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Bacteraemia as a result of *Campylobacter* species: a population-based study of epidemiology and clinical risk factors

H. Nielsen[1], K. K. Hansen[1], K. O. Gradel[1], B. Kristensen[3], T. Ejlertsen[2], C. Østergaard[4] and H. C. Schønheyder[2]

1) *Departments of Infectious Diseases, and* 2) *Clinical Microbiology, Aalborg Hospital, Aarhus University Hospital, Aalborg,* 3) *Department of Clinical Microbiology, Aarhus University Hospital, Skejby, Aarhus and* 4) *Department of Clinical Microbiology, Odense University Hospital, Odense, Denmark*

Abstract

Invasive disease as a result of *Campylobacter* is rarely reported. We reviewed 46 cases of blood stream infection with *Campylobacter* in a Danish population with complete follow-up. The incidence was 2.9 per 1 million person-years with a peak incidence in the age group above 80 years. In the population, the ratio of notified bacteraemia/enteritis patients with *Campylobacter* infection was 0.004. Patients with bacteraemia were older and had higher comorbidity, e.g. alcoholism, immunosuppression, previous gastrointestinal surgery or HIV infection. We found 26% of blood isolates resistant to ciprofloxacin. The length of hospitalization was significantly longer in bacteraemia patients, whereas the outcome was favourable with 28-day mortality of 4% in bacteraemia patients and 1% in enteritis patients. None of the bacteraemia patients relapsed within 365-day follow-up.

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Corresponding author and reprint requests: H. Nielsen, Department of Infectious Diseases Aalborg Hospital, DK9000 Aalborg, Denmark
E-mail: henrik.nielsen@rn.dk

Introduction

Campylobacter species (especially *C. jejuni*) are among the most commonly identified bacterial causes of acute gastroenteritis. Unlike other enteric infections such as salmonellosis, campylobacter infection is only rarely associated with systemic invasive illness [1,2]. Earlier reports on invasive campylobacteriosis were characterized by either a very limited number of cases [3,4] or were from reference laboratories with limited clinical information [5,6]. Bloodstream infection with *Campylobacter* species has been reported in immune-compromised patients and in the very young or very old [7–9]. However, information concerning clinical and bacteriological characteristics is limited, and the true population-based, age-related incidence is not known. Furthermore, the features which distinguish bacteraemic *Campylobacter* patients from patients with acute *Campylobacter* gastroenteritis and a concomitant negative blood culture have been poorly described. We reviewed a large cohort of unselected patients with proven invasive campylobacteriosis and present the clinical and bacteriological characteristics.

Materials and Methods

Setting

During the 10-year study period, 1995 through 2004, the three counties of Aarhus, Funen and North Jutland had a mean of 1 601 675 residents (30.1% of Denmark's population). The Danish public health system is tax financed and free of charge for all residents. All residents of the three counties in whom an infectious disease was suspected were admitted to the nearest hospital, or in more complicated cases, to the university hospital within their county. Thus, the entire population of the three counties served as the background population.

Microbiological procedures

Blood cultures. All blood cultures were carried out in a centralized laboratory in each of the three counties: Aarhus University Hospital (Aarhus County), Odense University Hospital (Funen County) or Aalborg Hospital (North Jutland County). During the study period, different procedures were used which included the use of two or three bottles per

sample (except for smaller children, for whom only one sample bottle was used). In North Jutland County, until December 1995, the Colorbact system (Statens Serum Institut, Copenhagen, Denmark) was in use, after which it was replaced by the BacT/Alert system (bioMerieux, Durham, NC, USA) with a nominal volume of 30 mL. In Aarhus County, the BacT/Alert (bioMérieux, Marcy l'Etoile, France) with a nominal volume of 2 × 20 mL was used throughout the study period. In Funen County, until 2004 the ESP system (Trek Diagnostic Systems, Cleveland, Ohio, USA) was in use, after which it was replaced by BACTEC (BD, Franklin Lakes, NJ, USA) with a nominal volume of 2 × 20 mL.

Faecal cultures. Bacteriological examination of faecal specimens was carried out the by the Statens Serum Institut, Copenhagen or at the Department of Clinical Microbiology in Aalborg (from 1998) and in Aarhus (from 2003).

Identification. Presumptive identification of *Campylobacter* isolates was based on colony morphology, wet smear, Gram stain and oxidase and catalase reactions (both positive). Isolates of *C. jejuni* and *C. coli* were not routinely differentiated. Blood culture isolates were referred to the Statens Serum Institute for species diagnosis.

