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Antimicrobial treatment of invasive non-perinatal human listeriosis and the impact of the underlying disease on prognosis

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Abstract

Listeriosis is a resurgent foodborne disease in European countries. Benefits of combined β-lactam-aminoglycoside treatment remain controversial and the impact of the underlying disease on prognosis has not been fully assessed. We conducted a retrospective review of cases of sporadic listeriosis in adults from 1995 to 2008 at two university-affiliated hospitals serving a population of 600 000 people in Madrid, Spain. The primary end-point was the associated in-hospital mortality. Sixty-four patients were studied. Estimated incidence of listeriosis was 0.76/100.000 persons/year. Seventy-four per cent had chronic underlying diseases; cirrhosis of the liver and haematological and solid neoplasias were the most common comorbidities. Primary bacteraemia (58%) and meningitis (42%) were the most frequent manifestations. Focal infections were seen in ten cases. In-hospital mortality was 31%. Patients treated with ampicillin or with an ampicillin-gentamicin combination did not differ in age, severity of underlying disease or type of presentation. Differences in mortality were not seen between patients treated with monotherapy and those given combined treatment (28% vs 35%; p 0.634). Ten patients were treated with trimethoprim-sulfamethozaxole alone and only one died. All patients without comorbidities survived infection but mortality of patients with cirrhosis of the liver was 21% and that of patients with haematological or solid neoplasias was 66%. Only haematological neoplasia (OR 6.67; 95% CI 1.71–26.04; p 0.006) was significantly associated with an increased risk of mortality ($R^2_{\text{Cox–Snell}}$ = 0.262). Mortality of listeriosis mainly depended on the severity of the underlying disease. Combined ampicillin-gentamicin therapy did not improved survival. Trimethoprim-sulfamethozaxole may be an effective alternative therapy for listerial infections.

Keywords: Bacteraemia, *Listeria monocytogenes*, listeriosis, meningitis, septicaemia
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Introduction

Listeriosis is a resurgent foodborne disease caused by the bacterium *Listeria monocytogenes*. It has been estimated that 1850 cases occur annually in the USA [1]. In Western Europe the incidence of listeriosis has ranged from 0.3 to 0.8/100 000 persons/year in France and Italy respectively, although it seems to be increasing in the UK and other countries [2–5].

Listeria monocytogenes is found in soil, silage, water and a variety of raw foods such as meats or vegetables, and in processed foods such as soft cheeses and cold cuts [1,4]. It produces a severe disease characterized by septicaemia and meningitis with mortality rates from 20 to 50% [6]. Pregnant women can transmit the infection to the fetus, for whom the result can be fatal.

Several high-risk conditions for listeriosis have been identified. Malignancies, kidney disease and renal transplant, diabetes, alcoholism, increased age, liver disease and connective tissue disorders are the main predisposing factors [1,5]. In addition, patients with AIDS and those on treatment with tumour necrosis factor-α inhibitors also have an increased risk of listeriosis [7,8]. The susceptibility of healthy persons

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is substantially less than that of persons with underlying conditions. This predisposition is a consequence of suppressed T-cell-mediated immunity caused by the condition or its treatment [1].

Recommendations regarding therapy are based on data from *in vitro* tests, animal models and clinical experience. Penicillin and ampicillin are the preferred agents but because of delayed bactericidal activity against *Listeria*, most experts suggest adding gentamicin to ampicillin for the treatment of listeriosis [1,9]. Nonetheless, the benefits of combined treatment remain controversial and the effect of the underlying disease on prognosis may be of paramount importance.

The objectives of this investigation were to determine the incidence of listeriosis in adults in a metropolitan area of Madrid, and to assess the effect on mortality of adding gentamicin to β-lactam therapy. Because the severity of the underlying disease may be of even greater prognostic importance, an analysis of risk factors of mortality was also performed.

Patients and Methods

We conducted a retrospective review of a cohort of consecutive cases of sporadic listeriosis in adult patients from 1995 to 2008 at two university-affiliated hospitals serving a population of 600 000 people in Madrid.

Diagnosis was based on the isolation of *L. monocytogenes* from blood or cerebrospinal fluid. Bacterial identification was done following conventional methods [10]. Gram-positive, non-spore-forming rod, facultative anaerobes, that produced catalase and a narrow haemolysis and tumbling at 20–25°C were presumptively identified as *Listeria*. Further identification was by means of biochemical tests using API-Coryne; (BioMerieux, Marcy l'Etoile France). Susceptibility tests were performed following the CLSI recommendations [11].

Diagnosis of central nervous system infection was established on clinical grounds, cerebrospinal fluid analysis and when indicated by neuroimaging.

Listeriosis was considered hospital-acquired when signs of infection and isolation of *Listeria* occurred ≥72 h after admission.

Full daily doses of ampicillin (12 g) for adult patients with normal renal function were used. Gentamicin was used at doses of 1.5 mg/kg/8 h. For both antibiotics, dosage adjustments were made in patients with renal dysfunction.

The main measurement was the associated in-hospital mortality defined as death occurring before day 21 of hospitalization in association with listeriosis (septic shock, persisting sepsis, multi-organ dysfunction, brain damage). Deaths related to the underlying condition (e.g. progression of haematological neoplasia, gastrointestinal bleeding or hepatic encephalopathy) were not considered associated with listeriosis and were not entered in the final analysis. Age over 65 years, gender, chronic debilitating disease, cirrhosis of the liver, haematological neoplasia, solid neoplasia, immunosuppressive disease, bacteraemia, meningitis, ampicillin monotherapy and combined ampicillin-gentamicin were the variables considered in the analysis of risk factors of mortality.

Statistics

SPSS 16.0 was used for the statistical analysis of the data. Continuous variables were expressed as mean ± standard difference. Discrete variables were expressed as percentages. Association between qualitative variables was tested using chi-squared tests or Fisher exact test when sample size was small. Strength of association was measured by odds ratio (OR) or Haldane's estimator for small sample 2×2 tables and their 95% CI. Differences between groups were considered significant at $p < 0.05$.

Multivariate analysis was performed using a logistic regression model. The selection of variables for this multivariate analysis was performed by a forward-conditional method, with significance levels of ≤0.05 for inclusion and ≥0.1 for exclusion. Cox–Snell R^2 was used to assess the overall model fit.

Results

Sixty-four patients with sporadic invasive listeriosis were assessed. The estimated incidence was 0.76/100.000 persons/year. Patients had a mean age of 58.8 years, ranging from 19 to 86 years. Sixty-seven per cent were men.

Forty-seven (74%) had a chronic underlying disease. Cirrhosis of the liver (14 patients; 30%), other chronic disease such a diabetes, alcoholism or chronic renal failure (ten patients; 21%), haematological neoplasia (12 patients; 25%), solid neoplasia (six patients; 13%), and a miscellaneous group of immunocompromised hosts on high-dose corticosteroid therapy (five patients; 11%) were the most common comorbidities. Seventeen patients (26%) were adults without predisposing factors.

Listeriosis was acquired in the community in 47 instances (73%) and was hospital-acquired in 17 (27%). Hospital outbreaks were not observed and in cases in which listeriosis developed during hospitalization we did not identify a foodborne or other source of infection.

Primary bacteraemia (37 patients; 58%) and meningitis (27 patients; 42%) were the most common manifestations. Signs of meningoencephalitis or rhombencephalitis were observed

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