women had an uneventful outcome. 26 (24%) of 107 mothers experienced fetal loss, but never after 29 weeks of gestation or beyond 2 days of admission to hospital. Neurolisteriosis presented as meningoencephalitis in 212 (84%) of 252 patients; brainstem involvement was only reported in 42 (17%) of 252 patients. 3-month mortality was higher for bacteraemia than neurolisteriosis (hazard ratio [HR] 0·54 [95% CI 0·41–0·69], p<0·0001). For both bacteraemia and neurolisteriosis, the strongest mortality predictors were ongoing cancer (odds ratio [OR] 5·19 [95% CI 3·01–8·95], p<0·0001), multi-organ failure (OR 7·98 [4·32–14·72], p<0·0001), aggravation of any pre-existing organ dysfunction (OR 4·35 [2·79–6·81], p<0·0001), and monocytopenia (OR 3·70 [1·82–7·49], p=0·0003). Neurolisteriosis mortality was higher in blood-culture positive patients (OR 3·67 [1·60–8·40], p=0·002) or those receiving adjunctive dexamethasone (OR 4·58 [1·50–13·98], p=0·008).

Interpretation: The severity of listeriosis is higher than reported elsewhere. We found evidence of a significantly reduced survival in patients with neurolisteriosis treated with adjunctive dexamethasone, and also determined the time window for fetal losses. MONALISA provides important new data to improve management and predict outcome in listeriosis.

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INTRODUCTION

Listeria monocytogenes causes listeriosis, a severe foodborne bacterial infection. *L monocytogenes* is the foodborne pathogen associated with the highest case-fatality rate in the western hemisphere, where its incidence is estimated at around three to six cases per 1 million population per year.[1,2] Invasive listeriosis is classified in three forms: bacteraemia, neurolisteriosis, and maternal–neonatal infection; localised forms are also reported.[3–5] Epidemiological studies have identified host risk factors for bacteraemia and neurolisteriosis, including older age, innate and cellular immune defects, malignancies, HIV infection, cirrhosis, diabetes mellitus, alcoholism, and immunosuppressive therapies.[6] However, all clinical and most epidemiological studies have been retrospective and have compiled data from heterogeneous timeframes and geographical areas.[3–10] Thus, a precise analysis of disease presentation based on homogeneous and prospectively acquired data is lacking. Furthermore, because listeriosis cases are relatively rare and scattered, no clinical trial has been done, and therapeutic guidelines are not evidence-based. The prognosis for listeriosis has not improved over the past decades.[3,7]

Listeriosis has been a notifiable disease in France since 1999, with mandatory notification of culture-confirmed cases and submission of isolates to the National Reference Center for Listeria (NRCL). A recent capture–recapture study estimated at 85–87% the exhaustiveness of the national surveillance system for the 2008–13 period, and since 2000, an average 98% of nationally reported cases have isolates submitted to the NRCL.[11] Taking advantage of the quasi-exhaustiveness of this surveillance system, we implemented the prospective Multicentric Observational NAtional Study on LISteriosis and ListeriA (MONALISA), a nationwide cohort, to precisely characterise the clinical patterns and identify prognostic factors for invasive listeriosis.

METHODS

Study design and patients

MONALISA is a national prospective observational cohort study. We enrolled eligible cases declared to the NRCL (all microbiologically proven), in the context of mandatory reporting. We report the study in accordance with the STROBE reporting guidelines for observational studies.[12] A case was defined as a patient in whom L monocytogenes was isolated from a normally sterile site. We included all cases from Nov 3, 2009, to July 31, 2013, and classified these as maternal–neonatal infection, bacteraemia, neuro- listeriosis, or other form. Patients originated from 372 centres within France. Maternal–neonatal infection was defined when *L monocytogenes* was isolated in pregnant women, fetuses, or infants 1 month old or younger. When *L monocytogenes* was isolated from samples of both mother and her infant, the event was counted as a single case. Bacteraemia was defined when *L monocytogenes* was isolated from blood culture, without neurolisteriosis or maternal– neonatal infection. Neurolisteriosis was defined when *L monocytogenes* was isolated from the cerebrospinal fluid (CSF) or a brain abscess, when *L monocytogenes* was isolated from blood cultures in a patient with otherwise unexplained neurological symptoms (altered consciousness, seizures, nuchal rigidity, or focal neurological symptoms), when *L monocytogenes* was isolated from blood cultures and identified in CSF by PCR, and finally, in a single patient with meningitis, when *L monocytogenes* was identified in CSF by PCR and all other microbiological analyses were negative. Patients with neurolisteriosis and positive blood cultures were classified as neurolisteriosis cases. Other forms were defined by the isolation of *L monocytogenes* from other normally sterile sites. Data on past history, features at admission, and treatments were collected. All patients (or their legal representatives when they were unable to consent) provided written informed consent. In accordance with French legislation, MONALISA received institutional review board approval by the local ethics committee (Comité de Protection des Personnes Ile-de-France 3, Nov 6, 2009). Biospecimen collection was declared to the Ministry of Research (DC 2012-1698 coll 16). In accordance with French legislation, data from patients who died before contact were included, provided that their next of kin agreed.

Procedures

L monocytogenes isolates were identified with API Listeria (BioMérieux, Marcy l'Etoile, France) and sequenced using Illumina technology (appendix). Multilocus sequence types and inlA gene variants were extracted from genome assemblies using Lm-BIGSdb.[13] DNA extraction was done using the DNeasy blood and tissue extraction kit (Qiagen, Aarhus, Denmark), from 5 mL of liquid cultures grown overnight at 35°C in brain–heart infusion medium under aerobic conditions, following the manufacturer's protocol. Library preparation was carried out using the Nextera XT DNA sample kit and whole genome sequencing was done on the NextSeq 500 platform using 2×150 bp runs (Illumina, San Diego, CA, USA) at a minimum coverage of 40×. Paired-end reads were trimmed with fqCleaner v05 to eliminate adapter sequences and discard reads with Phred scores of 20 or less. Assemblies were obtained using CLC Assembly Cell 430 (Qiagen, Aarhus, Denmark).

Outcomes

We analysed clinical features, characterised *L monocytogenes* isolates, and determined predictors of 3-month mortality or persisting impairment using logistic regression.

Statistics

The sample size was a convenience sample, determined by the number of eligible cases during the study period. We investigated the relation between unfavourable outcome and potential predictors by doing a multivariable logistic analysis. Unfavourable outcome was defined as fetal loss for maternal–neonatal infections, 3-month mortality for bacteraemia and neurolisteriosis, and also persisting neurological impairment for neurolisteriosis. Variables showing associations at a significance level of $\alpha=0.20$ in a univariable analysis were selected for inclusion in the multivariable model and a stepwise selection was done. Missing values were imputed using a multivariate imputation by a chained equations procedure. To further characterise cases associated with bacteraemia and neurolisteriosis, we did a hierarchical clustering on principal components. Statistical analysis was done with R software (version 3.2.2). All tests were two-tailed and p values less than 0.05 (calculated by $\chi2$ test, Student's t test, or Mann-Whitney test) were considered significant (appendix pp 8, 9). The study is registered at ClinicalTrials. gov, number NCT01520597.

Role of the funding sources

The funder had no role in study design, data collection, analysis and interpretation, or writing of the report. The corresponding authors had full access to the data and final responsibility for the decision to submit for publication.

RESULTS

Of the 1063 cases notified to the NRCL between Nov 9, 2009, and July 31, 2013, 869 patients gave informed consent, of whom 818 (94%) were included in the study (figure 1): 427 patients with bacteraemia, 252 patients with neuro- listeriosis, 107 patients with maternal–neonatal infection (table 1), and 32 patients with other forms. Follow-up was available for 99% of patients (median follow-up period 5 months [IQR 3–10]). Comparison between cases included and not included is shown in the appendix (p 10).

35 (33%) of 107 women with maternal–neonatal listeriosis were born in the Maghreb or sub-Saharan Africa, three times more than the general pregnant population in France in 2010 according to national records (88000 [11%] of 832000 women, p<0·0001).[14]

Mothers of neonates with late-onset listeriosis (six of 107) had normal examination throughout pregnancy and delivery, but all others reported symptoms (101 of 107). The most frequent presentations at admission were fever with obstetric signs (contractions, labour, or abnormal fetal heart rate; 62 [62%] of 101 cases) and fetal loss (21 [21%] of 101 cases; figure 2A, table 1).

Placenta and newborn gastric fluid were the most sensitive samples for microbiological diagnosis (positive in 50 [78%] of 64 placenta samples and 52 [78%] of 67 gastric fluid samples), whereas maternal blood cultures were positive in 47 [55%] of 85 samples (figure 2B). In 39 (98%) of 40 cases with maternal, placenta, and infant sample cultures, diagnosis was done with placenta or maternal blood cultures (without any other fetal–neonatal sample; figure 2C). Hypovirulent L monocytogenes clones (CC9 and CC121) were never isolated, whereas hypervirulent clones (CC1, CC2, CC4, and CC6) were identified in 70 (66%) of 106 cases (appendix p 27).[15] No strain with internalin (InlA) truncation was found, in agreement with the key contribution of this virulence factor in maternal–neonatal listeriosis.[16]

All pregnant women with maternal listeriosis recovered including ten (9%) of 107 who did not receive antimicrobials (table 2). Severe sepsis, neurolisteriosis, or death was not recorded in infected mothers, but only five (5%) of 107 had normal delivery and normal post-partum evolution (appendix p 10). 26 (24%) of 107 mothers experienced fetal loss, 48 (45%) of 107 premature delivery, and 22 (21%) of 107 had delivery with any combination of fever or meconium fluid or abnormal fetal heart rate indicative of acute fetal distress. 40 (40%) of 101 mothers had caesarean sections. Among 48 prematurely born infants, 20 (42%) were born earlier than 32 weeks of gestation, 21 (44%) between 32 and 34 weeks of gestation, and seven (15%) between 34 and 36 weeks of gestation. Six neonates developed late-onset listeriosis 7–17 days after uneventful pregnancy and delivery. Of 107 maternal–neonatal cases, 89 (83%) had major adverse outcomes: fetal death, very high prematurity (<32 weeks of gestation), or early or late onset disease. Fetal losses occurred before admission to hospital (21 of 26) or within 2 days after admission (five of 26). The term of pregnancy at the time of maternal listeriosis was crucial for fetal outcome, and multivariable analysis did not reveal other parameters associated with fetal loss, including maternal geographical origin, clinical features, and blood culture results (appendix p 23). Any benefit of amoxicillin-based therapy could not be demonstrated because of the low number of untreated mothers. Of the 82 neonates born alive, only ten (12%) had normal physical evaluation with no sign of infection and did not receive antimicrobial therapy. Four prematurely born and infected neonates (born at 25–32 weeks of gestation) died as a consequence of neurological lesions attributable to infection or prematurity.

Patients with bacteraemia had a mean age of 73 (SD 14) years and those with neurolisteriosis 67 (16) years. More male patients were found when compared with the French population of the same age (59% [398 of 679] vs 45% in the French 69–75-year-old population; p<0·0001).[17] The most frequent immunosuppressive comorbidities in patients with bacteraemia or neurolisteriosis were solid organ cancer (209 [31%] of 679) and diabetes mellitus (149 [22%] of 679; appendix p 12). Underlying cancer was revealed in 18 (3%) of 679 non-maternal patients. 293 (43%) of 679 patients had received corticosteroids or other immunosuppressive therapies (from one drug to 12 drugs received) over the past 5 years (appendix p 11). Ten (4%) of 252 patients with neurolisteriosis had distinctive features that could account for inherited susceptibility to listeriosis: they were younger than 40 years, had no comorbidity or ongoing pregnancy, and no report of substantial infection before listeriosis.

Patients with bacteraemia reported at least one of the following symptoms: fever, decompensated comorbidity, diarrhoea, influenza-like symptoms, and multi-organ failure (table 1). 390 (94%) of 415 patients had fever or tachycardia (>90 beats per min). C-reactive protein was elevated in 600 (96%) of 627 patients and procalcitonin in 123 (66%) of 186 patients. Among 252 patients with neurolisteriosis, 218 (87%) had encephalitis-associated symptoms and 34 (13%) had meningeal involvement without encephalitis. Meningoencephalitis was found in

212 (84%) of 252 patients, with a mean score on the Glasgow Coma Scale of 12 (SD 3; table 1). CSF was examined in 235 patients with neurolisteriosis; all had biological signs of meningeal involvement (figure 3). CSF findings are shown in the appendix (p 28). Clinical involvement of the brainstem, typically considered as indicative of neurolisteriosis, was observed in only 42 (17%) of 252 patients. Brain abscesses were observed in six (2%) of 252 patients. Neurolisteriosis patients with encephalitis were older than those without encephalitis (69 [SD 14] years vs 53 [22] years, p<0·0001) and exhibited more comorbidities (median 3 [IQR 2–4] vs 1 [0–3], p<0·0001). Median time interval from first symptom to diagnosis was not different in patients with neurolisteriosis with and without encephalitis (2 [IQR 1–4] days vs 2 [1–4] days, p=0·161). Lymphopenia (<1500 cells per μL) or monocytopenia (<200 cells per μL) were equally reported in patients with bacteraemia and patients with neurolisteriosis (table 1).

Among the 235 cases in which blood and CSF samples were cultured, 37 (16%) had positive blood cultures only, 93 (39%) had positive CSF culture (or PCR) only, and 105 (45%) had both. Strains belonging to hypervirulent clonal complexes15 were more frequently identified in neurolisteriosis than bacteraemia (142 [57%] of 250 vs 168 [40%] of 424, p<0·0001; appendix p 27). Antimicrobial susceptibility testing of the most commonly used antibiotics did not identify resistant isolates (appendix p 29).

Amoxicillin was the most prescribed drug (table 2). Of the 679 patients with bacteraemia or neurolisteriosis, 31 (5%) did not receive antimicrobial therapy: all died within 3 days after admission, before diagnosis (22 of 31), or 4–51 days after diagnosis (nine of 31). 32 (13%) of 252 patients with neurolisteriosis received adjunctive dexamethasone; these patients had lower survival than patients who did not receive adjunctive dexamethasone (17 [53%] of 32 vs 157 [73%] of 216, p=0·037, Fisher exact test).[18] Overall 3-month mortality estimated by the Kaplan- Meier method was 46% (194 of 427 patients) for bacteraemia and 30% (75 of 252 patients) for neurolisteriosis (p<0·0001; figure 4), and post-hospitalisation mortality accounted for 12% (24 of 194 patients) and 8% (six of 75 patients) of 3-month mortality in bacteraemia and neurolisteriosis, respectively. Post-hospitalisation mortality was attributed to severe pre-existing comorbidities but not to late complications of listeriosis. Neurolisteriosis patients with encephalitis had three times higher mortality than those without encephalitis (72 [33%] of 218 patients vs three [9%] of 34 patients, p=0·003).

