Predictors of mortality and impact of aminoglycosides on outcome in listeriosis in a retrospective cohort study

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Objectives: Gentamicin is often used to treat listeriosis, particularly in patients with meningitis; nonetheless, some clinicians question this practice because of the drug’s associated nephrotoxicity and inability to cross the blood–brain barrier. The aim of this study was to evaluate predictors of mortality and the impact of aminoglycosides on outcome in patients with listeriosis.

Methods: We conducted a retrospective study of all non-pregnant adult patients with Listeria monocytogenes infection detected in sterile body fluids between 1983 and 2006. Early mortality was defined as death occurring between days 3 and 14 after admission, and late mortality as in-hospital death after 14 days.

Results: Of 118 episodes, 16 were excluded because patients died in the first 48 h. Among the 102 patients analysed, 33 (32%) had received combined β-lactam and aminoglycoside therapy and 69 (68%) β-lactam monotherapy. Both groups had similar demographic and clinical features, and rate of appropriate initial therapy. Overall mortality was 21/102 (20.6%). Early overall mortality was 11.8%: 27.3% (9/33) in the combined group and 4.3% (3/69) in the monotherapy group (P = 0.003). Late mortality was 8.8%. In the multivariate analysis, the factors predicting early mortality were renal failure, previous corticosteroid therapy and age > 65 years, whereas neoplastic disease and coma were associated with late mortality. Gentamicin administration did not decrease early mortality, but seemed to increase it. In the late mortality analysis, gentamicin use had no impact. In an analysis with the propensity score method for the use of aminoglycosides, combined therapy with this antibiotic was associated with an increasing trend for early mortality (OR 3.40, 95% CI 0.82–14.07).

Conclusions: The addition of aminoglycosides to treatment for listeriosis did not improve the patients’ outcome.

Keywords: Listeria monocytogenes, treatment, mortality risk factors

Introduction

The penicillins, mainly ampicillin and sodium G penicillin, are considered the treatment of choice for listeriosis.1–8 The β-lactams are bacteriostatic against Listeria monocytogenes, and in vitro studies have shown synergy and a bactericidal effect when gentamicin is added.9–12 A β-lactam combined with gentamicin is the preferred treatment for Listeria infection in clinical practice, particularly for meningitis caused by this pathogen.1–8 Nonetheless, some authors question the value of adding an aminoglycoside to therapy for listeriosis because these drugs are unable to cross the blood–brain barrier12,13 and animal models have shown conflicting results with regard to synergy.4,13,14 In addition, our experience has shown that a quarter of non-pregnant adults affected by listeriosis have renal failure and a higher percentage have an elevated risk of developing it, such as older patients and those with cirrhosis or diabetes, in whom addition of an aminoglycoside could be more harmful than beneficial.15–23

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Because there have been no controlled trials to establish the antibiotic of choice and duration of therapy for listeriosis, current treatment is based on the patient’s clinical condition and the criteria of the attending physician. This study evaluates the effect on mortality of adding gentamicin to β-lactam treatment in patients with listeriosis.

Materials and methods

Patients and setting

We conducted a retrospective study of all non-pregnant adult patients with infection by *L. monocytogenes*, confirmed by culture of blood, CSF or other sterile body fluids, between January 1983 and December 2006 in the Vall d’Hebron University Hospital, a 1250 bed tertiary referral centre. During the study period, all patients were evaluated by staff members of the Department of Infectious Diseases. Approval by an ethics committee was not deemed necessary for this retrospective analysis.

Data collection

We analysed demographic data (age and sex), underlying medical illnesses, place of acquisition (hospital or community), duration of symptoms, clinical presentation, level of consciousness, serotype of the isolated strain, leucocyte count, type of infection (isolated bacteremia, CNS infection and extracranial focal infection), empirical and definite antibiotic treatment, outcome, and death related to the listeriosis episode.

Definitions

The diagnosis of CNS disease was established on clinical criteria (fever, headache, altered consciousness, focal neurological deficit or convulsions), pleocytosis in CSF (>5 leucocytes/mm³) and/or evidence of cerebral parenchyma involvement on neuroimaging. Lumbar puncture was not performed systematically in patients with no neurological manifestations or neuroimaging alterations.

We classified as hospital-acquired bacteremia all cases for which cultures were positive in samples obtained ≥72 h after admission. Systemic corticosteroid treatment was defined as administration of >15 mg/day of prednisone or an equivalent dose of another corticosteroid for >15 days in the previous 3 months. Renal failure was defined as a creatinine level >1.5 mg/dL in the initial blood analysis. A score on the Glasgow scale of <14 was used to define impaired consciousness and a score below eight to define coma.

