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Retrospective Multicentric Study on *Campylobacter* spp. Bacteremia in France: The Campylobacteremia Study

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Background. *Campylobacter* spp. bacteremia is a severe infection. A nationwide 5-year retrospective study was conducted to characterize its clinical features and prognostic factors.

Methods. The study included patients with *Campylobacter* spp. bacteremia diagnosed in 37 French hospitals participating in the surveillance network of the National Reference Center for Campylobacters and Helicobacters, from 1 January 2015 to 31 December 2019. The goal was to analyze the effects of a delay of appropriate antibiotic therapy and other risk factors on 30-day mortality rates, antibiotic resistance, patient characteristics, and prognosis according to the *Campylobacter* species.

Results. Among the 592 patients, *Campylobacter jejuni* and *Campylobacter fetus* were the most commonly identified species (in 42.9% and 42.6%, respectively). The patients were elderly (median age 68 years), and most had underlying conditions, mainly immunodepression (43.4%), hematologic cancers (25.9%), solid neoplasms (23%), and diabetes (22.3%). *C. jejuni* and *Campylobacter coli* were associated with gastrointestinal signs, and *C. fetus* was associated with secondary localizations. Among the 80 patients (13.5%) with secondary localizations, 12 had endocarditis, 38 vascular, 24 osteoarticular, and 9 ascitic fluid infections. The 30-day mortality rate was 11.7%, and an appropriate antibiotic treatment was independently associated with 30-day survival (odds ratio, 0.47 [95% confidence interval, .24–.93]; $P = .03$). The median efficient therapy initiation delay was quite short (2 days [interquartile range, 0–4 days]) but it had no significant impact on the 30-day mortality rate ($P = .78$).

Conclusions. *Campylobacter* spp. bacteremia mainly occurred in elderly immunocompromised individuals with variable clinical presentations according to the species involved. Appropriate antimicrobial therapy was associated with improved 30-day survival.

Keywords. *Campylobacter* spp.; bacteremia; immunosuppression; zoonosis.

Campylobacter is the leading cause of foodborne bacterial gastroenteritis and mainly affects children and young adults, particularly in low-income countries. However, it has the propensity to translocate through the digestive barrier, causing invasive infections. These complications are poorly described owing to their rarity, representing 1% of *Campylobacter* infections but burdened by a significant mortality rate (3%–28%) [1, 2].

In the largest series of *Campylobacter* bacteremia, published in 2008 (183 episodes) [3], *Campylobacter fetus* was the most commonly identified species (53%). However, this epidemiology has changed in France, as *Campylobacter jejuni* is currently the most frequently identified species in blood cultures [4]. *Campylobacter* bacteremia mostly affects elderly immunocompromised patients. Indeed, several underlying predisposing conditions are well known, such as cancers, liver disease, hypogammaglobulinemia, and human immunodeficiency virus (HIV) infection [1–3, 5–11]. However, it might also be associated with newly available immunosuppressive treatments.

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Bacteremia can also be complicated by secondary localizations, such as endovascular, joint, bone, and soft-tissue involvement or endocarditis [2, 3, 8]. Lack of awareness of this risk and the challenge of the diagnosis, due to the need for a fastidious culture, could be responsible for underdiagnosis.

Finally, there is currently no consensus on the treatment of *Campylobacter* bacteremia, and the antimicrobial susceptibility profile of these species is unknown. Indeed, patients included in previously published studies benefited from appropriate empirical treatment in only 18.5% to 39% of cases and from efficient targeted antibiotic therapy in 66% [2, 6, 8, 10]. Furthermore, acquired antimicrobial resistance to *Campylobacter* spp. is high, with acquired resistance to fluoroquinolones in up to 60% of strains [4].

Identification of the predisposing comorbid conditions for *Campylobacter* bacteremia and the evocative clinicobiological signs could lead to earlier effective antibiotic therapy. The aim of the current study was to analyze the impact of this delay on the 30-day mortality rate for *Campylobacter* bacteremia.

MATERIALS AND METHODS

Study Design and Patients

A multicentric retrospective study was conducted in 37 French general hospitals, either through the surveillance network of the National Reference Center for Campylobacters and Helicobacters (NRCCH) or through direct solicitation of infectious diseases physicians and microbiologists at French University Hospitals (Supplementary Table 1). Patients with *Campylobacter* bacteremia hospitalized between 1 January 2015 and 31 December 2019 were included.

Data Collection

Data on demographic characteristics, clinical signs, underlying conditions, and antibiotic treatments were retrospectively extracted from medical records through a standardized questionnaire. Microbiological data were also extracted, especially for identification to the species level, the results of concomitant stool culture or any other site culture, and susceptibility to amoxicillin, amoxicillin-clavulanate, erythromycin, tetracycline, gentamicin, fluoroquinolone, and imipenem, when tested.