Persisting impairment (altered consciousness or focal signs) was reported in 79 (44%) of 181 surviving patients with neurolisteriosis, and among them in 79 (52%) of 152 of those with symptoms of encephalitis (figure 3). Only 99 (39%) of 252 patients with neurolisteriosis (and among these only 68 [31%] of 218 of those with encephalitis) survived and fully recovered at follow-up. Limb motor deficiency (12 [7%] of 181), cerebellar symptoms (five [3%] of 181), and eighth cranial nerve palsy (four [2%] of 181) were the most common persisting defects in surviving patients with neurolisteriosis. Nuchal rigidity, extra- pyramidal syndrome, and third and sixth cranial nerves palsy resolved in all cases.

Parameters associated with 3-month mortality in bacteraemia and neurolisteriosis in the multivariable model were: female sex, older age, ongoing neoplasia, more than 5% weight loss, multi-organ failure, decompensated comorbidity, monocytopenia less than 200 cells per μL, and high neutrophil count (table 3). Survival was two times lower in patients with ongoing neoplasia than without (44 [32%] of 136 vs 366 [68%] of 541) and among patients with aggravation of any pre-existing organ dysfunction than without (85 [35%] of 240 vs 325 [74%] of 439). Survival was also three times lower in patients with multi-organ failure than without (23 [19%] of 124 vs 387 [70%] of 555, p<0·0001).

Parameters associated with survival among patients with bacteraemia and neurolisteriosis were: influenza-like symptoms, administration of anti-listeria beta-lactam, or cotrimoxazole or an aminoglycoside. Treated patients receiving anti-listeria beta-lactam had a 3·3 times higher survival than those who did not (402 [66%] of 608 vs eight [20%] of 40, p<0·0001). Those receiving amino- glycoside also had increased survival (292 [69%] of 423 vs 118 [52%] of 225, p<0·0001). Duration of amoxicillin– aminoglycoside combination therapy (>3 days) had an independent protective effect when added to the multivariable model (>3 days vs 0 days, odds ratio [OR] 0·35 [95% CI 0·22–0·56], p<0·0001). In multivariable analysis focusing on neurolisteriosis, positive blood cultures and adjunctive dexamethasone prescription (prescribed within the first 24 h after admission) were associated with 3-month mortality (table 3). Survival was significantly lower in patients with positive blood cultures than in patients without positive blood cultures (95 [60%] of 158 vs 82 [87%] of 94, p<0·0001). 17 (52%) of 32 patients receiving adjunctive dexamethasone survived and 157 (73%) of 216 of those who did not receive adjunctive dexamethasone survived (p=0·024), although both groups had similar mean Glasgow Coma Scale scores (12 [SD 3] in both) and similar proportions with encephalitis (28 [86%] of 32 vs 185 [84%] of 220). Presence of encephalitis-associated signs was the strongest parameter associated with persistent neurological impairment in neurolisteriosis cases (78 [52%] of 149 vs one [3%] of 32).

To assess the relevance of bacteraemia versus neuro- listeriosis (bacteraemic or not) classification, a hierarchical clustering was done (appendix p 9). The analysis showed three clusters, one almost exclusively neurolisteriosis cases (cluster 3), and two other clusters (clusters 1 and 2) comprising predominantly bacteraemia cases as well as neurolisteriosis cases with a higher rate of positive blood culture and poorer outcomes than in cluster 3: cluster 1 comprised patients with iatrogenic immunosuppression and cluster 2 older patients (appendix p 30). In agreement with these results, survival of patients with bacteraemic neurolisteriosis was significantly lower than in patients with non-bacteraemic neurolisteriosis, but in the range of those with bacteraemia alone (figure 4B).

DISCUSSION

The quasi-exhaustiveness of the National Surveillance System for listeriosis in France made it possible to do the first prospective clinical study on listeriosis. We found that more than 80% of infected mothers experienced major fetal or neonatal complications and only 39% of patients with neurolisteriosis survived and fully recovered. Fetal losses occurred at less than 29 weeks of gestation and within 2 days of hospital admission and new factors independently associated with mortality were identified. Our data show the deleterious effect of adjunctive dexamethasone in neurolisteriosis, and argue for the use of beta-lactam and gentamicin or co-trimoxazole over other anti- microbials for bacteraemia and neurolisteriosis.

The strengths of this study are its exhaustiveness at inclusion and follow-up (99% of patients had follow-up data available), and the wide array of data collected (more than 500 items) for each patient. It is unusual to capture an almost complete dataset associated with a given pathogen on such a large scale in space and time. MONALISA provides crucial new data on listeriosis.

An unexpectedly high proportion of mothers with listeriosis report an African origin (33%), associated in France with lower socioeconomic conditions, mirroring the increased incidence of maternal–neonatal listeriosis in US Hispanic and UK ethnic minorities.[19–21] Since higher fecundity rates cannot account for this phenomenon,[14] the role of specific dietary habits (as described in Hispanic minorities in the USA[21]) remains to be studied, along with the contribution of listeriosis awareness, health-seeking behaviour, and health-care system access in this population. The study highlights the challenges of maternal diagnosis. Mothers had a large array of symptoms, none of them sensitive for the diagnosis of listeriosis. Furthermore, symptoms might vary largely. Fever, for instance, has been reported in 16–65% of mothers.[5,22] Maternal blood cultures (on which diagnosis before delivery relies) were negative in 45%, arguing for the maintenance of anti-listeria therapy despite negative maternal blood cultures where listeriosis is suspected. This finding reflects previous retrospective analyses that report only a 45% positivity of maternal blood cultures.[5] The prospective design of the study allowed a precise evaluation of fetal outcomes, with 83% of infected mothers experiencing major fetal or neonatal complications, which is worse than has been estimated in retrospective studies.[3,5] Term at onset is the crucial outcome parameter. Risk of fetal death is minimal when listeriosis occurs after 29 weeks of gestation, and whatever the term of pregnancy after the first 2 days of admission to hospital. This 29 week cutoff is slightly lower than previously reported, with fetal losses even in late pregnancies being rarely reported.10 This finding might reflect an increased medical awareness, in the context of French recommendations on the empiric prescription of amoxicillin when listeriosis is suspected during pregnancy.[23]

The MONALISA study identified the clinical features and prognosis of non-maternal listeriosis with an unprecedented precision. Regarding neurolisteriosis, our findings show the lack of sensitivity of brainstem involvement, despite its frequent reporting in retrospective studies.[4] This result emphasises the rarity of isolated encephalitis, in agreement with previous data reporting the low frequency of "isolated brain abscesses/cerebritis".[4] Long-term neurological sequelae were observed in 44% of surviving patients with neurolisteriosis, reflecting that reported in the Dutch cohort of 92 patients with neurolisteriosis and more than that reported for bacterial meningitis (18%) and infectious encephalitis (33%).[24–26] That only 33% of patients with L monocytogenes encephalitis survived without persisting impairment further underscores the severity of neuro- listeriosis. New independent factors associated with mortality in bacteraemia and neurolisteriosis were identified. The strongest factors are ongoing cancer, multi- organ failure, decompensated comorbidity, monocytopenia, and also concomitant bacteraemia for neurolisteriosis. Only older age and malignancies were previously identified; other features such as alcoholism, antacid uptake, corticosteroid medication, chronic lung or kidney disease, blood transfusion, and Asian and Hispanic ethnicity recognised as risk factors for death in smaller cohorts were not shown in our study.[8,9,27]

Neurolisteriosis in human beings is a blood-borne infection. Positive blood cultures at the time of diagnosis could reflect higher bacterial load and weaker host defences, leading to higher mortality, as shown in other opportunistic infections (eg, cryptococcosis).[28] This hypothesis might also account for the counter-intuitive observation of poorer outcome in bacteraemia-only than with neurolisteriosis (46% vs 30% for 3-month mortality). Multivariate analyses suggest that beta-lactams and aminoglycosides or cotrimoxazole could improve survival more than other antibiotics in bacteraemia and neurolisteriosis, independently of any associated factor. Whereas smaller size studies and retrospective studies suggest a deleterious effect of amino- glycosides, our

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results, although not from a randomised trial, could be considered the strongest available evidence so far arguing for the use of combined amoxicillin– gentamicin as first-line therapy for invasive listeriosis.[29,30] The findings are in line with the documented in-vitro synergy and bactericidal effect of amoxicillin plus gentamicin on *L monocytogenes*—amoxicillin alone is only weakly bactericidal.[31] Whether the relatively short mean duration of bacteraemia treatment in our study (17 days) accounts, at least in part, for the poor prognosis remains to be determined.

Multivariate analyses showed for the first time a significantly reduced survival in patients with neuro- listeriosis treated with adjunctive dexamethasone. This deleterious effect had been suggested before in the Dutch cohort of 92 patients with neurolisteriosis[26] that showed a trend, although non-significant, towards poorer outcome among patients with neurolisteriosis treated with dexamethasone. Even though our result is not from a clinical trial and the number of treated patients was small (n=32), it suggests that dexamethasone should be avoided in the treatment of neurolisteriosis.[18] The identification of young patients with neurolisteriosis and without an identified comorbidity could suggest a genetic susceptibility to listeriosis, although one might not also exclude the possibility of a massive inoculum.[21]

Our study has limitations. First, all screened patients could not be included. The outcome of excluded neurolisteriosis cases was worse than included cases, with a higher mortality rate: this limitation suggests that the actual burden of listeriosis, at least for neurological infections, might be even higher than reported here. Potential biases were addressed by doing multivariable regressions to control for confounding factors. Multiple imputation was used for multivariable models to limit bias arising from missing data. No adjustment for multiple testing was done in our exploratory approach. The proportional hazards assumption was tested and no violation of the proportional assumption was found. Although dexamethasone was given within 24 h of management in all cases, the precise timing of administration (before or after the first antibiotic dose) was not recorded. For these reasons, confirmatory studies on external cohorts are needed to support our results.

In conclusion, this study highlights much more serious outcomes of listeriosis than has been reported to date, with greater than 80% of infected mothers experiencing major fetal or neonatal complications. Furthermore, only 39% of study shows a deleterious effect of adjunctive dexa- methasone in neurolisteriosis, and argues for the use of beta-lactam, gentamicin, and co-trimoxazole over other antibiotics for bacteraemia and neurolisteriosis. Given the practical difficulties in doing clinical trials in listeriosis, these results constitute a unique basis from which clinical practice might evolve to better diagnose and treat this deadly infection.

Tables and figures legends

Table 1. Characteristics of the study population
Data are mean (SD), median (IQR), n (%), or n/N (%), unless otherwise stated. *Mann-Whitney test. †χ2 test. ‡Immunosuppressive comorbidities included: daily alcohol intake more than three drinks per day, cirrhosis, diabetes mellitus, end-stage renal disease, solid organ cancer, haematological malignancy, haemopoietic stem-cell transplantation, solid organ transplantation, asplenia, pre-existing neutropenia, pre- existing lymphopenia, HIV infection, inflammatory bowel diseases, inflammatory rheumatic disorders, other autoimmune diseases, congenital immune deficiency, age older than 70 years, prescription of corticosteroids, or other immunosuppressive therapies in the past 5 years. §Fisher exact test.

Table 2. Summary of treatments and outcomes for patients with maternal listeriosis, bacteraemia, and neurolisteriosis

Data are mean (SD), median (IQR), n (%), or n/N (%), unless otherwise stated. Data were not available for all patients in the bacteraemia and neurolisteriosis groups where indicated. *Two mothers received erythromycin, and another two received ineffective cephalosporin-based therapy. †Treatment data were available for 251 patients with neurolisteriosis. ‡Of the ten mothers who did not receive antibiotic therapy, six were women whose infant was diagnosed with late onset disease. §Two deaths were censored because patients died more than 3 months after diagnosis but in hospital. ¶Infections included severe sepsis or septic shock (n=4), pneumonia (n=8), undocumented sepsis and bacteraemia (n=2 each), pyelonephritis, cellulitis, bile tract infection, otitis media, colitis, endocarditis, endovascular infection (n=1 each), and opportunistic infections (cytomegalovirus-related encephalitis, aspergillosis, and nocardiosis, n=1 each). ‖All recurrences were bacteraemia.

Table 3. Multivariable logistic regression analyses of factors associated with 3-month mortality for patients with bacteremia and neurological infections and with persisting neurological impairment for patients with neurological infections

Results from univariable analyses are presented in appendix (p12). * 269 died within 3 months after diagnosis (269/679, 40%). † Adjusted odds ratios calculated from the multivariable model after imputation of missing data. CI were estimated using Rubin's rules. ‡ Beta-lactams lacking activity towards *Listeria spp.* were excluded (i.e. oxacillin and cephalosporins). § 79 patients reported persisting impairment (79/181, 44%). ¶ Encephalitis symptoms included at least one of the following signs, with no alternative cause identified: altered consciousness (score on Glasgow Coma Scale <15), seizures, new onset of focal neurological sign and any abnormality on electroencephalography consistent with encephalitis (appendix, p9).

Figure 1: Patient selection

  *Patients not meeting the inclusion criteria were patients with no French health-care insurance, according to French ethics legislation, or patients for whom written consent could not be obtained (either from them of from their next of kin). †17 patients were classified as patients with neurolisteriosis although they did not have lumbar puncture performed; all had positive blood cultures, all reported fever, with either neck stiffness evocative of meningitis (n=4), coma (n=3), coma and neck stiffness (n=2), neurological signs (homonymous hemianopia, cerebellous syndrome, and seizures, n=1 each), brain abscess (n=1), or neck stiffness and focal neurological signs (aphasia and pyramidal syndrome, pyramidal syndrome alone, bilateral motor deficiency, and hemiparesis, n=1 each); these symptoms were regressive in all cases under antibiotic therapy, with no alternative cause identified; in all cases, clinicians considered neurological signs as the manifestation of neurolisteriosis, and prescribed high-dose antibiotic therapy. ‡Focal infections involved the peritoneal fluid (n=13), bones and joints (n=8), pleural space, cardiovascular infections (n=3, each), urinary tract infections (n=2), pneumonia, biliary tract, and adenitis (n=1, each).

Figure 2. Clinical and biological presentation of maternal–neonatal listeriosis

(A) Pattern of maternal and obstetric symptoms for maternal–neonatal presentation at admission. *Mothers of the six neonates with late onset disease had no symptoms and are not included in this panel; mean term at the diagnosis of listeriosis was 30 (SD 8) weeks of gestation. (B) Frequency of positive samples among the 107 maternal–neonatal cases. †Other samples included various organs collected at autopsy. (C) Distribution of culture-positive samples in the 40 maternal–neonatal cases with maternal blood cultures, placenta, and infant samples collected (green, maternal blood cultures [n=22]; pink, fetal or neonatal samples [n=31]; blue, placenta cultures [n=30]).