Intravenous administration of penicillin, ampicillin, amoxicillin/clavulanic acid, piperacillin/tazobactam, a carbapenem or co-trimoxazole was considered adequate empirical treatment. None of the patients received other active drugs, such as moxifloxacin, linezolid or gentamicin alone. Combined treatment was defined as empirical administration of an adequate antilisterial agent (as defined above) and gentamicin from the beginning, or addition of gentamicin after receiving the culture results, with administration for ≥7 days. Monotherapy was defined as administration of a β-lactam having antilisterial activity alone.

In-hospital mortality was defined as death from any cause during hospitalization. Early mortality was defined as death occurring 3–14 days after admission and late mortality as death occurring after day 14. Patients who died on days 1 and 2 were excluded, as deaths occurring this early are unlikely to be related to the treatment modality. The rationale for differentiating between early and late death was that in the early period antibiotic therapy could be an overwhelming factor influencing mortality, whereas after 14 days other factors, such as the presence or severity of the underlying disease or neurological sequelae (e.g. aspirative pneumonia), could have more relevance and thus the impact of antibiotic therapy on late mortality is difficult to analyse.

Statistical analysis

The primary objective of our study was to analyse differences in mortality between patients who received monotherapy with active β-lactam antibiotics and those who received combined treatment with an aminoglycoside. The secondary objective was to analyse the prognostic factors for death in these patients.

Univariate analyses of variables from the total patient population were performed using the χ² test for categorical data, and the t-test or Mann–Whitney U-test for continuous data. Prognostic factors for early mortality were analysed by logistic regression, which included the following variables: renal failure; age >65 years; nosocomial acquisition; corticosteroid treatment; coma; adequate empirical treatment; and combined therapy. Owing to the limited sample size, a propensity score method was applied to assess differences in mortality related to gentamicin use. For each case, the estimated probability of receiving gentamicin was calculated from a logistic regression model that predicted establishment of gentamicin treatment based on the following variables: age; sex; in-hospital acquisition; cirrhosis; diabetes mellitus; corticosteroid treatment; solid neoplasm; haematological neoplasm; renal failure; coma; neurological symptoms; and CNS involvement. Quintiles from these probabilities were used to stratify the two cohorts (one that had received gentamicin and the other that had not) and estimate the risk of death associated with gentamicin. Prognostic factors for late mortality were also analysed by logistic regression analysis, which included the variables: age >65 years; sex; coma; combined therapy with gentamicin; solid neoplasm; and haematological neoplasm. All multivariate logistic analyses were done using Firth’s method to overcome problems of separation in small samples. Data were analysed using SAS 9.1.3 (SAS Institute Inc., Cary, NC, USA) and SPSS 14.0 (SPSS Inc., Chicago, IL, USA).

Results

In the 24 year period studied, 118 episodes of listeriosis were identified. Sixteen patients were excluded from the analysis because they died on days 1 or 2. Among the 16 who were excluded, 12 had not received any antibiotic therapy or had been treated with an antibiotic that was inactive against *L. monocytogenes* (including four treated with cephalosporins), two had received combined treatment with a β-lactam with antilisterial activity and gentamicin, and two were given an active β-lactam monotherapy without gentamicin. Ultimately, a total of 102 patients were analysed, 33 (32%) who had received combined therapy with β-lactams and aminoglycosides and 69 (68%) who had received monotherapy.

Predisposing factors and clinical data

The mean age (standard deviation) was 57 (19) years and 44.1% of patients were older than 65 years. Predisposing conditions were present in 82 (80.4%) patients; liver cirrhosis (26.5%), immunosuppression by corticosteroids (32.4%) and malignant disease (32.4%) were the most common underlying conditions
It is noteworthy that almost a quarter (23.5%) of the patients had renal failure. The demographic data and clinical presentation of 102 patients with listeriosis are shown in Table 1. Nearly half the patients had primary bacteraemia, 44 (43.1%) had CNS involvement (75.0% with associated bacteraemia) and nine (8.8%) had focal extracranial infection. Of the 44 patients with CNS infection, 34 (77.3%) had neck stiffness and 17 (39%) focal neurological deficits (10 cranial nerve involvement and nine hemiparesis). Furthermore, 10 (22.7%) of the patients with CNS involvement had focal cerebral infection (six rhombencephalitis and four cerebral abscesses).

There were no differences between the combined therapy group and monotherapy group in CSF parameters, performed in 56 cases: median (interquartile range; IQR) WBC count [365 (109.75–772.50) versus 97 (1.75–574.50) cells/mL, \(P = 0.17\)]; mean protein level (165 ± 154 versus 222 ± 218 mg/dL, \(P = 0.45\)); presence of hypoglycorrachia [10/12 (83%) versus 22/34 (64.7%), \(P = 0.29\)]; and positive CSF culture [10/12 (83.3%) versus 16/38 (42.1%), \(P = 0.39\)]. Cranial CT scanning, performed in 42 patients, was normal in 80% of cases. Magnetic resonance imaging showed focal cerebral infection in 10 (76.9%) of 13 cases.