Antimicrobial susceptibility testing was performed using a disk diffusion method (Neo-Sensitabs; Rosco, Taastrup, Denmark) on Danish horse blood agar or Mueller–Hinton II agar.

Data retrieval

The Danish personal identification number was the unique key used for each patient and linkage between registries. To identify the study cohort, data were retrieved electronically by linkage to the laboratory information system of each of the participating departments of clinical microbiology. Patients were linked to the National Registry of Hospital Discharge Diagnoses coded according to the *International Classification of Diseases 10*, and the Central Population Registry (with the status alive or dead, and, in the latter case, date of death). As *Campylobacter* bacteraemia is very rare, we compared it with the characteristics of patients admitted to hospital for sepsis from 1996 through 2004, where a blood culture taken on admission was negative and where a stool culture indicated *Campylobacter* enteritis. These patients were at risk of invasive campylobacteriosis and had clinical symptoms severe enough to warrant a blood culture on clinical grounds. For calculations of incidence rates, the numbers of residents in the three counties were retrieved from a databank [10], using a population categorized by age (integer years) as of 1 January for each of the years 1995–2004.

We reviewed all medical records to obtain data on coexisting disease, exposure, travel history, clinical picture and medicine given during hospitalization. The Charlson index [11] was used to categorize comorbid diseases (with higher scores associated with more severe disease categories), as this index has proved its validity in several prognostic studies.

Statistical analysis

Incidence rates within 10-year age groups (ranging from 0–9 to >90 years) were calculated by summarizing populations over the period 1995–2004 [10]. Annual incidence rates within age groups were then calculated as numbers of bacteraemia patients per 1 000 000 person-years. The sampling date (i.e. the date of the first positive blood sample) was the start event. Demographic and clinical characteristics were cross-tabulated with the bacteraemia and enteritis patient groups. Categorical data were compared using Chi-square or two-sided Fisher exact tests and continuous data using the Mann–Whitney test. A significance level of 5% (p 0.05) was used in all cases. STATA (Intercooled Stata 8.0 for Windows; StataCorp LP, College Station, TX, USA) was used for all analyses.

Ethical considerations

The study was conducted according to guidelines of the Danish National Committee on Biomedical Research Ethics and approved by the Danish Data Protection Agency (record no. 2004–41–4004).

Results

A total of 46 patients with *Campylobacter* bacteraemia were identified in our population. The incidence was approxi-

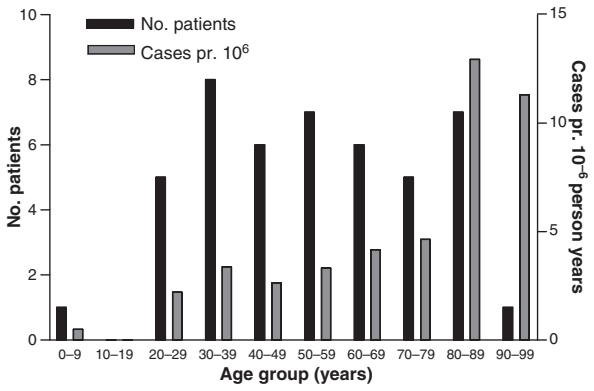

FIG. 1. Patients with *Campylobacter* bacteraemia in North Jutland, Aarhus and Funen Counties, Denmark, 1995–2004: numbers and incidence rates per 1 000 000 person-years, classified by 10-year age groups.

mately 2.9 per 1 million person-years, but with marked differences in age distribution (Fig. 1). We observed only one case during childhood. The peak incidence was in the age group >80 years. All bacteraemic patients were hospitalized and the infection was community-acquired as all blood cultures positive for *Campylobacter* were taken within 2 days after hospital admission of the patients. The numbers of faecal isolates in the three counties during 1995–2004 were 11 296, i.e. approximately 705 per 1 million person-years. Thus, the estimated ratio between blood and faecal isolates was 0.004. The bacteriological diagnoses of blood isolates were *C. jejuni* in 37 patients, *C. coli* in five patients, *C. fetus* in three patients and *C. lari* in one patient. Antibiotic susceptibility of blood isolates was to erythromycin 37/40 (92.5%), to gentamicin 17/18 (94%) and to ciprofloxacin 26/35 (74%), whereas other agents not used in clinical practice were rarely examined. From 102 patients with non-bacteraemic enteritis, all isolates were reported as *C. jejuni/coli.*