Figure 3. Clinical and biological presentation of neurolisteriosis

(A) Clinical features of neurolisteriosis. *Study population included the 252 patients with neurolisteriosis. †Brainstem involvement was defined by the presence of any cranial nerve lesion (except the first nerve). ‡Cerebrospinal fluid (CSF) examination was done in 235 patients with neurolisteriosis; opening pressures (intracranial presssure of the CSF measured during lumbar puncture) were not assessed. §Polymorphonuclear cells to nucleated cells ratio was assessed in 231 patients. ¶CSF to blood glucose ratio was determined for 197 patients. ‖Listeria *monocytogenes-specific* PCR results for CSF were positive in ten of 16 tested samples: one of one with a 16s amplification, eight of 14 with a *hly* amplification, and one of one other non-specified local amplification technique; of the three patients with PCR-positive CSF and concomitant negative cultures, two had antibiotics when lumbar puncture was done. (B) Schematic representation of clinical and microbiological baseline features of neurolisteriosis. Left: green, clinical encephalitis (n=218); blue, clinical meningitis (n=163); red, CSF abnormality among patients with neurolisteriosis (n=235). Right: red, positive blood culture (n=142); blue, positive CSF culture (n=197). **Encephalitis was defined by the presence of at least one of the following symptoms with no alternative cause than listeriosis identified: altered consciousness (score on Glasgow Coma Scale <15), seizures, new onset of neurological symptoms, and abnormality on electroencephalography consistent with encephalitis (appendix). ††CSF abnormality was defined by at least one of the following conditions: a nucleated cells count of more than 4 per μL, protein count of less than 0·5 g/L, or the presence of *Listeria monocytogenes* in the cerebrospinal fluid by culture or PCR. ‡‡11 patients and six patients with clinical encephalitis but no alteration of the CSF had no lumbar puncture performed.

Figure 4. Survival of patients with maternal listeriosis, bacteraemia, or neurolisteriosis
(A) Kaplan-Meier plot of the time to death of patients with maternal listeriosis, bacteraemia, or neurolisteriosis. Survival is significantly higher in patients with neurolisteriosis than in patients with bacteraemia (hazard ratio [HR] 0·54 [95% CI 0·41–0·69], p<0·0001). No test was done for maternal patients because there was no death in this group. (B) Kaplan-Meier plot of the time to death of patients with bacteraemia, neurolisteriosis and bacteraemia, and neurolisteriosis without bacteraemia. Survival is significantly higher in cases of neurolisteriosis without bacteraemia than in those of neurolisteriosis with bacteraemia (HR 0·27 [95% CI 0·15–0·49], p <0·0001). Survival is significantly higher in neurolisteriosis without bacteraemia than in bacteraemia alone (HR 0·21 [95% CI 0·12–0·36], p<0·0001). Survival is not significantly higher in neurolisteriosis with bacteraemia than in bacteraemia alone (HR 0·77 [95% CI 0·59–1·00], p=0·054).

Conflicts of interest
We declare no competing interests.

Contributors
CC, AL and ML did the literature search.
CC and ML conceived the study, together with VG, PR and OL.
CC, AL, BC, BP, BH, AL, PT and HBD did the data collection.
EP, AM, MM and CC did the statistical analyses and all authors helped to interpret the data.
CCW and ML wrote the manuscript and all authors reviewed the manuscript.

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Table 1

Characteristics*	Maternal (N=107)	Bacteremia (N=427)	Neurolisteriosis (N=252)	Difference in means or proportions between bacteremia and neurolisteriosis (95%CI)	p-value bacteremia versus neurolisteriosis
Age – years (no· evaluated)	30±5 (107)	73±14 (427)	67±16 (252)	6 (4; 8)	<0·001[‡]
Male gender – no·/ no· evaluated (%)	-	246/427 (58)	152/252 (60)	-3 (-10; 5)	0·489[§]
Associated comorbidities (no· evaluated)	(107)	(427)	(252)		
Median number of comorbidities	0 [0; 1]	3 [2; 5]	3 [1; 4]	0·7 (0·4; 1·0)	<0·001[‡]
Median number of immunosuppressive comorbidities[†]	0 [0 ;0]	2 [1; 4]	2 [1; 3]	0·5 (0·3; 0·8)	<0·001[‡]
At least one immunosuppressive comorbidity[‡]	7/107 (7)	416/427 (97)	216/252 (86)	12 (7; 16)	<0·001[§]
Median time interval from first symptom to diagnosis –days (no· evaluated)	1 [0; 3] (98)	2 [0; 6] (369)	2 [1; 4] (243)	1·6 (0·3; 3·0)	0·684[‡]
Temperature >37·7°C – no· / no· evaluated (%)	83/107 (78)	370/427 (87)	244/252 (97)	-10 (-14; -6)	<0·001[§]
Mean maximal body temperature (°C)(no· evaluated)	39±1 (100)	39±1 (389)	40 ±1 (246)	-0·5 (-0·6; -0·3)	<0·001[§]
Flu-like symptoms (muscle and joint pains, chills)	35/107 (33)	87/427 (20)	69/252 (27)	-7·0 (-13·7; -0·3)	0·036[§]
Systolic blood pressure <90 mm Hg – no· / no· evaluated (%)	1/93 (1)	27/390 (7)	8/247 (3)	3·7 (0·3; 7·0)	0·047[§]
Diarrhea (>3 stools / day)	8/107 (8)	92/427 (22)	38/252 (15)	6 (1; 12)	0·039[§]
Septic chock	0/107 (0)	5/427 (1)	5/252 (2)	-1 (-3; 1)	0·512[¶§]
Score on Glasgow Coma Scale					
Mean (no· evaluated)	15±0 (107)	14±2 (420)	12±3 (244)	2·1 (1·7; 2·4)	<0·001[‡]
<14 (change in mental status) – no· / no· evaluated (%)	1/107 (1)	57/420 (14)	121/244 (50)	-36 (-43; -29)	<0·001[§]
<8 (coma) – no· / no· evaluated (%)	0/107 (0)	12/420 (3)	24/244 (10)	-7 (-11; -3)	<0·001[§]
Blood cultures					
Performed	85/107 (79)	427/427 (100)	252/252 (100)	-	-
Positive	47/85 (55)	427/427 (100)	158/252 (63)	37 (31; 43)	<0·001[§]
Blood count					
Mean blood leucocytes count /mm^3 (no· evaluated)	14830±7410 (98)	10920±10740(420)	12890±9130 (251)	-1960 (-3560; -370)	<0·001[‡]
Mean blood polymorphonuclear cells /mm^3 (no· evaluated)	12350±9800 (88)	8400±6710 (408)	9920±5880 (248)	-1530 (-2540; -510)	<0·001[‡]
Blood leucocytes count <10^4/mm^3 – no· / no· evaluated (%)	28/98 (29)	239/420 (57)	93/251 (37)	20 (12; 27)	<0·001
Lymphopenia <1500 /mm^3 – no· / no· evaluated (%)	36/87 (41)	342/408 (84)	196/247 (79)	4 (-2; 11)	0·148[§]
Monocytopenia <200 /mm^3 – no· / no· evaluated (%)	1/59 (2)	49/358 (14)	24/230 (10)	3 (-2; 9)	0·243[§]
Monocytosis >1000 /mm^3 – no· / no· evaluated (%)	10/59 (17)	59/358 (16)	65/230 (28)	-12 (-19; -5)	<0·001[§]
Blood chemical tests					
C-reactive protein –mg/liter – no· evaluated	102±74 (91)	115±87 (394)	113±90(233)	2 (-12; 16)	0·571[‡]
C-reactive protein <10 mg/liter – no· / no· evaluated (%)	0/91 (0)	10/394 (3)	17/233 (7)	-5 (-8; -1)	0·005[§]
Serum procalcitonin – ng/ml (no· evaluated)	0·2 [0·1; 0·2] (5)	0·9 [0·3; 6··8] (71)	1·4 [0·3; 6·2] (115)	-1 (-7; 6)	0·515[‡]
Serum procalcitonin <0·5 ng/ml – no· / no· evaluated (%)	5/5 (100)	27/71 (38)	36/115 (31)	7 (-7; 21)	0·347[§]

Table 2

A· Treatment characteristics according to the form of infection*	Maternal[†] (N=107)	Bacteremia (N=427)	Neurolisteriosis (N=251)
Mean number of antibiotics	1·7±1·1	2·3±1·4	3·2±1·4
Median duration of antibiotics in days	15 [8; 21]	17 [9; 23]	22 [18; 25]
Amoxicillin – no· (%), median duration in days	91 (85), 15 [9; 22]	349 (82), 16 [11; 22]	244 (97), 22 [15; 23]
Imipenem – no· (%), median duration in days	0 (0)	13 (3), 8 [4; 16]	10 (4), 7 [5; 23]
Gentamicin – no· (%), median duration in days	32 (30), 3 [2; 4]	205 (48), 4 [3; 6]	200 (79), 7 [4; 8]
Cotrimoxazole – no· (%), median duration in days	0 (0)	49 (12), 11 [6; 22]	42 (17), 20 [14; 30]
Rifampicin – no· (%), median duration in days	0 (0)	6 (1), 21 [11; 25]	3 (1), 22 [19; 23]
Vancomycin – no· (%), median duration in days	1 (1), 3 [3; 3]	19 (4), 4 [2; 11]	24 (10), 2 [2; 6]
Linezolid – no· (%), median duration in days	1 (1), 15 [15; 15]	5 (1), 13 [10; 15]	4 (2), 14 [13; 21]
Amoxicillin+Gentamicin – no· (%), median duration in days	30 (28), 3 [2; 4]	170 (40), 4 [3; 6]	192 (76), 7 [4; 8]
Amoxicillin+Cotrimoxazole – no· (%), median duration in days	0 (0)	33 (8), 11 [6; 22]	37 (15), 20 [14; 30]
No treatment – no· (%)	10 (9)[‡]	30 (7)	1 (1)
Dexamethasone – no· (%)	-	-	32 (13)

B· Outcome according to the form of infection	Maternal (N=107)	Bacteremia (N=427)	Neurolisteriosis (N=252)
Intensive care unit management – no· / no· evaluated (%)	2/107 (2)	89/427 (21)	152/252 (60)
Median hospital-stay in days	6 [4; 11]	15 [7; 24]	23 [15; 33]
Mechanical ventilation – no· / no· evaluated (%)	0/107 (0)	43/427 (10)	83/252 (33)
Multi-organ failure – no· / no· evaluated (%)	0/107 (0)	75/427 (18)	49/252 (19)
Aggravation of any pre existing organ dysfunction – no· / no· evaluated (%)	0/107 (0)	182/427 (43)	58/252 (23)
3-month death – no· / no· evaluated (%)	0/107 (0)	194/427 (45)	75/252 (30)
Median interval from diagnosis to 3-month death in days	-	10 [3; 23]	14 [5; 30]
3-month in-hospital death – no· / no· evaluated (%)[§]	0/107 (0)	170/427 (40)	69[‡]/252 (27)
Median interval from diagnosis to 3-month in-hospital death in days	-	7 [2; 19]	11 [5; 24]
Post hospitalization follow-up – no· / no· evaluated (%)	104/107 (97)	256/257 (99)	181/181 (100)
Median post hospitalization follow-up in months	5 [3; 9]	5 [3; 11]	5 [3; 13]
3-month post hospitalization death – no· / no· evaluated (%)	-	24/257 (9)	6/181 (3)
Median interval from diagnosis to 3-month post hospitalization· death in days	-	54 [24; 68]	62 [58; 68]
New infection during post-hospitalization period– no· / no· evaluated (%)[¶]	0/104 (0)	19/255 (7)	7/181 (4)
Recurrence of listeriosis[‖]	0/104 (0)	2/255 (1)	1/179 (1)

Table 3

3-month death in bacteremias + neurolisteriosis (N=679)*		
Factors	**Odds ratio (95%CI)[†]**	**p-value**
Female sex	1·60 (1·04-2·46)	0·034
Age – years	1·03 (1·01-1·05)	0·001
At least one immunosuppressing comorbidity	0·43 (0·15-1·22)	0·113
Ongoing organ neoplasia	5·19 (3·01-8·95)	<0·001
Recent weight loss >5kgs	1·74 (1·05-2·87)	0·031
Intensive care unit management	1·48 (0·90-2·41)	0·120
Multi-organ failure	7·98 (4·32-14·72)	<0·001
Aggravation of any pre existing organ dysfunction	4·35 (2·79-6·81)	<0·001
Diarrhea	0·58 (0·33-1·01)	0·053
Flu-like symptoms	0·47 (0·27-0·80)	0·006
Monocytopenia <200/mm^3	3·70 (1·82-7·49)	<0·001
Neutrophils – cells /mm^3	1·05 (1·01-1·08)	0·006
Cotrimoxazole therapy	0·49 (0·26-0·92)	0·027
Aminoglycoside therapy	0·60 (0·38-0·94)	0·024
Active betalactam therapy[‡ †]	0·10 (0·04-0·26)	<0·001

3-month death in neurolisteriosis (N=252)		
Factors	**Odds ratio (95%CI)[†]**	**p-value**
Female sex	2·68 (1·24-5·83)	0·013
Age – years	1·35 (0·99-1·85)	0·058
On-going organ neoplasia	4·58 (1·53-13·73)	0·007
Recent major weight loss	2·65 (1·08-6·55)	0·034
Multi-organ failure	3·08 (1·25-7·58)	0·014
Aggravation of any pre existing organ dysfunction	2·75 (1·23-6·16)	0·014
Flu-like symptoms	0·47 (0·20-1·12)	0·087
Mechanical ventilation	2·89 (1·31-6·37)	0·009
Monocytopenia<200/mm^3	3·57 (1·24-10·23)	0·018
Positive blood cultures	3·67 (1·60-8·40)	0·002
Protein concentration in the cerebrospinal fluid	1·18 (0·99-1·41)	0·062
Adjunctive dexamethasone for meningitis	4·58 (1·50-13·98)	0·008

Neurological impairment in neurolisteriosis (N=181)[¶]		
Factors	**Odds ratio (95%CI)[†]**	**p-value**
Age – years	0·98 (0·96-1·00)	0·048
Encephalitis symptoms[§]	21·65 (2·58-181·59)	0·005
Number of neurological symptoms	1·37 (1·11-1·69)	0·004
Score on Glasgow Coma Scale	1·08 (0·98-1·20)	0·102

Supplementary Material

This appendix has been provided by the authors to give readers additional information about their work