Of the 102 patients evaluated, 49 (48%) initially received an inappropriate antibiotic (Table 2); 57.6% (19/33) in the combined therapy group and 43.4% (30/69) in the monotherapy group (\(P = 0.208\)). Combined \(\beta\)-lactam plus aminoglycoside therapy was used initially in 13 patients and, after receiving the culture result, in 20 more cases [33 (32.4%) in total]. A decrease in the use of aminoglycosides was observed in the last years of the study: before 2000, aminoglycosides were given to 28 of 64 patients (43.8%) and after this date to only 5 of 38 patients (13.2%) (Table 1). The percentage of cirrhotic patients in the combined therapy and monotherapy groups was similar (24.2% versus 27.5%, \(P = 0.72\)), as was the percentage of patients with renal failure (27.3% versus 21.7%, \(P = 0.72\)).

Table 1. Demographic data and clinical presentation of 102 patients with infection by L. monocytogenes

<table>
<thead>
<tr>
<th>Age (average ± SD)</th>
<th>Combined therapy (n=33)</th>
<th>Monotherapy (n=69)</th>
<th>OR (95% CI)</th>
<th>(P) value</th>
</tr>
</thead>
<tbody>
<tr>
<td>56.9 ± 17.9</td>
<td>58.6 ± 19.9</td>
<td>0.99 (0.97–1.01)</td>
<td>0.67</td>
<td></td>
</tr>
<tr>
<td>Over 65 years old 11 (33.3%)</td>
<td>34 (49.3%)</td>
<td>0.51 (0.21–1.22)</td>
<td>0.132</td>
<td></td>
</tr>
<tr>
<td>Sex male 22 (66.6%)</td>
<td>37 (53.6%)</td>
<td>1.73 (0.72–4.10)</td>
<td>0.21</td>
<td></td>
</tr>
<tr>
<td>Diagnosis before year 2000 28 (84.8%)</td>
<td>36 (52.2%)</td>
<td>5.13 (1.77–14.85)</td>
<td>0.003</td>
<td></td>
</tr>
<tr>
<td>Predisposing factors 29 (87.8%)</td>
<td>53 (76.8%)</td>
<td>2.18 (0.66–7.16)</td>
<td>0.19</td>
<td></td>
</tr>
<tr>
<td>corticosteroids 19 (57.6%)</td>
<td>14 (20.3%)</td>
<td>5.33 (2.15–13.19)</td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>liver cirrhosis 8 (24.2%)</td>
<td>19 (27.5%)</td>
<td>0.84 (0.32–2.18)</td>
<td>0.72</td>
<td></td>
</tr>
<tr>
<td>underlying malignancy 12 (36.4%)</td>
<td>21 (30.4%)</td>
<td>1.30 (0.54–3.13)</td>
<td>0.55</td>
<td></td>
</tr>
<tr>
<td>HIV infection 0 (0%)</td>
<td>3 (4.3%)</td>
<td>0 (0–5.1)</td>
<td>0.55</td>
<td></td>
</tr>
<tr>
<td>diabetes mellitus 11 (33.3%)</td>
<td>8 (11.6%)</td>
<td>3.81 (1.35–10.71)</td>
<td>0.01</td>
<td></td>
</tr>
<tr>
<td>Renal failure 9 (27.3%)</td>
<td>15 (21.7%)</td>
<td>1.35 (0.51–3.51)</td>
<td>0.53</td>
<td></td>
</tr>
<tr>
<td>Duration of symptoms (days) (average ± SD) 3.06 ± 4.0</td>
<td>3.14 ± 2.9</td>
<td>0.99 (0.87–1.12)</td>
<td>0.90</td>
<td></td>
</tr>
<tr>
<td>Hospital-acquired 13 (39.4%)</td>
<td>18 (26.0%)</td>
<td>1.84 (0.76–4.44)</td>
<td>0.17</td>
<td></td>
</tr>
<tr>
<td>Clinical data</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>fever</td>
<td>33 (100%)</td>
<td>62 (89.9%)</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>neck stiffness</td>
<td>12 (36.4%)</td>
<td>22 (31.9%)</td>
<td>1.22 (0.51–2.91)</td>
<td>0.65</td>
</tr>
<tr>
<td>focal neurological deficits(a)</td>
<td>6 (18.2%)</td>
<td>11 (15.9%)</td>
<td>1.17 (0.39–3.50)</td>
<td>0.77</td>
</tr>
<tr>
<td>impaired consciousness</td>
<td>12 (36.4%)</td>
<td>20 (29.0%)</td>
<td>1.40 (0.58–3.37)</td>
<td>0.45</td>
</tr>
<tr>
<td>coma</td>
<td>7 (21.2%)</td>
<td>4 (5.7%)</td>
<td>4.37 (1.18–16.21)</td>
<td>0.027</td>
</tr>
<tr>
<td>Type of infection</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>primary bacteraemia</td>
<td>14 (42.4%)</td>
<td>35 (50.7%)</td>
<td>0.71 (0.31–1.65)</td>
<td>0.43</td>
</tr>
<tr>
<td>CNS involvement</td>
<td>17 (51.5%)</td>
<td>27 (39.1%)</td>
<td>1.65 (0.71–3.81)</td>
<td>0.23</td>
</tr>
<tr>
<td>focal extracranial(b)</td>
<td>2 (6.1%)</td>
<td>7 (10.1%)</td>
<td>0.57 (0.11–2.91)</td>
<td>0.57</td>
</tr>
<tr>
<td>Laboratory data</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>positive blood culture</td>
<td>30/30 (100%)</td>
<td>56/63 (88.9%)</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>serotype 4b</td>
<td>22/27 (81.5%)</td>
<td>42/55 (76.3%)</td>
<td>1.36 (0.43–4.31)</td>
<td>0.60</td>
</tr>
<tr>
<td>Mortality</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>overall mortality</td>
<td>11 (33.3%)</td>
<td>10 (14.5%)</td>
<td>2.95 (1.10–7.91)</td>
<td>0.03</td>
</tr>
<tr>
<td>early mortality</td>
<td>9 (27.3%)</td>
<td>3 (4.3%)</td>
<td>8.25 (2.06–33.04)</td>
<td>0.003</td>
</tr>
<tr>
<td>late mortality</td>
<td>2 (8.3%)</td>
<td>7 (10.6%)</td>
<td>1.30 (0.25–6.76)</td>
<td>0.75</td>
</tr>
</tbody>
</table>