Definitions

Bacteremia was defined by *Campylobacter* spp. isolation from ≥1 blood culture. Antibiotic treatment was considered appropriate if the strain was susceptible to ≥1 of the drugs prescribed. All isolates were naturally resistant to third-generation cephalosporins, ticarcillin, and piperacillin, and these antibiotics were considered inappropriate. Antibiotic therapy was defined as empirical if based on clinical data only without any microbiological result. Treatment based on the results of blood culture and susceptibility testing was considered targeted. Relapse was defined by ≥1 new blood culture positive for *Campylobacter* spp. after resolution of clinical signs and apyrexia or a negative control blood culture. Thirty-day mortality was defined as death occurring within 30 days of the first positive blood culture.

Microbiological Diagnosis

All participating laboratories used continually monitored noninvasive blood culture systems (BacT/Alert, Virtuo (bioMérieux) or Bactec (Becton Dickinson). Each blood culture set included an aerobic and an anaerobic bottle inoculated with 10 mL of blood and incubated for 5 days. Two sets of blood culture were recommended. Gram and fresh examinations were performed for positive samples. Curved or spiral-shaped gram-negative rods were identified as *Campylobacter* spp. A blood agar plate was inoculated and incubated in a microaerobic atmosphere (6% oxygen, 7% carbon dioxide, 7% hydrogen, and 78% nitrogen) at 35°C. Bacterial identification was performed by matrix-assisted laser desorption ionization-time of flight-mass spectrometry [12]. Susceptibility testing was interpreted according to recommendations from the Antibiogram Committee of the French Society of Microbiology and European Committee on Antimicrobial Susceptibility Testing [13].

Outcomes

The primary outcome evaluated was the impact of the delay to initiation of effective antibiotic therapy on 30-day mortality rates in patients with *Campylobacter* bacteremia. The secondary objectives were to describe the epidemiology, clinical presentation, and secondary localizations, to investigate risk factors for 30-day mortality rate, and to assess the level of antibiotic resistance. We also compared these characteristics according to *Campylobacter* species.

Ethical Approval

We declared our study to the French National Institute of Health Data and the French Data Protection Authority. In accordance with French legislation, the data were pseudonymized, and the included patients who were still alive did not object to analysis of their data for research issues.

Statistical Analysis

Descriptive statistics are expressed as percentages for categorical variables and as means with standard deviations or medians with interquartile ranges (IQRs) for continuous variables. Patient characteristics were compared according to *Campylobacter* species, using Pearson χ^2 test for categorical variables or Fisher exact test for continuous variables. The impact of the delay before appropriate antibiotic treatment on mortality rate and rate of relapse at 30 days was evaluated using the Kruskal-Wallis test. Univariate and multivariate analyses using logistic regression models were performed to identify factors associated with 30-day mortality rates. Results with

P values <.05 were considered statistically significant, using R studio software, version 1.2.5033 [14].

RESULTS

Demographic Data and Clinical Characteristics

During the study period, 592 patients with ≥1 episode of *Campylobacter* bacteremia were included (Table 1). Male and elderly patients were predominantly affected, and only 27 patients were <15 years old. Most patients had underlying comorbid conditions that impaired their immunity, particularly hematologic cancer, solid neoplasm, diabetes, chronic renal failure, and liver disease (ethanol, viral, and nonalcoholic steatohepatitis origin in 62.7%, 13.3%, and 12%, respectively).

Almost half of the patients were immunocompromised (43.4%): 81 patients among the 560 for whom information was available had hypogammaglobulinemia (median gamma globulin level [IQR], 5.3 g/L [3.4–8] g/L), 4.4% had received an organ transplant, and 3.4% had received a hematopoietic stem cell transplant. A third of patients were receiving immunosuppressive therapy, either steroids (19.3%) or other molecules, including anticancer polychemotherapy, anti-CD20, anticalcineurin, or tyrosine kinase inhibitors. Only 3 patients were receiving checkpoint inhibitor therapy. Three patients had HIV infection, but none had $CD4^+$ cell counts <200/µL. *C. jejuni* and *C. fetus* were the most commonly identified species (in 42.9% and 42.6%, respectively), followed by *Campylobacter coli* (6.8%) and *Campylobacter ureolyticus* (3.7%) (Figure 1, Supplementary Table 1, and Supplementary Figure 1).

The clinical presentation varied among species (Supplementary Figure 2); *C. jejuni* and *C. coli* were significantly associated with immunodeficiency, especially among patients with hypogammaglobulinemia or those receiving rituximab, and fever and gastrointestinal symptoms were more often described with these species. *C. fetus* infection affected elderly patients and was characterized by less frequent gastrointestinal symptoms and more frequent cellulitis or secondary localizations.