Clinical features and prognostic factors of listeriosis: the MONALISA study

Online Supplemental Materials

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Matheron, Slavius Matica, Olivier Matray, Marie-Françoise Mattei, Bertrand Maubert, Jeanne Maugein, Juan-Pablo Maureira, Thierry May, Adrien May, Vincent Maze, Eric Meaudre Desgouttes, Alexandre Mebazaa, Frédéric Mechai, Virginie Medeau, Richard Megbemado, Mona Mehri, Myriam Mein-Bottini, Adrien Melis, Joelle Mellier, Philippe Ménager, Céline Ménard, Lucile Mendes-Martin, Anne-Claude Menguy, Mohamed Menouar, Taoufik Merabet, Paul Mercury, Corinne Meregnani, Philippe Mérigot, Sylvain Mermont, Yacine Merrouche, Pierre-Gilles Merville, Renaud Mesnage, Louis Mesnard, Aurélie Messager, Thierry Messiaen, Jonathan Messika, Patrick Messner Pellenc, Hervé Métenier, Pierre Metton, Christian Meyer, Michel Mialon, Jordi Miatello, Alban Michaud-herbst, Alain Michault, Sophie Micheli, Jocelyn Michon, Jean Baptiste Michot, Severine Mielczarek, Sophie Mignart, Virginie Mignaut, Audrey Migraine Bouvagnet, Fabrice Mihout, Catherine Mille, Olivier Millet, Noel Milpied, Olivier Mimoz, Jacques Minet, Bertrand Minguet, Mohamad Mohty, Marie-Pierre Moiton, Richard Monarchi, Yannick Monceau, Mehran Monchi, Eric Monlun, Jacques Monsegu, Nathalie Montagne, Ambroise Montcriol, Bernard Montmasson, Paramasiven Mootien, Olivier Moquet, Virginie Morando, Anne-Sohie Moreau, Yves Morel, Emmanuel Morelon, Armelle Morin-Fatome, Mathieu Morincomme, Philippe Morlat, Laurent Mosser, Annie Motard-Picheloup, Philippe Mottaz, Claire Moulinoux, Laurence Mouly, Georges Mourad, Jean-Claude Mouries, Hecham Moussa, Audrey Moustache, Jean-François Muir, Valérie Murbach, Yohann N'guyen, Jean-Claude N'guyen, Florence N'guyen-Khac, Jean, Marc Nabholtz, Tarik Naceur, Jean Nakhleh, Aline Nare, Xavier Nassif, Frédérique Nathan-Bonnet, Huguette Negrery, Claude Negrier, Dominique Neri, Hakima Nesrine, Catherine Neuwirth, Eugène Ngami, Elisabeth Carole Ngo Bell, Dieudonné Nicobaharaye, Laurent Nicolet, Laurence Nicolet, Marc Nicolino, , Philippe Niel, Karine Nikodijevic, Jean-Marie Nkunzimana , Christian Noel, Alain Noirot, Philippe Noto, Marie-Noelle Noulard, Christophe Ntalu Nkato, Martine Nyunga, Julien Obiols, Patrick Ochocki, Sylvie Odent, Brigitte Olivier, Gérard Oliviero, Basile Ondze, Oléna Orléva, Paul Orode, Henri Osman, Eric Oswald, Paola Otean, Abderkader Ouazir, Christophe Ozanon, Marc Paccalin, Marie-Christine Pages, Bénédicte Paindaveine, Béatrice Pangon, Jean-Marie Pannecouck, Jean-Christophe Paquet, Sabrina Parent, Elisabeth Parisi-Duchene, Jérôme Pasche, Thierry Pasdeloup, David Patin, René-Gilles Patrigeon, Isabelle Patry, Jean-Gabriel Paul, Simona Pavel, Michel Pavic, Jean-Michel Pawlotsky, Christopher Payan, Christiane Payen, Yves Péan, Frédérique Péchinot, André Péchinot, Matthieu Pecquet, Agnès Pélaquier, Hervé Peltier, Pascale Penn, Jean-Loup Pennaforte, Didier Perez, Caroline Périsson, Dominique Perotin, Michèle Perouse de Montclos, Sophie Perreve, Christian Perronne, Dominique Perrotin, Valerie Pesque, Martine Pestel-Caron, Vincent Pestre, Fabrice Petassou, Marie-Cécile Petit, Camille Petit Hoang, Philippe Petitjean, François Pettinelli, Anne-Sophie Peultier,Jean-Marie Piala, Gilles Pialoux, Caroline Piau, Aurélia Picard, Jean-Charles Picaud, Eric Pichard, Martin Pierre, Fabrice Pierre, Paul Pierrot, Emilie Piet, Marie-Claude Piffaut, Bertrand Pigeon, Carole Pignon, Georges Pinon, Jacques Piquet, Vincent Piriou, Eric Placidi, Gillles Plainfosse, Christophe Plane, Isabelle Plantier, Nicolai Claudiu-Plesa, Patrick Plésiat, Patrick Plessis, Chloé Plouzeau-Jayle, Marie-Cécile Ploy, Gilbert Pochmalicki, Joanna Pofelski, Yves Poinsignon, Anne-Sophie Poirier, Françoise Poitevin, Christian Pommier, Bénédicte Ponceau, Christophe Poncelet, Daniela Pop, Martine Porcheron, Réginald Pordes, Eric Porthault, Marc Portneuf, Anne Pottier, Pascal Pouedras, Jocelyne Poulain, Gérard Poulain, Hélène Poupet, Julien Pouyanne, Marie Pouzoullic, Claire Poyart, Bruno Pozzetto, Thierry Prazuck, Dominique Pressac, Fabrice Prévost, Sylvie Prince, Pascal Priollet, Olivier Proost, Daniel Protar, Eric Pujade Lauraine, Antoine Pujol, Louis Puybasset, Jean Puyhardy, Vincent Quentin, Denis Quinsat, Valérie Rabier, Fouzia Radaoui, Florian Radenac, Sylvie Radenne, Didier Raffenot, François Raffi, Hassène Rahmani, Céline Ramanantsoa, Guillaume Ranchon, Dana Ranta, Didier Raoult, Jean-Philippe Rasigade, Emmanuel Rassiat, Olivia Raulin, Alain Ravaud, Nathalie Ravet, Hasinrina Razafimahefa, Mirana Razafimahery, Daniel

Methods

Definitions

Fetal losses included spontaneous abortion and stillbirths Neonatal infections diagnosed ≥7 days of life were classified as late-onset listeriosis. The diagnosis of early onset infection was made when *Lm* was identified in CSF or blood cultures, or when *Lm* was identified in any other neonatal sample with concomitant C-reactive protein level >20 mg/L at birth. Neonates were considered healthy if they fulfilled the following criteria: normal physical examination, C-reactive protein level <5 mg/L, CSF nucleated cells count ≤30/mm^3 when a lumbar puncture was performed and all bacteriological samples tested negative.

Meningeal involvement was defined clinically (nuchal rigidity evocative of listeriosis for the clinician) or biologically (CSF nucleated cells count >4/mm^3 and/or CSF protein >0·5g/L and/or evidence of *Lm* by culture or quantitative polymerase chain reaction in the CSF). Encephalitis was defined by the presence of at least one of the following symptoms, with no alternative cause than listeriosis identified: altered consciousness (score on Glasgow Coma Scale <15), seizures, new onset of neurological symptoms and abnormality on electroencephalography consistent with encephalitis according to the International Encephalitis Consortium.[1] Brainstem involvement was defined by cranial nerve palsy involvement (except the olfactive nerve). Patients with neurolisteriosis and positive blood cultures, hence patients with both neurolisteriosis and bacteremia, were classified as patients with neurolisteriosis.

Comorbidities were defined as any significant past or concomitant disease or condition reported at listeriosis onset. To better categorize patients' conditions and distinguish those with possible increased risk of infection, we listed among them those possibly associated with immunosuppression. They were labeled "immunosuppressive comorbidities" and defined as follow: congenital immune deficiency, hematopoietic stem cell transplantation, solid organ transplantation, hematological malignancy, preexisting lymphopenia, preexisting neutropenia, inflammatory rheumatic disorders, inflammatory bowel diseases, other auto-immune diseases, asplenia, HIV infection, prescription of corticosteroids or other immunosuppressive therapies in the past five years, solid organ cancer, diabetes mellitus, cirrhosis, alcohol uptake >3 drinks/day, end-stage renal disease.[2] In addition, age >70 years was also retained as an immunosuppressive condition, because of the immunological impairments occur after the age of 70 years.[2]

Aggravation of any pre existing organ dysfunction was defined as any aggravation of preexisting liver, kidney, lung, heart, or pancreas (diabetes) dysfunction at the moment of infection onset.

Multi-organ failure was defined according to the international definition.[3]

Anti-*Listeria* betalactam included penicillin G, amoxicillin, ticarcillin, piperacillin, imipenem and meropenem.

Data collection and management

Baseline data at admission were indeed collected at the moment of inclusion. Subsequent in-hospital follow-up and post hospitalization follow-up were also prospectively collected at the end of hospitalization and at least 3 months after diagnosis.

Data presented are those reported by clinicians in charge of the patients Inconsistencies and missing data were checked and corrected and/or completed with clinicians of the 388 centers that included the 818 patients.

All human bio-resources were processed at the ICAReB biobanking platform, Institut Pasteur (NF S96-900, Biobanking and Biomolecular Resources Research Infrastructure participating member (BB-0033-00062)).

Statistical analysis

The study followed the STROBE reporting guidelines for observational studies.[4] The sample size was a convenient sample, determined by the number of eligible cases during the study period. This sample size gives a power of 80% to detect a Cohen's effect size of 022 between neurolisteriosis and bacteremia cases (n=252 and 427 respectively).[5] Categorical variables were described with frequencies and percentages Quantitative variables were described with the mean and standard deviation (SD) or median and interquartile range [25th–75th percentile]. To identify differences between patients and between clinical forms of listeriosis we used parametric and non-parametric tests; using Chi² or Fisher's exact tests to compare categorical variables and Student's t-test or Mann-Whitney tests to compare categorical variables. Fisher's exact tests were used whenever expected counts were below 5 for at least one category and Mann-Whitney tests were used in case of asymmetrical behavior.

We investigated the relation between unfavorable outcome and potential predictors by performing a multivariable logistic analysis. Factors tested for univariable analysis were chosen *a priori* based on available

data and pathophysiological relevance. Unfavorable outcome was defined as fetal loss for maternal-neonatal infections, three-month mortality for bacteremia and neurolisteriosis and also persisting neurological impairment for neurolisteriosis. In a first step, variables showing associations at a significance level of $\alpha=0\cdot20$ in a univariable analysis were selected for inclusion in the multivariable model. Missing values were then imputed using a Multivariate Imputation by Chained Equations procedure generating 50 imputed data sets assuming data were missing at random. A stepwise selection was performed on the stacked data set with a fixed weight applied to all individuals (w=(1-f)/m, where f is the average fraction of missing data across all variables and m is the number of imputed data sets). The final multivariable logistic model was applied to each of the 50 imputed data sets and OR and their 95 percent confidence intervals were estimated by using Rubin's rules.[6] To further characterize cases associated with bacteremia and neurolisteriosis, we performed a hierarchical clustering on principal components. Variables used for this classification were socio-demographics data, medical history, past treatments, clinical and microbiological data. As these variables are not all continuous, we first performed a multiple correspondence analysis (MCA) and then used the coordinates of the individuals on the principal components for the classification. MCA is used to transform categorical variables into continuous ones. We categorized the continuous variables so that they could be introduced into the MCA, according to clinically-relevant cut-offs. To ensure stability of the partition, we kept axes of the MCA capturing 90% of the information, the last axes being considered as noise. We performed a k-means consolidation. This analysis was conducted by using the package FactoMineR.[7] Missing data for active variables were handled using the package missMDA.[8]

Statistical analysis was conducted with R statistical software (version 322).[9] All statistical tests were two-tailed and p-values <0·05 were considered statistically significant.

Supplemental tables

Table S1

Characteristic	Maternal-neonatal			Bacteremia			Neurolisteriosis		
	Included	Not included	p-value	Included	Not included	p- value	Included	Not included	p- value
N=	N=107	N=29		N=427	N=173		N=252	N=32	
Age – years	30±5	32±7	0·38†	73±14	76±15	0·03†	67±16	76±14‡	0·02†
Male gender – no (%)	0/107 (0)	0/29 (0)		246/427 (58)	108/173 (62)	0·27†	152 (60)	16 (50)	0·26†
Death – no / no evaluated (%)*	0/107 (0)	0/29 (0)		194/427 (45)	54/130 (42)	0·43 §	75/252 (30)	10/18 (56)	0·02§
Feta loss– no / no evaluated (%)	26/107 (24)	8/19 (42)	0·1§	-	-		-	-	

Table S2

Pregnancy outcome – no / no evaluated (%)*	Mothers (N=107)	Term at presentation (weeks of gestation)					
		< 25 N=25	[25-28[N=6	[28-33[N=26	[33-37[N=24	[37-41[N=20	Late-onset listeriosis N=6
Normal pregnancy/delivery	5/107 (5)	3/25 (12)	0/6 (0)	1/26 (4)	1/24 (4)	0/20 (0)	-
Fetal loss	26/107 (24)	21/25 (84)	3/6 (50)	2/26 (8)	0/24 (0)	0/20 (0)	-
Premature delivery	48/107 (45)	1/25 (4)	3/6 (50)	23/26 (88)	21/24 (88)	0/20 (0)	-
Abnormal delivery at term†	22/107 (21)	0/25 (0)	0/6 (0)	0/26 (0)	2/24 (8)	20/20 (100)	-
Late-onset neonatal listeriosis	6/107 (6)	-	-	-	-	-	6/6 (100)
Neonatal outcome for alive infants‡	**Neonates (N=82)**	**Term of birth (weeks of gestation)**					
		<25 N= 0	[25-28[N=3	[28-33[N=25	[33-37[N=21	[37-41[N=27	Late-onset listeriosis N=6
Intensive care unit management – no / no evaluated (%)	40/82 (49)		3/3 (100)	20/25 (80)	8/21 (38)	8/27 (30)	1/6 (17)
Median hospitalization duration (days)	15 [8; 24]		32 [20; 41]	25 [20; 41]	17 [13; 21]	7 [5; 11]	18 [8; 21]
In-hospital death – no / no evaluated (%)	4/82 (5)		1/3 (33)	3/25 (12)	0/21 (100)	0/27 (100)	0/6 (0)
Hydrocephaly reported at 3 months of life – no / no evaluated (%)	2/82 (2)		0/3 (0)	2/25 (8)	0/21 (0)	0/27 (0)	0/6 (0)
Healthy neonate – no / no evaluated (%)§	10/82 (12)		0/3 (0)	1/25 (4)	0/21 (0)	9/27 (33)	0/6 (0)