OR, odds ratio. Combined therapy, \(\beta\)-lactam with antilisterial activity + aminoglycosides; monotherapy, \(\beta\)-lactam with antilisterial activity.

\(a\)Includes 10 cases of cranial nerve affection, nine of hemiparesis, three of ataxia and one of aphasia.

\(b\)Includes five bacterial peritonitis, one arthritis and three intravascular infections (one endocarditis, one myocardial and one abdominal aortic aneurysm).
Mortality prediction and aminoglycosides in listeriosis

Table 2. Empirical antibiotic treatment in 102 evaluable patients with L. monocytogenes infection

<table>
<thead>
<tr>
<th></th>
<th>Total (n=102)</th>
<th>Combined therapy (n=33)</th>
<th>Monotherapy (n=69)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Active antibiotic</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ampicillin</td>
<td>53 (51.9%)</td>
<td>14 (42.4%)</td>
<td>39 (56.5%)</td>
</tr>
<tr>
<td>ampicillin/gentamicin</td>
<td>10 (9.8%)</td>
<td>0 (0%)</td>
<td>10 (14.4%)</td>
</tr>
<tr>
<td>ampicillin/cephalosporin</td>
<td>13 (12.7%)</td>
<td>13 (39.4%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>amoxicillin/clavulanate</td>
<td>10 (9.8%)</td>
<td>0 (0%)</td>
<td>10 (14.4%)</td>
</tr>
<tr>
<td>other antibiotic</td>
<td>16 (15.6%)</td>
<td>1 (3%)</td>
<td>15 (21.7%)</td>
</tr>
<tr>
<td></td>
<td>4 (3.9%)</td>
<td>0 (0%)</td>
<td>4 (5.7%)</td>
</tr>
<tr>
<td>Non-adequate treatment</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>cephalosporin</td>
<td>49 (48.0%)</td>
<td>19 (57.6%)</td>
<td>30 (43.4%)</td>
</tr>
<tr>
<td>other</td>
<td>29 (28.4%)</td>
<td>14 (42.4%)</td>
<td>15 (21.7%)</td>
</tr>
<tr>
<td></td>
<td>6 (5.8%)</td>
<td>1 (3%)</td>
<td>5 (7.2%)</td>
</tr>
<tr>
<td>none</td>
<td>14 (13.7%)</td>
<td>4 (12%)</td>
<td>10 (14.4%)</td>
</tr>
</tbody>
</table>

*Two cases were treated with carbapenems and two with piperacillin/tazobactam.
*Ampicillin/clavulanate (500/125 mg) every 8 h orally.
*Three cases were treated with amoxicillin/clavulanate (500/125 mg) orally, one with erythromycin orally and one with clindamycin orally.