Since the occurrence of *Campylobacter* bacteraemia is very rare, we compared it with the characteristics of patients admitted to hospital for sepsis. Acquisition of infection was domestic in 84% of all cases, with no difference between bacteraemia and enteritis groups. The bacteraemia patients were older (median 56 years vs. 32 years) and had higher comorbidity (one or more of the diseases implemented in the Charlson index: 59% vs. 31%; p 0.006), Table 1. The major comorbidities were cardiovascular disease (n = 11), malignancy (n = 7), chronic obstructive pulmonary disease (n = 4), HIV (n = 4), cerebrovascular insult (n = 4) and diabetes mellitus (n = 3). Patients in the bacteraemia group frequently had more problems with alcoholism (8% vs. 2%, p 0.008), more previous major gastrointestinal surgery (12% vs. 3%, p 0.005) and they were more often on immunosuppressive drug therapy (12% vs. 1%, p 0.002), Table 1. We observed no differences between the two groups with respect to baseline assessment of blood pressure, heart rate, temperature, C-reactive protein, haemoglobin, leukocyte count, creatinine or albumin.

TABLE 1. Demographic and clinical characteristics of patients with *Campylobacter* bacteraemia and patients with *Campylobacter* enteritis and a concomitant negative blood culture, Aarhus, Funen and North Jutland counties, Denmark 1995–2004

	Bacteraemia (n = 46)	Enteritis (n = 102)
Median age (range)	56 year (1–94 years)	32 year (1–85 years)
Gender %		
females	28	41
males	72	59
Charlson-index		
0	19 (41%)	70 (69%)
1–2	18 (39%)	19 (19%)
>2	9 (20%)	13 (12%)
Previous major gastrointestinal surgery	6 (12%)	3 (3%)
Alcoholism	4 (8%)	2 (2%)
Immunosuppressive drug therapy	6 (12%)	1 (1%)
Median length of hospitalization (range)	8 days (1–113 days)	3 days (1–29 days)
Mortality within		
day 28	2 (4%)	1 (1%)
day 180	3 (6%)	1 (1%)

By definition, all enteritis patients had diarrhoea, which was present in only 27/46 (59%) of bacteraemia patients. Antibiotic therapy was initiated on admission in 13 out of 19 (68%) bacteraemia patients without diarrhoea, in 14 out of 27 (52%) bacteraemia patients with enteritis and in 42 (41%) enteritis patients (as a result of sepsis and clinical suspicion of bacteraemia). Upon microbiological diagnosis, antimicrobial treatment was initiated in 16 (35%) additional bacteraemia patients, whereas three patients with *Campylobacter* bacteraemia recovered without antimicrobial therapy. A total of 21 patients were treated with a combination, which included gentamicin. A secondary focus was documented in two cases. One patient had endocarditis which was successfully treated and another patient had skin and soft tissue infection in the lower right leg. The length of hospitalization was significantly longer in bacteraemia patients, but the outcome was favourable with a low mortality in both patient groups (Table 1). None of the survivors was readmitted with *Campylobacter* infection within the 365-day follow-up period, indicating that they had all recovered.

Discussion

The findings in our population-based survey of invasive *Campylobacter* infection confirm that it is a rare disease with a markedly skewed age distribution. It has been reported that *Campylobacter* bacteraemia often occurs at the extremes of age [5]. However, we detected only a single case in childhood, whereas the incidence increased considerably in the age group >80 years. The reasons for the lack of positive samples in infants remain speculative. The blood sample volume in small children is often critically low, and paediatric bottles may not sustain growth of *Campylobacter* to the same extent as flasks for adult use. However, the affluence of the Danish society, the attention of parents to hygiene and the high standard of drinking water in Denmark may also have an impact on the epidemiology. Compared with the group of hospitalized patients with sepsis as a result of *Campylobacter* enteritis (but with negative blood culture) the median age of bacteraemia patients was markedly higher. The ratio

between blood and faecal *Campylobacter* isolates in the populations studied over a 10-year period was 0.004, a figure that may reflect both the invasiveness of the pathogen and the frequency of positive bacteriological blood cultures in cases of diarrhoea.