Table S3

Characteristics*	Maternal (N=107)	Bacteremia (N=427)	Neurolisteriosis (N=252)
Non-immunosuppressive comorbidity			
Chronic respiratory disease	2/107 (2)	77/427 (18)	32/252 (13)
Chronic heart disease	0/107 (0)	102 /427(24)	20/252 (8)
Other cardiopathy	0/107 (0)	157/426 (37)	60/252 (24)
Hypertension	0/107 (0)	188/427 (44)	110/252 (44)
Renal insufficiency	0/107 (0)	109/427 (26)	27/252 (11)
Chronic liver disease[†]	0/107 (0)	67/427 (16)	34/252 (14)
Foreign material or implant[‡]	2/107 (2)	153/427 (36)	54/252 (21)
Atopy	7/104 (7)	29/426 (7)	14/249 (6)
Psychiatric disorder	0/107 (0)	30/427 (7)	14/252 (6)
Recent major weight loss	0/106 (0)	115/424 (27)	45/249 (18)
Immunosuppressive comorbidity			
Daily alcohol uptake >3 glasses / day	1/107 (1)	20/421 (5)	32/246 (13)
Cirrhosis	0/107 (0)	49/427 (12)	20/251 (8)
Diabetes mellitus	0/107 (0)	94/427 (22)	55/252 (22)
End stage renal disease	0/107 (0)	33/427 (8)	4/252 (2)
Solid organ cancer	0/107 (0)	160/427 (38)	49/252 (19)
Hematological malignancy	0/107 (0)	59/427 (14)	34/252 (14)
Hematopoietic stem cell transplantation	0/107 (0)	11/427 (3)	0/252 (0)
Solid organ transplantation[§]	0/107 (0)	14/427 (3)	5/252 (2)
Asplenia	0/107 (0)	7 /427(2)	3/252 (1)
Pre-existing neutropenia (neutrophils count <500/mm^3)	0/107 (0)	24/427 (6)	8/252 (3)
Pre-existing lymphopenia (lymphocytes count <1000/mm^3)	0/107 (0)	81/426 (19)	27/252 (11)
HIV infection[¶]	2/107 (2)	4 /427(1)	4/252 (2)
Inflammatory bowel diseases[‖]	1/107 (1)	9/427 (2)	12/252 (5)
Inflammatory rheumatic disorders**	2/107 (2)	26/427 (6)	20/252 (8)
Other auto-immune diseases	2/107 (2)	28 /427 (7)	11/252 (4)
Congenital immune deficiency	0/107 (0)	1/427 (1)	0/252 (0)
Age >70 years	0/107 (0)	266/427 (62)	117/252 (46)
Administration of therapies in the past 5 years			
Corticosteroids	1/107 (1)	146/427 (34)	79/252 (31)
Anti-TNF biotherapy	1/107 (1)	5/427 (1)	6/252 (2)
Other immunosuppressive therapy	1/107 (1)	137/427 (32)	71/252 (28)
Any corticosteroid/immunosuppressive therapy	2/107 (2)	190/427 (45)	103/252 (40)
Administration of drugs at the moment of listeriosis			
Corticosteroids	1/107 (1)	103/425 (24)	48/251 (19)
Anti-TNF biotherapy	0/107 (0)	1/427 (1)	6/252 (2)
Any corticosteroid/immunosuppressive therapy	1/107 (1)	138/427 (32)	71/252 (28)
Administration of anti-acid therapy	12/103 (12)	189/416 (45)	81/250 (32)
Administration of prophylactic cotrimoxazole	0/105 (0)	14/422 (3)	7/249 (3)

Table S4

A· Univariable analysis of fetal loss in maternal cases

Characteristics	No, n = 77	Yes, n = 30	p-value
Socio-demographic parameters			
Geographic origin			0·709*
Missing data	0 (0)	0 (0)	
Africa	26 (74·3)	9 (25·7)	
Else	51 (70·8)	21 (29·2)	
Past history			
Past history of fetal loss (<14weeks of gestation or 14-21 weeks of gestation)			0·768 †
Missing data	0 (0)	0 (0)	
No	66 (72·5)	25 (27·5)	
Yes	11 (68·8)	5 (31·2)	
Clinical / Biological parameters			
Maternal fever			0·372*
Missing data	0 (0)	0 (0)	
No	19 (79·2)	5 (20·8)	
Yes	58 (69·9)	25 (30·1)	
Maternal diarrhoea			0·684 †
Missing data	0 (0)	0 (0)	
No	72 (72·7)	27 (27·3)	
Yes	5 (62·5)	3 (37·5)	
Maternal flu-like symptoms			0·932*
Missing data	0 (0)	0 (0)	
No	52 (72·2)	20 (27·8)	
Yes	25 (71·4)	10 (28·6)	
Amniotic fluid macroscopic aspect			0·431*
Missing data	0 (0)	14 (46·7)	
Normal	35 (79·5)	9 (20·5)	
Stained	42 (85·7)	7 (14·3)	
Maternal blood cultures			0·896*
Missing data	16 (20·8)	6 (20)	
Negative	27 (71·1)	11 (28·9)	
Positive (*L· monocytogenes*)	34 (72·3)	13 (27·7)	
Term at maternal diagnosis of listeriosis			<0·001 †
Missing data	0 (0)	0 (0)	
[0,25)	4 (16)	21 (84)	
[25,28)	2 (33·3)	4 (66·7)	
[28,33)	21 (80·8)	5 (19·2)	
[33,37)	24 (100)	0 (0)	
[37,41]	20 (100)	0 (0)	
Post-natal infection	6 (100)	0 (0)	
Maternal C-reactive protein level– mg/L			0·311‡
Missing data	14 (18·2)	2 (6·7)	
Min/Max	10/331	10/321	
Med [Q1 ; Q3]	71 [37 ; 133]	110 [57·5 ; 148·25]	
Mean (sd)	96·78 (77·52)	113 (66·25)	
Maternal blood polymorphonuclear cells count– cells /mm³			0·593‡
Missing data	16 (20·8)	3 (10)	
Min/Max	1233/83000	2213/30210	
Med [Q1 ; Q3]	9750 [5900 ; 14424]	12800 [10193 ; 15970]	
Mean (sd)	12051·33 (11094·09)	13036·56 (6033·17)	
Maternal blood monocytes count– cells /mm³			0·606‡
Missing data	35 (45·5)	13 (43·3)	
Min/Max	65/2056	201/1410	
Med [Q1 ; Q3]	690 [460 ; 828·25]	733 [490 ; 990]	
Mean (sd)	702·79 (377·95)	758·71 (371·21)	
Monocytopenia < 200/mm³			1
Missing data	35 (45·5)	13 (43·3)	
>=200	41 (70·7)	17 (29·3)	
<200	1 (100)	0 (0)	
Maternal blood lymphocytes count– cells /mm³			0·753‡
Missing data	17 (22·1)	3 (10)	

Min/Max	128/12000	331/5750	
Med [Q1 ; Q3]	1645 [1087·5 ; 2306·5]	2260 [1360 ; 2735]	
Mean (sd)	1997·65 (1906·16)	2102·22 (1148·16)	
Maternal lymphopenia (< 1500 /mm³)			0·307*
Missing data	17 (22·1)	3 (10)	
>=1500	33 (64·7)	18 (35·3)	
<1500	27 (75)	9 (25)	
Clonal complex			0·945*
Missing data	0 (0)	1 (3·3)	
Other	26 (72·2)	10 (27·8)	
CC1 2 4 or 6	51 (72·9)	19 (27·1)	
Clonal complex			0·584*
Missing data	0 (0)	1 (3·3)	
Other	60 (71·4)	24 (28·6)	
CC4	17 (77·3)	5 (22·7)	
Clonal complex			1 †
Missing data	0 (0)	1 (3·3)	
Other	64 (72·7)	24 (27·3)	
CC6	13 (72·2)	5 (27·8)	
Urinary tract signs			0·051 †
Missing data	0 (0)	0 (0)	
Absent	75 (74·3)	26 (25·7)	
Present	2 (33·3)	4 (66·7)	

Treatment

Time interval from first symptom to treatment			0·137 †
Missing data	0 (0)	0 (0)	
No treatment	9 (90)	1 (10)	
<0 day	15 (57·7)	11 (42·3)	
[0 ; 1] day	47 (77)	14 (23)	
>1 day	6 (60)	4 (40)	
Time interval from diagnosis to treatment			0·005 †
Missing data	0 (0)	0 (0)	
No treatment	9 (90)	1 (10)	
<0 day	15 (57·7)	11 (42·3)	
[0 ; 3] day	53 (77·9)	15 (22·1)	
>3 day	0 (0)	3 (100)	
Time interval from admission to treatment			0·294 †
Missing data	0 (0)	0 (0)	
No treatment	9 (90)	1 (10)	
[0 ; 1] day	59 (72)	23 (28)	
>1 day	9 (60)	6 (40)	
Time interval from diagnosis to treatment			0·212 †
Missing data	5 (6·5)	2 (6·7)	
No treatment	9 (90)	1 (10)	
[0 ; 1] day	43 (74·1)	15 (25·9)	
>1 day	20 (62·5)	12 (37·5)	

B· Univariable analysis of 3-month death in bacteremia + neurolisteriosis cases

Characteristic	No, n = 410	Yes, n = 269	p-value
Socio-demographic parameters			
Sex			0·029*
Missing data	0 (0)	0 (0)	
Female	156 (55·5)	125 (44·5)	
Male	254 (63·8)	144 (36·2)	
Age at diagnostic			<0·001‡
Missing data	0 (0)	0 (0)	
Min/Max	0·79/98·81	22·78/99·69	
Med [Q1 ; Q3]	71·36 [60·46 ; 79·55]	77·36 [64·44 ; 83·01]	
Mean (sd)	68·26 (16·26)	73·94 (12·66)	
Geographical origin			0·003+
Missing data	3 (0·7)	5 (1·9)	
Africa	29 (78·4)	8 (21·6)	
Other	19 (76)	6 (24)	
Europe	32 (45·7)	38 (54·3)	
France	327 (60·7)	212 (39·3)	
Past history			
At least one comorbidity¶			0·002*
Missing data	0 (0)	0 (0)	
No	30 (85·7)	5 (14·3)	
Yes	380 (59)	264 (41)	
At least one immunosuppressing comorbidity‖			<0·001*
Missing data	0 (0)	0 (0)	
No	41 (87·2)	6 (12·8)	
Yes	369 (58·4)	263 (41·6)	
Past history of neoplasia or ongoing neoplasia			0*
Missing data	0 (0)	0 (0)	
No	322 (68·5)	148 (31·5)	
Yes	88 (42·1)	121 (57·9)	
Ongoing organ neoplasia			0*
Missing data	0 (0)	2 (0·7)	
No	366 (67·7)	175 (32·3)	
Yes	44 (32·4)	92 (67·6)	
Bone marrow transplantation			1+
Missing data	0 (0)	0 (0)	
No	403 (60·3)	265 (39·7)	
Yes	7 (63·6)	4 (36·4)	
Recent weight loss >5kgs			<0·001*
Missing data	2 (0·5)	4 (1·5)	
No	332 (64·7)	181 (35·3)	
Yes	76 (47·5)	84 (52·5)	
Hemodialysis			0·050*
Missing data	0 (0)	0 (0)	
No	382 (59·5)	260 (40·5)	
Yes	28 (75·7)	9 (24·3)	
Clinical / Biological parameters			
Listeriosis form			<0·001*
Missing data	0 (0)	0 (0)	
Neurolisteriosis	177 (70·2)	75 (29·8)	
Bacteremia	233 (54·6)	194 (45·4)	
Intensive care unit management			0·084*
Missing data	0 (0)	0 (0)	
No	275 (62·8)	163 (37·2)	
Yes	135 (56)	106 (44)	
Multiorgan failure			<0·001*
Missing data	0 (0)	0 (0)	
No	387 (69·7)	168 (30·3)	
Yes	23 (18·5)	101 (81·5)	
Aggravation of any pre existing organ dysfunction			<0·001*
Missing data	0 (0)	0 (0)	
No	325 (74)	114 (26)	
Yes	85 (35·4)	155 (64·6)	

Systolic blood pressure < 80 mmHg			0·403†
Missing data	10 (2·4)	32 (11·9)	
No	393 (63·1)	230 (36·9)	
Yes	7 (50)	7 (50)	
Diastolic blood pressure < 60 mmHg			0·137*
Missing data	10 (2·4)	34 (12·6)	
No	343 (64·2)	191 (35·8)	
Yes	57 (56·4)	44 (43·6)	
Heart rate > 120/min			0·002*
Missing data	23 (5·6)	43 (16)	
No	358 (65·2)	191 (34·8)	
Yes	29 (45·3)	35 (54·7)	
Glasgow coma scale			0·001‡
Missing data	6 (1·5)	9 (3·3)	
Min/Max	3/15	3/15	
Med [Q1 ; Q3]	15 [14 ; 15]	14 [12 ; 15]	
Mean (sd)	13·72 (2·36)	12·97 (3·09)	
Diarrhoea			0·058*
Missing data	0 (0)	0 (0)	
No	322 (58·7)	227 (41·3)	
Yes	88 (67·7)	42 (32·3)	
Septic shock			1†
Missing data	0 (0)	0 (0)	
No	404 (60·4)	265 (39·6)	
Yes	6 (60)	4 (40)	
Flu-like symptoms			<0·001*
Missing data	0 (0)	0 (0)	
No	291 (55·6)	232 (44·4)	
Yes	119 (76·3)	37 (23·7)	
C-reactive protein level– mg/L			<0·001‡
Missing data	26 (6·3)	26 (9·7)	
Min/Max	0/360	3/524	
Med [Q1 ; Q3]	81·5 [39 ; 150]	108 [61 ; 188]	
Mean (sd)	103·41 (80·6)	130·55 (96·83)	
Blood monocytes count < 200 /mm3			0·001*
Missing data	53 (12·9)	38 (14·1)	
No	326 (63·3)	189 (36·7)	
Yes	31 (42·5)	42 (57·5)	
Blood PMN cells count– cells /mm3			0·002‡
Missing data	7 (1·7)	16 (5·9)	
Min/Max	100/34900	20/67000	
Med [Q1 ; Q3]	7320 [4463·5 ; 10770·5]	8700 [5370 ; 13511]	
Mean (sd)	8297·3 (5475·96)	10047·33 (7639·23)	
Blood lymphocytes count <1500 /mm3			0·123*
Missing data	9 (2·2)	15 (5·6)	
No	79 (67·5)	38 (32·5)	
Yes	322 (59·9)	216 (40·1)	
Clonal complex			0·832*
Missing data	2 (0·5)	3 (1·1)	
Other	219 (60·2)	145 (39·8)	
CC1 2 4 or 6	189 (61)	121 (39)	