Outcome

Overall, 21 (20.6%) of 102 patients died after ≥48 h of hospitalization (Table 1). Twelve (11.8%) died within 14 days (early mortality), including 27.3% (9/33) in the combined β-lactam/aminoglycoside group and 4.3% (3/69) in the monotherapy group [odds ratio (OR) 8.25, 95% confidence interval (CI) 2.06–33.4]. Early mortality in the 44 cases with CNS involvement was 5/17 (29.4%) in the combination therapy group and 1/27 (3.7%) in the monotherapy group (OR 10.8, 95% CI 1.13–103.1). In patients with isolated bacteraemia, early mortality was 27 (3.7%) in the monotherapy group (OR 10.8, 95% CI 1.13–33.04). Early mortality in the 44 cases with CNS involvement was 5/17 (29.4%) in the combination therapy group and 1/27 (3.7%) in the monotherapy group (OR 10.8, 95% CI 1.13–103.1). In patients with isolated bacteraemia, early mortality was 27 (3.7%) in the monotherapy group (OR 10.8, 95% CI 1.13–33.04).

Nine patients (8.8%) died after 14 days, all after having completed L. monocytogenes therapy. There were two deaths from fulminant Pseudomonas aeruginosa sepsis related to neutropenia due to haematological disease; one from disseminated aspergillosis in a lung transplant recipient; one from neoplastic colon perforation; two from bleeding oesophageal varices in liver cirrhosis patients; two from disseminated neoplastic disease; and one from aspirative pneumonia in a patient with neurological sequelae due to L. monocytogenes meningitis.

Predictors of outcome

On univariate analysis, numerous factors were found to be significantly associated with early mortality due to L. monocytogenes (Table 3): hospital-acquired infection; previous corticosteroid therapy; renal failure; coma; and combined therapy with aminoglycosides. Administration of an adequate empirical antibiotic treatment had a tendency to be a protective factor.

On multivariate analysis (Table 3), the independent risk factors predicting early mortality were renal failure (OR 4.88, 95% CI 1.04–23.0), age >65 years (OR 12.2, 95% CI 1.62–91.8) and previous corticosteroid therapy (OR 5.89, 95% CI 1.04–33.4). Combined antimicrobial therapy with gentamicin OR 3.90, (95% CI 0.78–19.4), coma and hospital-acquired infection were also associated with a poor prognosis, although they did not reach statistical significance. Again, empirical administration of an adequate antibiotic treatment showed a tendency to be a protective factor.

The model used to estimate the propensity score for gentamicin administration showed a good predictive capacity (c=0.835). When this score was used to adjust the analysis, mortality was higher in patients with the combination of β-lactam therapy and aminoglycosides than in those with β-lactam monotherapy, although the results did not reach significance (OR 3.40, 95% CI 0.82–14.07).

Table 4 shows the univariate and multivariate predictors associated with late mortality. Neoplastic disease and coma were the only factors independently associated with late mortality.

Discussion

Mortality remains high in L. monocytogenes infection, although it has decreased over recent years, with a reported range of 16%–38%.8,15,20–23,25,26 In the present study, the factors predicting early mortality were renal failure, previous corticosteroid therapy and age >65 years, and those predicting late mortality were neoplastic disease and coma. Gentamicin administration did not result in a decrease in early mortality, but conversely seemed to increase these deaths. In the late mortality analysis, gentamicin use had no impact. Since the treatment modality is expected to influence early mortality, our discussion will focus on this period.

Overall mortality was 31.4% (37/118). Late mortality was related to the underlying diseases or their complications; hence, mortality attributable to L. monocytogenes (fulminant and early deaths) was 23.7% (28/118). This figure includes 12.2% in patients diagnosed after 2000, an evident decrease from the 33% mortality reported in our previous study period of 1983–91.27 Although several factors that are difficult to analyse in retrospective studies may have been implicated in this decrease, two changes in our hospital antibiotic policy could have had an effect on mortality in these patients. First, in 1993, guidelines for treating most common infectious diseases, including therapy for patients with CNS infection, were established in our infectious disease department. In patients with meningitis and risk factors for Listeria infection (elderly, immunosuppressive therapy, etc.) ampicillin was empirically added to a third-generation cephalosporin. Second, in the first period a second- or third-generation cephalosporin was recommended for patients with suspected...
Table 3. Association between characteristics of patients and *L. monocytogenes* early mortality