Tee and Wijch reported 1.6% cases of bacteraemia in patients with *Campylobacter* enteritis [9], but this result was obtained from a hospital-based study and not from the background population. Skirrow *et al.* reported a frequency of 0.15% blood isolates of the total national cases in the United Kingdom [6], and during a survey in the United States the extraintestinal sources accounted for 0.26% of all *Campylobacter* isolates [12]. In any case, *Campylobacter* blood stream infection is rare, and the incidence of 2.9 per 1 million person-years is *c.* 1/10 the rate of invasive non-typhoid salmonellosis in our region [13]. Members of the genus *Campylobacter* are micro-aerophilic and fastidious, and it is possible that the type of blood culture system affects the isolation rate. It is noteworthy that we detected *Campylobacter* from blood with all four types of blood culture system used, but most were observed with the Bact/Alert system. After a change in methodology within the same institution, an increase in the incidence of positive blood cultures for *Campylobacter* has been reported [9].

We also observed clear differences in clinical characteristics between our two patient groups as expressed by the Charlson index [10]. Patients with bacteraemia had considerably more comorbidity as a risk factor, although this had no negative impact as indicated by their low mortality. Tee and Mijch found a five-fold increase of invasive *Campylobacter* disease in subjects with human immunodeficiency virus infection [9], and four of our patients had concomitant HIV-infection. Comorbidity included more frequently major disease categories such as cardiovascular disorders and malignancies. The clinical presentation of *Campylobacter* bacteraemia was generally a mild, acute-onset febrile illness of a transient nature with self-limiting enteritis. Initial reports described *Campylobacter* bacteraemia predominantly in enteritis patients [6]. However, the clinical picture of *Campylobacter* bacteraemia may show a febrile illness without gastrointestinal symptoms [8], and 43% of our bacteraemic patients did not report gastrointestinal symptoms. Travel history was not a significant risk factor, and most infections were domestically acquired. In Denmark, the seasonal occurrence of campylobacteriosis peaks in July–August, and for bacteraemic patients a peak in the summer and early autumn months has been reported as well [8]. We did not observe any clear seasonal distribution in our bacteraemia patients, which may suggest another pathogenesis for invasive disease in comparison with the more common acute gastroenteritis disorder. We previously reported a similar disparity in seasonality for invasive vs. non-invasive non-typhoid salmonellosis [14]. It is not clear if any bacterial characteristics determine the invasiveness. Blaser *et al.* [5] showed that bacteraemia in healthy subjects was usually caused by serum-resistant isolates, and blood isolates from Australia were predominantly of Penner serotype O:2 and O:4;O:64 [9]. In contrast, blood isolates from England and Wales were genomically heterogeneous and this suggests that an invasive disease is not related to particular genotypes [15].

Extraintestinal manifestations including cellulitis have been described in *Campylobacter* bacteraemia [4,7], and we detected one of these complications in our cohort. However, this patient did not have hypogammaglobulinaemia, the most frequent association of this complication [4]. In immunosuppressed patients, infection with *Campylobacter* may persist for many months [9], but we did not detect any recurrence or persistence in our cohort.

The mortality associated with *Campylobacter* bacteraemia has been reported very differently, from 2.5% to 12.5% [6–9]. In our cohort, the 28-day all-cause mortality was 4%, which was considerably lower than for bacteraemias in general. As a result of the very low invasiveness of *Campylobacter*, we hypothesized that our bacteraemia patients could possibly be frailer and less likely to survive than bacteremic patients with more common bacteria, but our results actually document a favourable outcome in the majority of cases. The possibility of resistant strains must be considered in all cases of C*ampylobacter* bacteraemia. Immunosuppressed patients in particular require more aggressive treatment with a combination of antibiotics. Considering that 94% of our isolates were susceptible to gentamicin *in vitro*, the treatment regimen for *Campylobacter* bacteraemia should include aminoglycosides for severely ill patients. Previous surveys from our region on bacteraemia with *Campylobacter* [7] did not detect resistance to ciprofloxacin, but during the last decade it has been increasingly recognized that fluoroquinolone susceptibility is no longer predictable for enteric pathogens [16]. We now find 26% of blood isolates resistant to ciprofloxacin.

In conclusion, bacteraemia with *Campylobacter* species is rare in Denmark, and the frequency is <1% of enteric *Campylobacter* infections. Patients with invasive campylobacteriosis are older and have higher comorbidity in comparison with enteritis patients with a concomitant negative blood culture, but the outcome is generally favourable. As fluoroquinolone resistance is increasingly encountered, antimicrobial chemotherapy for *Campylobacter* bacteraemia should include an aminoglycoside.

Transparency Declaration

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