Treatment

Time interval from diagnosis to treatment			<0·001*
Missing data	1 (0·2)	0 (0)	
No treatment	0 (0)	31 (100)	
<0 d	71 (57·7)	52 (42·3)	
[0 ; 1] d	233 (62·5)	140 (37·5)	
>1 d	105 (69·5)	46 (30·5)	
Time interval from admission to treatment			<0·001*
Missing data	1 (0·2)	0 (0)	
No treatment	0 (0)	31 (100)	
[0 ; 1] d	271 (64·7)	148 (35·3)	

>1 d	138 (60·5)	90 (39·5)	
Time interval from first symptom to treatment			<0·001✝
Missing data	11 (2·7)	42 (15·6)	
No treatment	0 (0)	31 (100)	
<0 d	5 (71·4)	2 (28·6)	
[0 ; 1] d	132 (62·9)	78 (37·1)	
>1 d	262 (69·3)	116 (30·7)	
Duration of bitherapy Anti-listeria betalactamin** + aminoglycoside			<0·001*
Missing data	0 (0)	0 (0)	
0 d	121 (45·1)	147 (54·9)	
<= 3 d	76 (59·8)	51 (40·2)	
> 3 d	213 (75)	71 (25)	
Duration of bitherapy Cotrimoxazole + aminoglycoside			0·521*
Missing data	0 (0)	0 (0)	
0 d	385 (59·9)	258 (40·1)	
<= 3 d	16 (69·6)	7 (30·4)	
> 3 d	9 (69·2)	4 (30·8)	
Duration of tritherapy Anti-listeria betalactam**, cotrimoxazole and aminoglycoside			0·224✝
Missing data	0 (0)	0 (0)	
0 d	387 (59·6)	262 (40·4)	
<= 3 d	15 (75)	5 (25)	
> 3 d	8 (80)	2 (20)	
Cotrimoxazole administration			0·011*
Missing data	0 (0)	0 (0)	
No	344 (58·5)	244 (41·5)	
Yes	66 (72·5)	25 (27·5)	
Aminoglycoside administration			<0·001*
Missing data	0 (0)	0 (0)	
No	118 (46·1)	138 (53·9)	
Yes	292 (69)	131 (31)	
Anti-listeria betalactam administration**			<0·001*
Missing data	0 (0)	0 (0)	
No	8 (11·3)	63 (88·7)	
Yes	402 (66·1)	206 (33·9)	

C· Univariable analysis of 3-month death in neurolisteriosis cases

Characteristic	No, n = 177	Yes, n = 75	p-value
Socio-demographic parameters			
Sex			0·079*
Missing data	0 (0)	0 (0)	
Female	64 (64)	36 (36)	
Male	113 (74·3)	39 (25·7)	
Age at diagnostic			<0·001‡
Missing data	0 (0)	0 (0)	
Min/Max	0·8/97·1	38·5/92·4	
Med [Q1 ; Q3]	67·2 [57·6 ; 75·5]	75·9 [65·1 ; 82·1]	
Mean (sd)	64·2 (17·4)	72·9 (12)	
Geographical origin			0·094†
Missing data	0 (0)	0 (0)	
Africa	12 (80)	3 (20)	
Other	6 (100)	0 (0)	
Europe	14 (53·8)	12 (46·2)	
France	145 (70·7)	60 (29·3)	
Past history			
At least one comorbidity¶			0·072*
Missing data	0 (0)	0 (0)	
No	23 (85·2)	4 (14·8)	
Yes	154 (68·4)	71 (31·6)	
At least one immunosuppressing comorbidity‖			0·024*
Missing data	0 (0)	0 (0)	
No	31 (86·1)	5 (13·9)	
Yes	146 (67·6)	70 (32·4)	
Past history of neoplasia or ongoing neoplasia			<0·001*
Missing data	0 (0)	0 (0)	
No	154 (75·9)	49 (24·1)	
Yes	23 (46·9)	26 (53·1)	
Ongoing organ neoplasia			<0·001*
Missing data	0 (0)	0 (0)	
No	167 (73·9)	59 (26·1)	
Yes	10 (38·5)	16 (61·5)	
Bone marrow transplantation			1†
Missing data	0 (0)	0 (0)	
No	177 (70·2)	75 (29·8)	
Yes	0	0	
Recent weight loss >5kgs			0·082*
Missing data	1 (0·6)	2 (2·7)	
No	149 (73)	55 (27)	
Yes	27 (60)	18 (40)	
Hemodialysis			0·321†
Missing data	0 (0)	0 (0)	
No	173 (69·8)	75 (30·2)	
Yes	4 (100)	0 (0)	
Clinical / Biological parameters			
Intensive care unit management			0·029*
Missing data	0 (0)	0 (0)	
No	78 (78)	22 (22)	
Yes	99 (65·1)	53 (34·9)	
Multiorgan failure			<0·001*
Missing data	0 (0)	0 (0)	
No	158 (77·8)	45 (22·2)	
Yes	19 (38·8)	30 (61·2)	
Aggravation of any pre existing organ dysfunction			<0·001*
Missing data	0 (0)	0 (0)	
No	150 (77·3)	44 (22·7)	
Yes	27 (46·6)	31 (53·4)	
Systolic blood pressure < 80 mmHg			0·499†
Missing data	2 (1·1)	3 (4)	
No	174 (71)	71 (29)	
Yes	1 (50)	1 (50)	

Diastolic blood pressure < 60 mmHg			0·741*
Missing data	2 (1·1)	3 (4)	
No	158 (71·2)	64 (28·8)	
Yes	17 (68)	8 (32)	
Heart rate > 120/min			0·385*
Missing data	7 (4)	7 (9·3)	
No	154 (72·3)	59 (27·7)	
Yes	16 (64)	9 (36)	
Glasgow coma scale			0·001‡
Missing data	5 (2·8)	3 (4)	
Min/Max	3/15	3/15	
Med [Q1 ; Q3]	14 [11 ; 15]	12 [9 ; 14]	
Mean (sd)	12·58 (2·96)	11·04 (3·42)	
Diarrhoea			0·614*
Missing data	0 (0)	0 (0)	
No	149 (69·6)	65 (30·4)	
Yes	28 (73·7)	10 (26·3)	
Septic shock			1‡
Missing data	0 (0)	0 (0)	
No	173 (70)	74 (30)	
Yes	4 (80)	1 (20)	
Flu-like symptoms			0·043*
Missing data	0 (0)	0 (0)	
No	122 (66·7)	61 (33·3)	
Yes	55 (79·7)	14 (20·3)	
Mechanical ventilation			<0·001*
Missing data	0 (0)	0 (0)	
No	133 (78·7)	36 (21·3)	
Yes	44 (53)	39 (47)	
Hydrocephaly			0·321†
Missing data	0 (0)	0 (0)	
No	173 (69·8)	75 (30·2)	
Yes	4 (100)	0 (0)	
C-reactive protein level– mg/L			0·056‡
Missing data	14 (7·9)	5 (6·7)	
Min/Max	1/346	6/433	
Med [Q1 ; Q3]	81 [39 ; 166]	89·5 [59·25 ; 189·5]	
Mean (sd)	104·52 (81·14)	131·69 (105·05)	
Blood monocytes count < 200 /mm3			0·001*
Missing data	15 (8·5)	7 (9·3)	
No	152 (73·8)	54 (26·2)	
Yes	10 (41·7)	14 (58·3)	
Blood polymorphonuclear cells count– cells /mm3			0·581‡
Missing data	2 (1·1)	2 (2·7)	
Min/Max	540/34900	20/43976	
Med [Q1 ; Q3]	9764 [6440 ; 13201]	8700 [5390 ; 12900]	
Mean (sd)	10068·7 (5418·9)	9568 (6879·8)	
Blood lymphocytes count <1500 /mm3			0·475*
Missing data	3 (1·7)	2 (2·7)	
No	38 (74·5)	13 (25·5)	
Yes	136 (69·4)	60 (30·6)	
Clonal complex			0·343*
Missing data	2 (1·1)	0 (0)	
Other	79 (73·1)	29 (26·9)	
CC1 2 4 or 6	96 (67·6)	46 (32·4)	
Positive blood cultures for *L. monocytogenes*			<0·001*
Missing data	0 (0)	0 (0)	
No	82 (87·2)	12 (12·8)	
Yes	95 (60·1)	63 (39·9)	
Encephalitis††			0·003*
Missing data	0 (0)	0 (0)	
No	32 (91·4)	3 (8·6)	
Yes	145 (66·8)	72 (33·2)	
Number of neurological signs			0·285‡
Missing data	0 (0)	0 (0)	

Min/Max	0/8	0/8	
Med [Q1 ; Q3]	2 [1 ; 3]	2 [1·5 ; 3·5]	
Mean (sd)	2·32 (1·42)	2·55 (1·56)	
Nucleated cells number in the cerebrospinal fluid			0·387‡
Missing data	8 (4·5)	9 (12)	
Min/Max	0/12400	0/8484	
Med [Q1 ; Q3]	500 [200 ; 1150]	355 [128·75 ; 984]	
Mean (sd)	1108·43 (1868·68)	908·83 (1459·48)	
Polymorphonuclear cells number in the cerebrospinal fluid			0·303§
Missing data	11 (6·2)	10 (13·3)	
Min/Max	0/9520	0/7395	
Med [Q1 ; Q3]	265·5 [76·25 ; 795]	181 [56 ; 422]	
Mean (sd)	775·27 (1423·15)	658·71 (1244·65)	
Polymorphonuclear cells /all nucleated cells ratio			0·615‡
Missing data	12 (6·8)	11 (14·7)	
Min/Max	0/100	0/100	
Med [Q1 ; Q3]	64 [38 ; 84·1]	67·35 [42·62 ; 81·25]	
Mean (sd)	58·14 (29·18)	60·24 (27·86)	
Protein levels in the cerebrospinal fluid			0·011‡
Missing data	8 (4·5)	9 (12)	
Min/Max	0·3/8·9	0·4/20	
Med [Q1 ; Q3]	1·9 [1·3 ; 2·9]	2·6 [1·7 ; 3·98]	
Mean (sd)	2·32 (1·5)	3·47 (3·46)	
Cerebrospinal/blood glucose ratio			0·036§
Missing data	39 (22)	16 (21·3)	
Min/Max	0·01/1·4	0·02/0·97	
Med [Q1 ; Q3]	0·33 [0·23 ; 0·52]	0·27 [0·16 ; 0·45]	
Mean (sd)	0·39 (0·23)	0·34 (0·26)	
Treatment			
Time interval from diagnosis to treatment			0·121†
Missing data	1 (0·6)	0 (0)	
No treatment	0 (0)	1 (100)	
<0 d	34 (60·7)	22 (39·3)	
[0 ; 1] d	120 (73·2)	44 (26·8)	
>1 d	22 (73·3)	8 (26·7)	
Time interval from admission to treatment			0·373†
Missing data	1 (0·6)	0 (0)	
No treatment	0 (0)	1 (100)	
[0 ; 1] d	142 (70·6)	59 (29·4)	
>1 d	34 (69·4)	15 (30·6)	
Time interval from first symptom to treatment			0·025†
Missing data	2 (1·1)	7 (9·3)	
No treatment	0 (0)	1 (100)	
<0 d	2 (100)	0 (0)	
[0 ; 1] d	68 (64·8)	37 (35·2)	
>1 d	105 (77·8)	30 (22·2)	
Duration of bitherapy			
Anti-listeria betalactamin** + aminoglycoside			0·005*
Missing data	0 (0)	0 (0)	
0 d	29 (59·2)	20 (40·8)	
<= 3 d	27 (57·4)	20 (42·6)	
> 3 d	121 (77·6)	35 (22·4)	
Duration of bitherapy			
Cotrimoxazole + aminoglycoside			1†
Missing data	0 (0)	0 (0)	
0 d	163 (70·3)	69 (29·7)	
<= 3 d	10 (71·4)	4 (28·6)	
> 3 d	4 (66·7)	2 (33·3)	
Duration of tritherapy**			
Anti-listeria betalactam, cotrimoxazole and aminoglycoside			1†
Missing data	0 (0)	0 (0)	
0 d	164 (70·4)	69 (29·6)	
<= 3 d	9 (69·2)	4 (30·8)	
> 3 d	4 (66·7)	2 (33·3)	
Cotrimoxazole administration			0·196*
Missing data	0 (0)	0 (0)	
No	144 (68·6)	66 (31·4)	

Yes	33 (78·6)	9 (21·4)	
Aminoglycoside administration			0·076*
Missing data	0 (0)	0 (0)	
No	28 (59·6)	19 (40·4)	
Yes	149 (72·7)	56 (27·3)	
Anti-listeria betalactam administration[**]			0·053†
Missing data	0 (0)	0 (0)	
No	3 (37·5)	5 (62·5)	
Yes	174 (71·3)	70 (28·7)	
Adjunctive dexamethasone prescription			0·037†
Missing data	3 (1·7)	1 (1·3)	
No	157 (72·7)	59 (27·3)	
Yes	17 (53·1)	15 (46·9)	

D· Univariable analysis of persisting neurological impairment in neurolisteriosis cases

Characteristic	No, n = 102	Yes, n = 79	p-value
Socio-demographic parameters			
Sex			0·586*
Missing data	0 (0)	0 (0)	
Female	36 (53·7)	31 (46·3)	
Male	66 (57·9)	48 (42·1)	
Age at diagnostic			0·141‡
Missing data	0 (0)	0 (0)	
Min/Max	2·8/97·1	0·8/95·1	
Med [Q1 ; Q3]	65·9 [54·8 ; 75]	67·5 [59·4 ; 75·8]	
Mean (sd)	62·5 (18·6)	66·2 (15·4)	
Geographical origin			0·776†
Missing data	0 (0)	0 (0)	
Africa	6 (46·2)	7 (53·8)	
Other	3 (50)	3 (50)	
Europe	8 (50)	8 (50)	
France	85 (58·2)	61 (41·8)	
Past history			
At least one comorbidity[¶]			0·986*
Missing data	0 (0)	0 (0)	
No	13 (56·5)	10 (43·5)	
Yes	89 (56·3)	69 (43·7)	
At least one immunosuppressing comorbidity[‖]			0·244*
Missing data	0 (0)	0 (0)	
No	21 (65·6)	11 (34·4)	
Yes	81 (54·4)	68 (45·6)	
Past history of neoplasia or ongoing neoplasia			0·316*
Missing data	0 (0)	0 (0)	
No	85 (54·8)	70 (45·2)	
Yes	17 (65·4)	9 (34·6)	
Ongoing organ neoplasia			0·331*
Missing data	0 (0)	0 (0)	
No	93 (55·4)	75 (44·6)	
Yes	9 (69·2)	4 (30·8)	
Bone marrow transplantation			1†
Missing data	0 (0)	0 (0)	
No	102 (56·4)	79 (43·6)	
Yes	0 (NaN)	0 (NaN)	
Recent weight loss >5kgs			0·265*
Missing data	1 (1)	0 (0)	
No	82 (54·3)	69 (45·7)	
Yes	19 (65·5)	10 (34·5)	
Hemodialysis			0·319†
Missing data	0 (0)	0 (0)	
No	101 (57·1)	76 (42·9)	
Yes	1 (25)	3 (75)	
Clinical / Biological parameters			
Intensive care unit management			0·002*