<table>
<thead>
<tr>
<th>Variable</th>
<th>Patients who died (n=12)</th>
<th>Patients who survived (n=90)</th>
<th>Univariate analysis</th>
<th></th>
<th>Multivariate analysis</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>OR (95% CI)</td>
<td>P value</td>
<td>OR (95% CI)</td>
<td>P value</td>
</tr>
<tr>
<td>Demographic data</td>
<td></td>
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<td></td>
</tr>
<tr>
<td>over 65 years old</td>
<td>7 (58.3%)</td>
<td>38 (42.2%)</td>
<td>1.91 (0.56–6.49)</td>
<td>0.29</td>
<td>12.2 (1.62–91.8)</td>
<td>0.015</td>
</tr>
<tr>
<td>sex, male</td>
<td>9 (75%)</td>
<td>50 (55.5%)</td>
<td>2.4 (0.60–9.45)</td>
<td>0.21</td>
<td></td>
<td></td>
</tr>
<tr>
<td>diagnosis before 2000</td>
<td>10 (83.3%)</td>
<td>54 (60%)</td>
<td>3.33 (0.69–16.11)</td>
<td>0.13</td>
<td></td>
<td></td>
</tr>
<tr>
<td>hospital-acquired</td>
<td>7 (58.3%)</td>
<td>24 (26.7%)</td>
<td>3.85 (1.11–13.29)</td>
<td>0.03</td>
<td>4.15 (0.69–25.1)</td>
<td>0.122</td>
</tr>
<tr>
<td>Clinical data</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>predisposing factors</td>
<td>11 (91.7%)</td>
<td>71 (78.9%)</td>
<td>2.94 (0.35–24.25)</td>
<td>0.31</td>
<td></td>
<td></td>
</tr>
<tr>
<td>neoplastic disease</td>
<td>4 (33.3%)</td>
<td>29 (32.2%)</td>
<td>1.05 (0.29–3.77)</td>
<td>0.93</td>
<td></td>
<td></td>
</tr>
<tr>
<td>corticosteroids</td>
<td>9 (75%)</td>
<td>24 (26.7%)</td>
<td>8.25 (2.06–33.0)</td>
<td>0.003</td>
<td>5.89 (1.04–33.4)</td>
<td>0.045</td>
</tr>
<tr>
<td>liver cirrhosis</td>
<td>2 (16.7%)</td>
<td>25 (27.8%)</td>
<td>0.52 (0.10–2.54)</td>
<td>0.41</td>
<td></td>
<td></td>
</tr>
<tr>
<td>renal failure</td>
<td>6 (50%)</td>
<td>18 (20%)</td>
<td>4.0 (1.15–13.87)</td>
<td>0.029</td>
<td>4.88 (1.04–23.0)</td>
<td>0.045</td>
</tr>
<tr>
<td>CNS infection</td>
<td>6 (50%)</td>
<td>38 (42.2%)</td>
<td>1.36 (0.41–4.57)</td>
<td>0.61</td>
<td></td>
<td></td>
</tr>
<tr>
<td>coma</td>
<td>4 (33.3%)</td>
<td>7 (7.8%)</td>
<td>5.92 (1.42–24.69)</td>
<td>0.01</td>
<td>5.31 (0.85–33.1)</td>
<td>0.073</td>
</tr>
<tr>
<td>Laboratory data</td>
<td></td>
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<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>serotype 4b</td>
<td>8 (88.9%)</td>
<td>56 (76.7%)</td>
<td>2.42 (0.28–20.81)</td>
<td>0.41</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Treatment</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>adequate empirical treatment</td>
<td>3 (25%)</td>
<td>50 (55.6%)</td>
<td>0.26 (0.06–1.05)</td>
<td>0.06</td>
<td>0.45 (0.09–2.20)</td>
<td>0.321</td>
</tr>
<tr>
<td>combined therapy</td>
<td>9 (75%)</td>
<td>24 (26.7%)</td>
<td>8.25 (2.06–33.04)</td>
<td>0.003</td>
<td>3.90 (0.78–19.4)</td>
<td>0.096</td>
</tr>
</tbody>
</table>

A P value <0.05 was considered to be statistically significant.

Table 4. Association between characteristics of patients and *L. monocytogenes* late mortality

