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# Invasive listeriosis in Denmark 1994–2003: a review of 299 cases with special emphasis on risk factors for mortality

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## ABSTRACT

Listeriosis is a rare, but serious, foodborne infection which, in the invasive form, presents as bloodstream (BS) infection, an infection of the central nervous system (CNS), a maternofetal infection or a focal infection. The disease is notifiable in Denmark. This paper reviews the results of the Danish surveillance of invasive listeriosis from 1994 to 2003, excluding maternofetal cases. In total, 299 invasive cases of listeriosis were reported. Two-thirds of the cases were caused by isolates of serogroup 1/2, and one-third by serogroup 4. Most (70%) cases had conditions known to predispose to listeriosis. More patients with BS infection were predisposed because of concurrent underlying illness than were patients with CNS infection. Half of the patients were aged >70 years, and 21% died of the disease. There was no change in the case fatality rate (CFR) during the 10-year period. The CFR was identical for men and women. BS and CNS infection caused the same incidence of mortality, but no mortality was observed in patients with focal infections at normally sterile body sites. In a multivariate analysis, isolates belonging to serogroup 4 were associated with a higher CFR than were isolates of serogroup 1/2. In patients aged <70 years, underlying conditions predisposing to disease were related strongly to mortality, which was not the case in patients aged >70 years. The underlying conditions associated most strongly with mortality in the younger age group were non-haematological malignancies.

**Keywords** Invasive disease, listeriosis, mortality, multivariate analysis, risk factors

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## INTRODUCTION

Listeriosis is a foodborne disease caused by the Gram-positive bacterium *Listeria monocytogenes*. This organism occurs ubiquitously in nature, and it is therefore not possible to eliminate it totally from raw produce or ready-to-eat products that have been prepared without a bacterial inactivating step, e.g., heat treatment. Consequently, humans are exposed regularly to *Listeria*. Considering the high exposure rate, the pathogenicity of the organism must be low, as listeriosis is a rare disease, with an annual incidence in most countries of <1/100 000 inhabitants [1]. However, when *Listeria* causes disease, it is usually severe with a high case fatality rate (CFR) of 20–50% [2]. The disease has three major clinical presentations, i.e., bloodstream (BS) infection, infection of the central nervous system (CNS), and maternofetal listeriosis, which is a systemic infection transmitted from the mother to the neonate before or during birth. Less severe presentations, such as cutaneous listeriosis and infectious gastroenteritis, also occur [3,4], but these presentations are rarely reported to surveillance systems or in the scientific literature.

Certain conditions have been identified as risk-factors for severe invasive listeriosis, including the extremes of age, malignancies, diabetes mellitus, alcoholism, liver disease and other immunosuppressing diseases and treatments [5–9]. The major host defence against listeriosis is cell-mediated immunity, and therefore individuals with T-cell dysfunction seem to be particularly at risk of contracting the disease [10,11]. In addition to host factors, pathogen-specific factors also seem to be important in causing disease. Three

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serotypes of *L. monocytogenes*, 1/2a, 1/2b, and 4b, cause >95% of cases in humans [2]. Most isolates from food belong to serogroup 1/2 [12–14], but most outbreaks of human disease are caused by strains of serotype 4b, whereas serogroup 1/2 strains predominate in cases of sporadic listeriosis [2]. This indicates that serotype 4b strains may be more pathogenic for humans than strains of other serotypes.

In the present study, cases of invasive listeriosis identified by the Danish surveillance system were reviewed for the period 1994–2003. As the epidemiology of maternofetal listeriosis differs from the non-pregnancy-related presentations [2,15], such cases were excluded. A comprehensive study of risk-factors for mortality resulting from listeriosis has not been published previously. Therefore, a multivariate analysis of possible risk-factors available in the Danish listeriosis surveillance database was performed.

## MATERIALS AND METHODS

Culture-confirmed cases of listeriosis have been subject to mandatory notification by Danish diagnostic laboratories to the *Listeria* Reference Centre at Statens Serum Institut since 1993. Only the age, sex, isolation site, collection date of the diagnostic specimen and hospital department from which the specimen was sent are notifiable. All non-neonatal cases of listeriosis involving isolation of *L. monocytogenes* from a normally sterile site were included.

Most diagnostic laboratories also submit the infecting isolate to the reference laboratory on a voluntary basis for confirmation and subtyping. At the same time, information regarding the clinical presentation, underlying disease, immunosuppressive treatment, current antibiotic therapy, and the general condition of the patient, including survival, was also reported. If this information was missing or incomplete, the reference centre contacted the submitting laboratory in order to obtain as much information as possible. Cases that were diagnosed by blood culture only were registered as BS infections unless the clinical condition was stated clearly as meningitis and/or encephalitis. Cases in which *Listeria* was isolated from cerebrospinal fluid were registered as CNS infections. If the patient was in a critical condition at the time of contact, the outcome was checked 1 month after the initial isolation of *Listeria*. All surviving patients at that point were considered to have survived the infection; those who had died were recorded as having had listeriosis as at least a contributing factor leading to death. Identification of isolates was confirmed in the reference laboratory by standard methods [16], followed by serogrouping with antisera (Difco; Becton Dickinson, Brøndby, Denmark) according to the recommendations of the manufacturer.

Statistical analyses were performed using SAS software v. 8.2 (SAS Institute, Cary, NC, USA). The multivariate logistic regression model was built by trying all combinations of available variables and eliminating those that were either not significant at the 95% level or were confounding other variables, with subsequent tests for statistical interactions.

## RESULTS

### Basic demographic results

In total, 299 invasive episodes of listeriosis (164 in males and 135 in females) were reported in 298 patients; 221 presented with BS infection, 71 with CNS infection and seven with focal infections at normally sterile body sites (bones, joints and peritoneum). The annual incidence of disease in Denmark ranged from 0.42 to 0.75/100 000 inhabitants, peaking in 1999 (Fig. 1). Geographically, patients were distributed evenly, and there was no clear seasonal trend in the occurrence of disease. No general outbreaks of invasive disease were detected during the study period. The age distribution of all patients and those who died is shown in Fig. 2, along with the general age distribution of the Danish population. There was an obvious association between increased age and the risk of invasive listeriosis. Nine patients were found in the lowest age group (< 10 years); these patients were aged 1–7 years and had no known predisposing conditions, except for the oldest patient, a boy aged 7 years with diabetes. Seven of these patients had BS infections.

Isolates were received from 294 cases. Of these, 174 belonged to serogroup 1/2, 118 belonged to serogroup 4, and two did not belong to either. The serogroup 1/2:4 ratio did not change during the study period. There was a trend towards patients infected with serogroup 4 isolates presenting with a CNS infection rather than a BS infection (data not shown). Information about

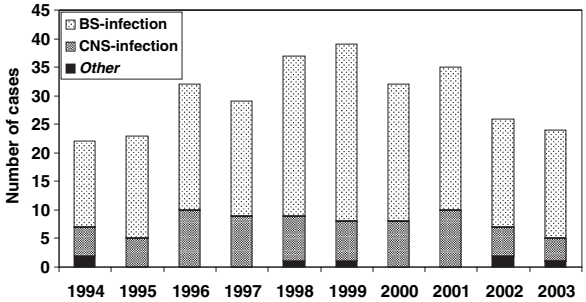


**Fig. 1.** Annual number of cases of invasive listeriosis in Denmark, 1994–2003. The group 'Other' denotes focal infections (arthritis/osteitis/peritonitis/pleuritis). BS, bloodstream; CNS, central nervous system.