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Missing data	0 (0)	0 (0)	
No	55 (69·6)	24 (30·4)	
Yes	47 (46·1)	55 (53·9)	
Multiorgan failure			0·012*
Missing data	0 (0)	0 (0)	
No	96 (59·6)	65 (40·4)	
Yes	6 (30)	14 (70)	
Aggravation of any pre existing organ dysfunction			0·461*
Missing data	0 (0)	0 (0)	
No	88 (57·5)	65 (42·5)	
Yes	14 (50)	14 (50)	
Systolic blood pressure < 80 mmHg			1†
Missing data	3 (2·9)	0 (0)	
No	98 (55·4)	79 (44·6)	
Yes	1 (100)	0 (0)	
Diastolic blood pressure < 60 mmHg			0·268*
Missing data	3 (2·9)	0 (0)	
No	88 (54·3)	74 (45·7)	
Yes	11 (68·8)	5 (31·2)	
Heart rate > 120/min			0·284*
Missing data	5 (4·9)	4 (5·1)	
No	90 (57·7)	66 (42·3)	
Yes	7 (43·8)	9 (56·2)	
Glasgow coma scale			0·043‡
Missing data	4 (3·9)	1 (1·3)	
Min/Max	3/15	3/15	
Med [Q1 ; Q3]	14 [12·25 ; 15]	13 [11 ; 14]	
Mean (sd)	13·02 (2·66)	12·12 (3·12)	
Diarrhoea			0·927*
Missing data	0 (0)	0 (0)	
No	86 (56·2)	67 (43·8)	
Yes	16 (57·1)	12 (42·9)	
Septic shock			0·319†
Missing data	0 (0)	0 (0)	
No	101 (57·1)	76 (42·9)	
Yes	1 (25)	3 (75)	
Flu-like symptoms			0·314*
Missing data	0 (0)	0 (0)	
No	73 (58·9)	51 (41·1)	
Yes	29 (50·9)	28 (49·1)	
Mechanical ventilation			0·001*
Missing data	0 (0)	0 (0)	
No	86 (63·2)	50 (36·8)	
Yes	16 (35·6)	29 (64·4)	
Hydrocephaly			0·035†
Missing data	0 (0)	0 (0)	
No	102 (57·6)	75 (42·4)	
Yes	0 (0)	4 (100)	
C-reactive protein level– mg/L			0·727‡
Missing data	8 (7·8)	6 (7·6)	
Min/Max	3/433	1/323	
Med [Q1 ; Q3]	82·5 [44·5 ; 168]	93 [33 ; 165]	
Mean (sd)	109·93 (88·28)	105·38 (79·2)	
Blood monocytes count < 200 /mm3			0·298*
Missing data	9 (8·8)	6 (7·6)	
No	88 (57·1)	66 (42·9)	
Yes	5 (41·7)	7 (58·3)	
Blood polymorphonuclear cells count– cells /mm3			0·896‡
Missing data	1 (1)	1 (1·3)	
Min/Max	450/34900	1031/29000	
Med [Q1 ; Q3]	9976 [6345 ; 13370]	9610 [6522·5 ; 12971·5]	
Mean (sd)	9984·3 (5692·3)	10089·9 (5112·3)	
Blood lymphocytes count <1500 /mm3			0·410*
Missing data	2 (2)	1 (1·3)	

No	23 (62·2)	14 (37·8)	
Yes	77 (54·6)	64 (45·4)	
Clonal complex			0·719*
Missing data	2 (2)	0 (0)	
Other	47 (57·3)	35 (42·7)	
CC1 2 4 or 6	53 (54·6)	44 (45·4)	
Positive blood cultures for *L. monocytogenes*			0·59*
Missing data	0 (0)	0 (0)	
No	48 (58·5)	34 (41·5)	
Yes	54 (54·5)	45 (45·5)	
Encephalitis[††]			<0·001*
Missing data	0 (0)	0 (0)	
No	31 (96·9)	1 (3·1)	
Yes	71 (47·7)	78 (52·3)	
Number of neurological signs			<0·001‡
Missing data	0 (0)	0 (0)	
Min/Max	0/6	1/8	
Med [Q1 ; Q3]	2 [1 ; 2]	3 [2 ; 3]	
Mean (sd)	1·9 (1·21)	2·96 (1·57)	
Nucleated cells number in the cerebrospinal fluid			0·567‡
Missing data	6 (5·9)	4 (5·1)	
Min/Max	0/12400	0/11825	
Med [Q1 ; Q3]	490 [200 ; 1108·5]	456 [162 ; 1125]	
Mean (sd)	1158·9 (2017·01)	998·13 (1646·38)	
Polymorphonuclear cells number in the cerebrospinal fluid			0·465§
Missing data	7 (6·9)	5 (6·3)	
Min/Max	0/9520	0/8375	
Med [Q1 ; Q3]	274 [89·5 ; 702·5]	212 [51 ; 795]	
Mean (sd)	809·17 (1520·32)	682·26 (1264·59)	
Polymorphonuclear cells /all nucleated cells ratio			0·246‡
Missing data	8 (7·8)	5 (6·3)	
Min/Max	0/100	0/95·1	
Med [Q1 ; Q3]	70 [40·33 ; 85·07]	58·95 [34·47 ; 80]	
Mean (sd)	60·43 (29·31)	55·24 (28·12)	
Protein levels in the cerebrospinal fluid			0·093‡
Missing data	6 (5·9)	4 (5·1)	
Min/Max	0·3/6	0·4/8·9	
Med [Q1 ; Q3]	1·8 [1·2 ; 2·8]	2·2 [1·4 ; 3·2]	
Mean (sd)	2·12 (1·28)	2·52 (1·71)	
Cerebrospinal/blood glucose ratio			0·935§
Missing data	25 (24·5)	16 (20·3)	
Min/Max	0·05/1·17	0·01/1·4	
Med [Q1 ; Q3]	0·33 [0·24 ; 0·51]	0·36 [0·22 ; 0·55]	
Mean (sd)	0·38 (0·21)	0·4 (0·27)	
Treatment			
Time interval from diagnosis to treatment			0·571[†]
Missing data	1 (1)	0 (0)	
<0 d	17 (50)	17 (50)	
[0 ; 1] d	68 (56·2)	53 (43·8)	
>1 d	16 (64)	9 (36)	
Time interval from admission to treatment			0·579[†]
Missing data	1 (1)	0 (0)	
[0 ; 1] d	82 (57·3)	61 (42·7)	
>1 d	19 (51·4)	18 (48·6)	
Time interval from first symptom to treatment			0·939[†]
Missing data	1 (1)	1 (1·3)	
<0 d	1 (50)	1 (50)	
[0 ; 1] d	38 (55·1)	31 (44·9)	
>1 d	62 (57·4)	46 (42·6)	
Duration of bitherapy			
Anti-listeria betalactamin + aminoglycoside**			0·678*
Missing data	0 (0)	0 (0)	
0 d	19 (61·3)	12 (38·7)	
<= 3 d	17 (60·7)	11 (39·3)	
> 3 d	66 (54·1)	56 (45·9)	
Duration of bitherapy			0·139[†]

Cotrimoxazole + aminoglycoside			
Missing data	0 (0)	0 (0)	
0 d	97 (58·4)	69 (41·6)	
<= 3 d	4 (40)	6 (60)	
> 3 d	1 (20)	4 (80)	
Duration of tritherapy**			
Anti-listeria betalactam, cotrimoxazole and aminoglycoside			0·185[†]
Missing data	0 (0)	0 (0)	
0 d	97 (58·1)	70 (41·9)	
<= 3 d	4 (44·4)	5 (55·6)	
> 3 d	1 (20)	4 (80)	
Cotrimoxazole administration			0·163*
Missing data	0 (0)	0 (0)	
No	87 (58·8)	61 (41·2)	
Yes	15 (45·5)	18 (54·5)	
Aminoglycoside administration			0·399*
Missing data	0 (0)	0 (0)	
No	19 (63·3)	11 (36·7)	
Yes	83 (55)	68 (45)	
Anti-listeria betalactam administration**			1[†]
Missing data	0 (0)	0 (0)	
No	2 (50)	2 (50)	
Yes	100 (56·5)	77 (43·5)	
Adjunctive dexamethasone prescription			1[†]
Missing data	2 (2)	2 (2·5)	
No	89 (56·3)	69 (43·7)	
Yes	11 (57·9)	8 (42·1)	

Table S5

Fetal loss in maternal-neonatal cases (N=107)		
Factors	Odds ratio (95%CI)*	p-value
Maternal urinary tract symptoms	4·73 (0·16-142·53)	0·371
Time interval from diagnosis to treatment (Reference = no treatment)		
< 0 day	9·73 (0·38-246·18)	0·168
[0; 1] day	1·03 (0·04-23·75)	0·984
> 1 day	2·99 (0·07-125·84)	0·566
Term at maternal diagnosis of listeriosis (Reference = [0,25WG))[†]		
[25,28WG)	0·58 (007-481)	0·610
[28,41WG]	0·01 (0-0·05)	<0·001

Titles and legends for supplemental tables

Table S1 Characteristics of the patients included and not included in the study

* Mortality data were those collected at 3-month for included patients and at the moment of screening for non-included patients.

† Mann-Whitney test.

‡ Age was evaluated in 22 patients.

§ Chi-squared test.

Table S2 Obstetrical and neonatal outcome of maternal-neonatal cases according to the term of pregnancy at diagnosis

* The study involved the 107 cases of maternal-neonatal infections, including 4 mothers with twin pregnancies, and the 82 neonates born alive. Values inside brackets denote interquartile range [25%; 75%].

† Abnormal delivery at term was defined as delivery with fever and/or meconium fluid and/or abnormal fetal heart rate.

‡ The neonates group included one pair of twins.

§ Neonates were considered healthy if they had normal examination at birth, C-reactive protein level <5mg/L, nucleated cells count in the cerebrospinal fluid ≤30/mm^3 (in case a lumbar puncture was performed) and all bacteriological samples negative.

Table S3 Detailed associated comorbidities of the study population

* Patients were: 427 cases with bacteremia, 252 cases with neurolisteriosis, 107 cases with maternal-neonatal infection, Plus-minus values are means ±SD.

† Chronic liver diseases were: alcoholic liver disease (n= 64), viral hepatitis C (n= 10), viral hepatitis B (n= 9), and other liver disease (n=31).

‡ Foreign materials or implants were: bone/joint prosthetic devices (n=54), cardiac valve/prosthetic arterial tubes (n= 61), pacemakers (n=37), central venous catheters (n= 53), other types of material (n=37) Patients could report more than one foreign material.

§ Solid organ transplantation involved the kidney (n=15) and the heart (n=5).

¶ Patients with HIV infection had a mean CD4$^+$cells count of 239/mm^3 (±214), 8 reported antiretroviral treatment, and 1 reported cotrimoxazole prophylaxis.

‖ Inflammatory bowel diseases include Crohn disease and hemorrhagic recto-colitis.

** Inflammatory rheumatic disorders included: rheumatoid arthritis, ankylosing spondylitis, polymyalgia rheumatic, psoriatic arthritis and other non-specified inflammatory rheumatic disorders.

Table S4 Univariable analyses of fetal loss in maternal cases, of 3-month death in bacteremia + neurolisteriosis cases, of 3-month death in neurolisteriosis cases, and of of persisting neurological impairment in neurolisteriosis cases.

* Chi-squared test.

† Fisher-exact test.

‡ Student's t-test.

§ Mann-Whitney test.

¶ Comorbidities included: chronic respiratory disease, hypertension, chronic heart disease, cardiopathy, thrombophilia, hemoglobinopathy, seizures, psychiatric disorder, atopy, renal insufficiency, chronic liver disease, foreign material or implant, recent major weight loss, daily alcohol uptake >3 glasses / day, cirrhosis, diabetes mellitus, end stage renal disease, solid organ cancer, hematological malignancy, hematopoietic stem cell transplantation, solid organ transplantation, asplenia, pre-existing neutropenia (neutrophils count <500/mm^3), pre-existing lymphopenia (lymphocytes count <1000/mm^3), HIV infection, inflammatory bowel diseases (Crohn disease and hemorrhagic recto-colitis), inflammatory rheumatic disorders (rheumatoid arthritis,

ankylosing spondylitis, polymyalgia rheumatic, psoriatic arthritis and other non-specified inflammatory rheumatic disorders), obesity, congenital immune deficiency, other auto-immune diseases, other comorbidity.

‖ Immunosuppressive comorbidities included: daily alcohol uptake >3 drinks/day, cirrhosis, diabetes mellitus, end-stage renal disease, solid organ cancer, hematological malignancy, hematopoietic stem cell transplantation, solid organ transplantation, asplenia, preexisting neutropenia, preexisting lymphopenia, HIV infection, inflammatory bowel diseases, inflammatory rheumatic disorders, other auto-immune diseases, congenital immune deficiency, age >70 years, prescription of corticosteroids or other immunosuppressive therapies in the last 5 years.

** Betalactams lacking activity towards *Listeria sp* were excluded: oxacillin and cephalosporins.

†† Encephalitis was defined by the presence of at least one of the following symptoms, with no alternative cause than listeriosis identified: altered consciousness (score on Glasgow Coma Scale <15), seizures, new onset of neurological symptoms and abnormality on electroencephalography consistent with encephalitis[1]

Table S5 Multivariable logistic regression analysis of factors associated with fetal loss for mothers with maternal infections (30 fetal loss out of 107 mothers).

* CI denotes confidence interval. Adjusted odds ratio were odds ratio calculated from the multivariable model after imputation of missing data.

† WG denotes weeks of gestation.

Titles and legends for supplemental figures

Figure S1 A Multilocus sequence typing of 812 isolates from patients with listeriosis B Distribution of hypervirulent, hypovirulent and intermediate virulence clones for each form of infection Tests are Chi-squared tests unless specified otherwise.

* All available isolates were analyzed.
† Fisher-exact test.

Figure S2 Biochemical and cellular features of the cerebrospinal fluid in the 235 patients with neurolisteriosis who had lumbar puncture performed. CSF denotes cerebrospinal fluid PMN denotes polymorphonuclear cells.

Figure S3 Inhibition zone diameters distribution of *Listeria monocytogenes* isolates with amoxicillin, cotrimoxazole and gentamicin.

Figure S4 Hierarchical clustering analysis of the patients with bacteremia and neurolisteriosis.

A Cluster dendrogram B Inertia gain C Factorial map resulting from the multiple correspondence analyses Each color denotes a specific cluster (cluster 1 in green, cluster 2 in yellow and cluster 3 in blue); triangles denote neurolisteriosis cases and crosses denote septicemia cases D Main characteristics of the clusters * This variable was not used for the classification.