<table>
<thead>
<tr>
<th>Variable</th>
<th>Patients who died (n=9)</th>
<th>Patients who survived (n=81)</th>
<th>Univariate analysis</th>
<th></th>
<th>Multivariate analysis</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>OR (95% CI)</td>
<td>P value</td>
<td>OR (95% CI)</td>
<td>P value</td>
</tr>
<tr>
<td>Demographic data</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>over 65 years old</td>
<td>4 (44.4%)</td>
<td>34 (42.0%)</td>
<td>1.10 (0.27–4.42)</td>
<td>0.88</td>
<td>0.62 (0.15–2.55)</td>
<td>0.50</td>
</tr>
<tr>
<td>sex, male</td>
<td>6 (6.7%)</td>
<td>44 (54.3%)</td>
<td>1.16 (0.39–7.19)</td>
<td>0.48</td>
<td>0.70 (0.17–2.90)</td>
<td>0.62</td>
</tr>
<tr>
<td>diagnosis before year 2000</td>
<td>5 (55.6%)</td>
<td>49 (60.5%)</td>
<td>1.22 (0.30–4.90)</td>
<td>0.77</td>
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</tr>
<tr>
<td>hospital-acquired</td>
<td>3 (33.3%)</td>
<td>21 (25.9%)</td>
<td>1.42 (0.32–6.22)</td>
<td>0.63</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Clinical data</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>predisposing factors</td>
<td>8 (88.9%)</td>
<td>63 (77.8%)</td>
<td>2.28 (0.26–19.50)</td>
<td>0.45</td>
<td></td>
<td></td>
</tr>
<tr>
<td>neoplastic disease</td>
<td>6 (66.7%)</td>
<td>23 (28.4%)</td>
<td>5.04 (1.16–21.88)</td>
<td>0.03</td>
<td>10.57 (1.74–64.09)</td>
<td>0.01</td>
</tr>
<tr>
<td>solid neoplasia</td>
<td>2 (22.2%)</td>
<td>11 (13.6%)</td>
<td>1.81 (0.33–9.90)</td>
<td>0.48</td>
<td></td>
<td></td>
</tr>
<tr>
<td>haematological neoplasia</td>
<td>4 (44.4%)</td>
<td>12 (14.8%)</td>
<td>4.60 (1.07–19.62)</td>
<td>0.04</td>
<td></td>
<td></td>
</tr>
<tr>
<td>corticosteroids</td>
<td>3 (33.3%)</td>
<td>21 (25.9%)</td>
<td>1.42 (0.32–6.22)</td>
<td>0.63</td>
<td></td>
<td></td>
</tr>
<tr>
<td>liver cirrhosis</td>
<td>1 (11.1%)</td>
<td>24 (29.6%)</td>
<td>0.29 (0.03–2.50)</td>
<td>0.26</td>
<td></td>
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</tr>
<tr>
<td>renal failure</td>
<td>1 (11.1%)</td>
<td>17 (20.9%)</td>
<td>0.47 (0.05–4.02)</td>
<td>0.49</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CNS infection</td>
<td>2 (22.2%)</td>
<td>36 (44.4%)</td>
<td>0.35 (0.07–1.82)</td>
<td>0.21</td>
<td></td>
<td></td>
</tr>
<tr>
<td>coma</td>
<td>2 (22.2%)</td>
<td>5 (6.2%)</td>
<td>4.34 (0.70–26.62)</td>
<td>0.11</td>
<td>15.07 (1.58–143.20)</td>
<td>0.01</td>
</tr>
<tr>
<td>Laboratory data</td>
<td></td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>serotype 4b</td>
<td>7 (77.7%)</td>
<td>49 (60.4%)</td>
<td>2.28 (0.26–20.01)</td>
<td>0.45</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Treatment</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>adequate empirical treatment</td>
<td>3 (33.3%)</td>
<td>47 (58.0%)</td>
<td>0.36 (0.08–1.54)</td>
<td>0.17</td>
<td></td>
<td></td>
</tr>
<tr>
<td>combined therapy</td>
<td>2 (22.2%)</td>
<td>22 (27.2%)</td>
<td>0.76 (0.14–3.97)</td>
<td>0.75</td>
<td>0.31 (0.05–1.71)</td>
<td>0.18</td>
</tr>
</tbody>
</table>

A P value <0.05 was considered to be statistically significant.

b Neoplastic disease includes solid neoplasia and haematological neoplasia.
Mortality prediction and aminoglycosides in listeriosis

bacteraemia of unknown source, whereas in the second period amoxicillin/clavulanate was the preferred therapy in this situation. Thus, it is likely that in the second period more patients received adequate empirical antibiotic therapy, which in previous studies has been associated with a lower mortality rate.

Other factors have been implicated in high case-fatality rates in patients with L. monocytogenes, such as the presence of underlying conditions, severe immunosuppression and infection with serotype 4b, which in our study was not associated with increased early mortality. Previous epidemiological studies have correlated increased mortality with advancing age; however, in recent studies age is a prognostic factor only in patients with no underlying conditions.

Currently, a high percentage of L. monocytogenes infections are hospital-acquired (16% of 369 cases in a literature review and 30% in our experience). Because listeriosis has a long incubation period (11–70 days) and faecal carriage is not uncommon (5%–10%), colonization could have been acquired before hospitalization, with development of infection in the hospital, probably triggered by increased immunosuppression. Although hospital acquisition was associated with early mortality in the univariate analysis, this factor did not retain significance in the multivariate study. It is likely that the higher degree of immunosuppression in the in-hospital cases had an influence on mortality in these patients.

The presence of renal failure at the diagnosis of listeriosis, a possible prognostic factor that to our knowledge has not been previously analysed, was an independent risk factor for early mortality in this study. This finding is noteworthy because aminoglycosides have a well-recognized association with renal toxicity and their use could actually lead to a poorer prognosis in patients with listeriosis. The results of the multivariate analysis and the propensity score analysis for early mortality suggest that after controlling for other risk factors of death, administration of gentamicin did not decrease early mortality due to L. monocytogenes, but conversely seemed to increase it. Gentamicin use had no impact in the late mortality analysis.