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A. Multi Locus Sequence Typing results of the 812 *Listeria monocytogenes* isolates*

Clonal complexes (CC) – no. (%)	Maternal-neonatal isolates	Bacteremia isolates	Neurolisteriosis isolates	p-value	
				Neurolisteriosis vs. bacteremia cases	Maternal vs. non-maternal cases
	N=106	N=424	N=250		
Hypervirulent clones	**70 (66)**	**168 (40)**	**142 (57)**	<0·001	<0·001
CC1	22 (21)	59 (14)	59 (24)	0·001	0·565
CC6	18 (17)	49 (12)	32 (13)	0·632	0·154
CC4	22 (21)	25 (6)	35 (14)	<0·001	<0·001
CC2	8 (8)	35 (8)	16 (6)	0·379	0·994
Hypovirulent clones	**0 (0)**	**34 (8)**	**12 (5)**	0·109	0·006
CC9	0 (0)	19 (4)	4 (2)	0·047	0·060 [†]
CC121	0 (0)	15 (4)	8 (3)	0·816	0·060 [†]
Intermediate virulence clones	**36 (34)**	**222 (52)**	**96 (38)**	-	-
CC5	10 (9)	17 (4)	10 (4)	0·995	0·015
CC8	1 (1)	25 (6)	12 (5)	0·546	0·043
CC3	5 (5)	7 (2)	5 (2)	0·768**	0·068 [†]
CC37	0 (0)	18 (4)	3 (1)	0·028	0·098
CC101 + CC90	3 (3)	14 (3)	5 (2)	0·324	1 [†]
CC7	2 (2)	12 (3)	8 (3)	0·785	0·756 [†]
CC155	2 (2)	11 (3)	4 (2)	0·398	1 [†]
CC77	1 (1)	11 (3)	5 (2)	0·624	0·493 [†]
Other	12 (11)	107 (25)	44 (18)	0·022	0·009

B.

Legend:
- Hypovirulent clones
- Intermediate virulence clones
- Hypervirulent clones
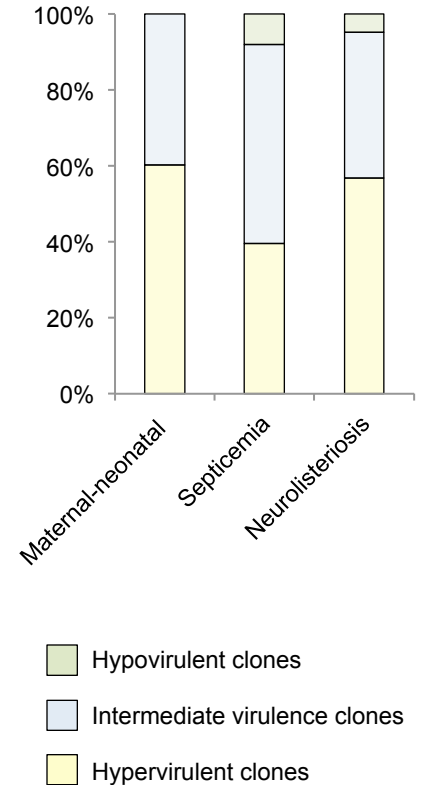
Figure S1

Figure S2

Figure S3

A.

B.

Inertia gain

C.

- Cluster 1
- Cluster 2
- Cluster 3
- + Neurological cases
- △ Bacteremia cases

Dim 2 (3.82%)

Dim 1 (4.94%)
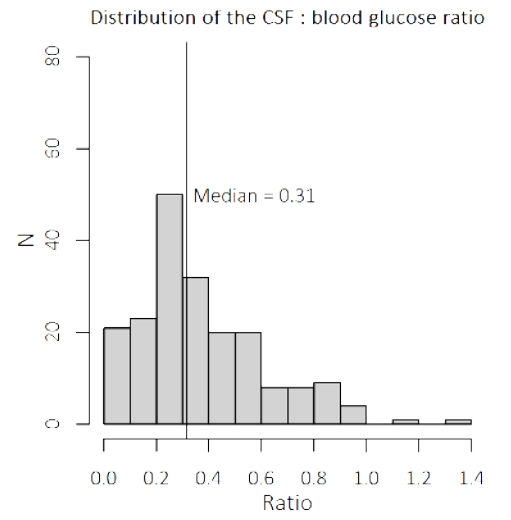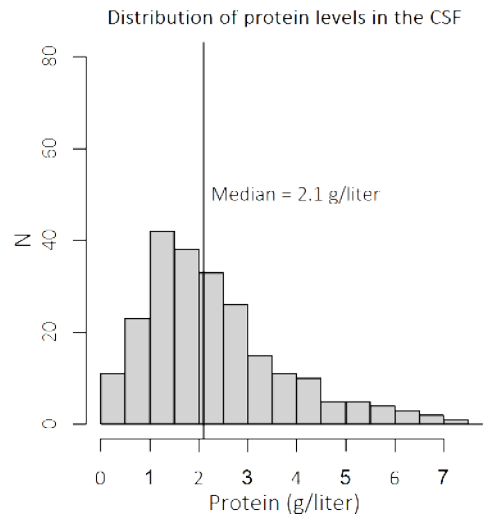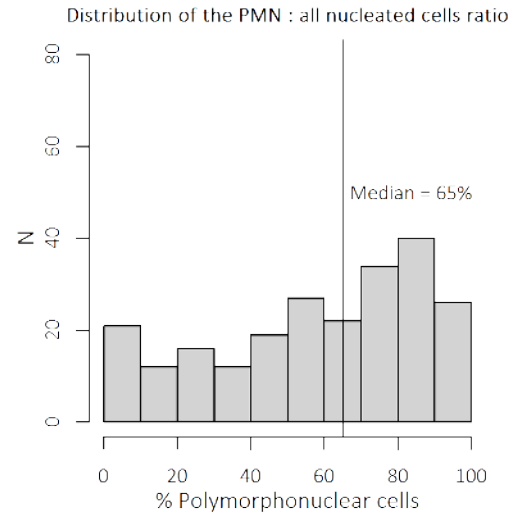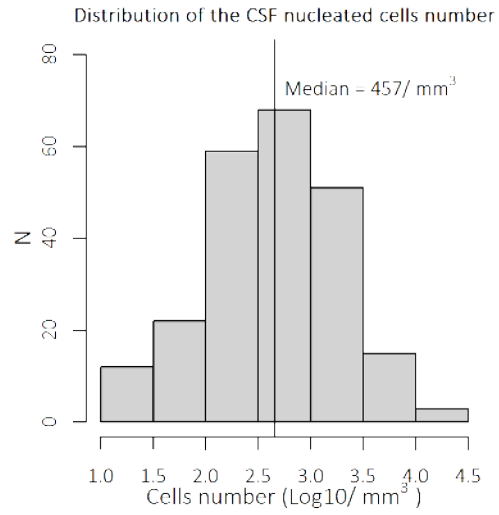
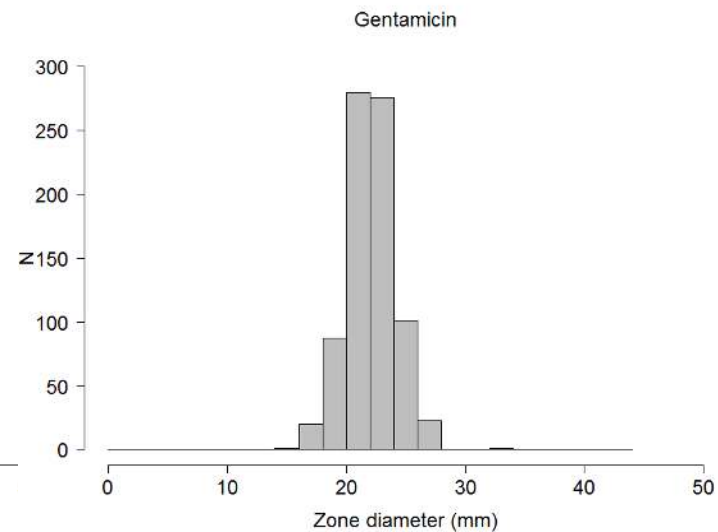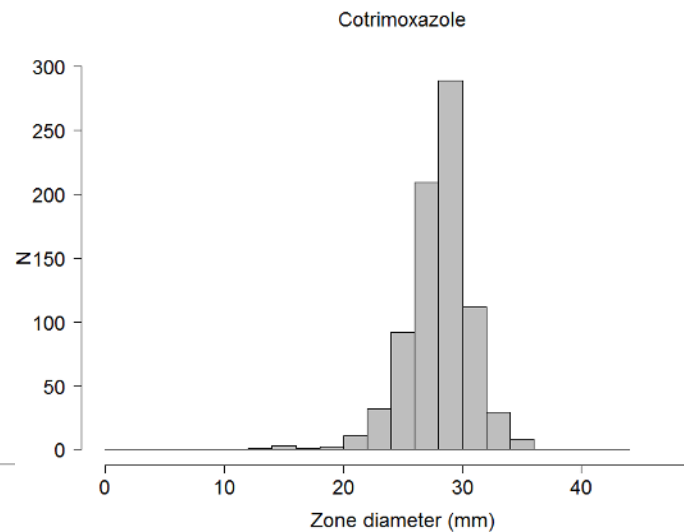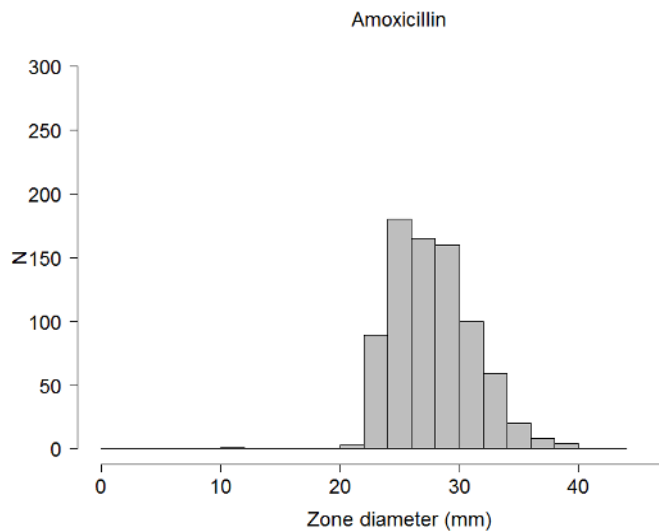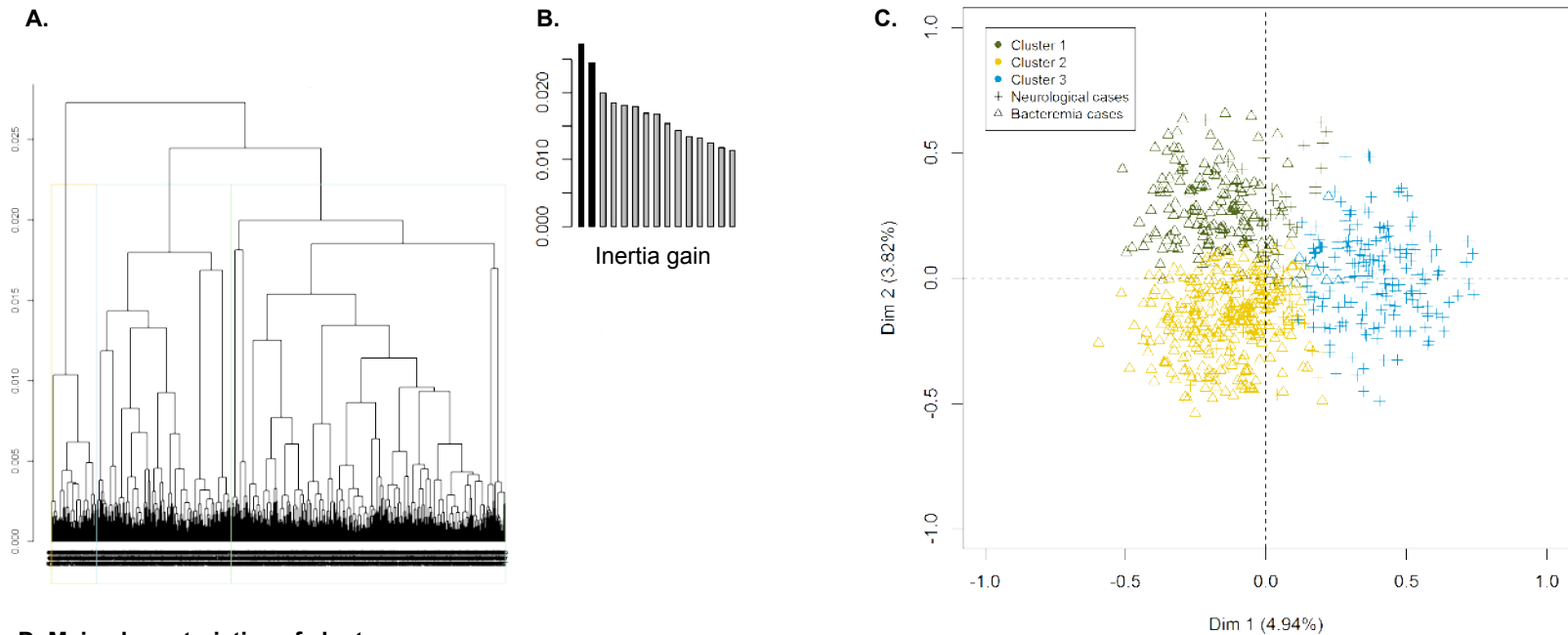**D. Main characteristics of clusters**

	Cluster 1 – no. (%) N=183	Cluster 2 – no. (%) N=314	Cluster 3 – no. (%) N=182
Form of infection*			
Bacteremia	146/183 (80%)	274/314 (87%)	7/182 (4%)
Neurolisteriosis	37/183 (20%)	40/314 (13%)	175/182 (96%)
Immunosuppressants	144/183 (79%)	26/314 (8%)	38/182 (21%)
Mean number of comorbidities*	3·6±1·9	3·7±2·0	2·6±2·0
Mean number of immunosuppressive comorbidities*	3·9±1·4	2·1±1·3	1·9±1·5
Mean age in years	68±12	76±13	64±18
Percentage of patients with age ≥80 years	0/183 (0%)	56/314 (18%)	10/182 (5%)
Positive blood cultures	177/183 (97%)	312/314 (99%)	96/182 (53%)
Strains			
Hypervirulent	59/182(32%)	137/312 (44%)	114/181 (63%)
Intermediate	99/182 (54%)	157/312 (50%)	62/181(34%)
Hypovirulent	24/182 (13%)	18/312 (6%)	4/181 (2%)

Figure S4