L. monocytogenes is susceptible to a wide range of antibiotics, but ampicillin plays a central role in the treatment of this infection. Since β-lactams with antilisterial activity are bacteriostatic for L. monocytogenes, and based on the bactericidal effect observed in in vitro studies with the addition of aminoglycosides, most authors suggest adding gentamicin to ampicillin for the treatment of bacteraemia in patients with severely impaired T-cell function and in all patients with meningitis. Nevertheless, experimental animal studies have shown conflicting results regarding the synergy of these drugs. In a mouse model, Hof and Gückl found that addition of gentamicin to ampicillin did not improve the therapeutic outcome, probably because aminoglycosides have poor intracellular penetration and less activity in a low-pH environment, such as the conditions present in phagocytic vacuoles, and therefore may be inactive against intracellular listeria. In addition, although β-lactam antibiotics do not belong to the group of intracellular accumulated antibiotics and exhibit slow activity against intracytoplasmic bacterial growth, in vitro models have shown that high-dose penicillins are capable of significant intracellular killing of Listeria, whereas at lower concentrations they are only bacteriostatic within the cell. In our hospital since 1993 the recommended dose of ampicillin for patients with L. monocytogenes meningitis is high (50 mg/kg/4 h with a maximum of 18 g/day) and this could partially explain the efficacy of this drug in the monotherapy group in our study.

The extremely limited capacity of aminoglycosides to cross the blood–brain barrier has led some physicians to question the value of adding an aminoglycoside to the treatment of patients with L. monocytogenes meningitis. Since listeriosis is a rare disease in humans, there have been no controlled trials to establish the optimal antimicrobial regimen for these patients. On the basis of the synergy observed in experimental studies, most authorities suggest adding gentamicin to ampicillin for treating listerial bacteraemia in patients with severely impaired T-cell function, and in patients with meningitis and endocarditis. Unfortunately, there is little reliable clinical experience comparing monotherapy or combination therapy; many series are small, the results are compared with historical controls or detailed information about antibiotic therapy, and outcome is not available.

In one review of L. monocytogenes CNS infection, among 284 patients for whom detailed data on antibiotic therapy were available, mortality was 22% in the 109 patients treated with penicillin or ampicillin and 14% in the 54 cases treated with combined therapy. However, in other studies no differences in the outcome were observed in patients treated with and without aminoglycosides. In a recent series of 110 bacteraemia episodes, 29 of 35 patients with meningitis were treated with ampicillin, 11 of them associated with an aminoglycoside. Mortality in the two groups was similar (4/18 versus 3/11, P=0.88). In a review of brain abscesses due to L. monocytogenes, attributable mortality was also similar (2/10 in the monotherapy group and 1/12 in the aminoglycoside group). In two other listeriosis series, mortality was also similar at 8/11 (73%) and 0/6 (0%) versus 7/10 (70%) and 1/9 (11%) in the monotherapy and combined therapy groups, respectively.

Currently, severely immunosuppressed patients usually receive co-trimoxazole prophylaxis, which is also active against L. monocytogenes. Therefore, nowadays, listeriosis commonly affects elderly patients (44% in our study and 40%–50% in the literature), patients with liver cirrhosis (26% in our study and 11%–36% in the literature), and diabetic patients (19% in our study and 10%–25% in the literature), underlying conditions that are associated with an increased risk of nephrotoxicity. Moreover, many patients initially have renal failure: 24% of our patients and 9%–12.6% in the literature. Thus, a significant percentage of patients with listeriosis have an associated co-morbid condition, in which addition of an aminoglycoside may be harmful. This fact could partially explain the decrease in gentamicin use during recent years in our hospital (from 45.2% of cases before 2000 to 15.2% thereafter).

Our study has some limitations. First, it is a retrospective study: several uncontrolled factors could have influenced the mortality rates observed and it is difficult to exclude the possibility that patients who received aminoglycosides might have had more severe disease. However, the known factors associated with mortality and therapy choice were controlled, and the similar results obtained with the different approaches used in the analyses strengthen our findings. Second, the sample size is small and the number of deaths related to L. monocytogenes and avoidable by antibiotic treatment is limited.

Prospective studies are needed to define the most suitable therapy for patients with L. monocytogenes infection and the role of aminoglycosides, particularly in immunosuppressed
patients and those with CNS involvement. In the interim, we advise against the classic attitude of systematic association of an aminoglycoside, especially in patients with underlying conditions (e.g. liver cirrhosis, advanced age and renal insufficiency), in whom the risk of developing or exacerbating kidney failure could contribute to an increase in mortality.

It would also be useful to clinically validate other antimicrobials or combinations such as co-trimoxazole, linezolid and the newest fluoroquinolones, such as moxifloxacin, which all have a good CSF penetration and are highly active in vitro. However, until definitive results become available, β-lactam antibiotics remain the drugs of choice for this condition.

In conclusion, our results suggest that the addition of aminoglycosides to treatment for patients with listeriosis does not improve the outcome and may be harmful, especially in patients with underlying conditions that predispose to renal failure. Prospective studies are needed to define the role of aminoglycosides in L. monocytogenes infection.

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Transparency declarations
None to declare.

References
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