Among the 66 patients who underwent colonoscopy, 31 had abnormalities: 21 had benign polyps or diverticulosis, 5 had inflammatory lesions (colitis or ileitis), and only 2 had a diagnosis of colic cancer (including 1 cancer recurrence). Consistent with overall *Campylobacter* infections, there was a summer seasonality, particularly among *C. jejuni* and *C. coli,* though less pronounced (Supplementary Figure 3) [4].

Secondary Localizations

A secondary localization was diagnosed in 13.5% (80 patients), including 38 endovascular infections, 24 osteoarticular localizations, 12 cases of endocarditis, and 9 ascitic fluid infections, mostly due to *C. fetus* (in 91.7%, 81.6%, 79.2%, and 66.7% of cases, respectively) (Supplementary Figure 4). Among cases of endocarditis cases, 6 occurred on a prosthetic aortic valve. The endovascular infections were mainly aortitis, 8 occurring in a preexisting aneurysm and 8 in a vascular (endo) graft. The osteoarticular localizations were diverse, including spondylodiscitis (n = 10), knee infections (n = 4), hip prosthesis (n = 6), and shoulder arthritis (n = 3), and in 33.3% of cased involved a foreign implant.

Infection of serous membranes was documented in 11 cases, 9 ascites and 2 pleurisies. Ascitic fluid infection occurred mainly in cirrhotic patients (n = 6), and the 3 remaining patients underwent peritoneal dialysis. Ten patients had deep abscesses, mostly due to *C. ureolyticus* (50%) and either renal (n = 2), sacrococcygeal, mandibular, pulmonary, splenic, peritoneal, retrouterine, tubo-ovarian, or multiple (thoracic and gluteal) abscesses.

Bloodstream Coinfections

Thirty patients (5.1%), often neutropenic (30%), had bloodstream bacterial coinfection, mostly due to Enterobacterales (*Escherichia coli*, *Klebsiella* spp., *Enterobacter* spp. [56.7%]), followed by *Streptococcus* spp. (33.3%), *Staphylococcus aureus* (10%), and nonfermenting gram-negative bacilli (6.7%). Interestingly, unusual *Campylobacter* species presented more often with bacterial coinfections (22.2%) than *C. fetus* and *C. jejuni* (4% and 3.5%, respectively). Indeed, 33.3% of these coinfections were related to unusual species and involved mainly commensal bacteria of the oral cavity, such as *Leptotrichia* spp., *Parvimonas micra*, *Streptococcus mitis,* and *Streptococcus milleri* groups. Fungal coinfection affected 4 patients, including invasive aspergillosis (n = 2), fusariosis (n = 1) and candidemia (n = 1).

Microbiological Diagnosis and Antimicrobial Susceptibilities

The median (IQR) time to positive blood samples was 54 (6–72) hours. Coproculture was positive in 57.8% of available samples from patients with gastrointestinal symptoms (n = 160), and isolated mostly *C. jejuni* or *C. coli* (75.8%). Antimicrobial resistance is described in Table 2. *C. coli* was globally more resistant, particularly to macrolides (23.7%).

Clinical Outcome

Survival without relapse at 30 days was observed for 84.7% of patients who completed follow-up (n = 483), with mortality and relapse rates estimated at 11.7% and 3%, respectively (Supplementary Figure 5). Among the 551 patients for whom antimicrobial therapy was documented, 77.9% received an appropriate treatment. Appropriate antimicrobial treatment was significantly associated with reduced 30-day mortality rate after multivariate analysis (8.9 vs 19.5%, respectively; odds ratio [OR], 0.47 [95% confidence interval (CI), .24–.93]; *P* = .03)

Table 1. Characteristics of the Study Population by *Campylobacter* spp. Species (N = 592)

Characteristics	Patients by *Campylobacter* species, No. (%)[a]					
	All Species	*C. jejuni*	*C. fetus*	*C. coli*	Other Species	*P* Value (Comparison by Species)
All patients	592 (100)	254 (42.9)	252 (42.6)	40 (6.8)	46 (7.8)	…
Age, median (IQR), y	68 (53–78)	61.5 (45.8–73.3)	73 (63.5–83)	59.5 (22.3–72.3)	68.5 (53.25–77.75)	<.001[b,c]
Male sex	402 (67.9)	173 (67.8)	172 (68.3)	29 (72.5)	28 (63.6)	.86[d]
Underlying condition						
Chronic liver disease	75 (12.3)	37 (14.6)	29 (11.7)	4 (10)	5 (11.4)	.72[e]
Diabetes	128 (22.3)	60 (23.9)	56 (23.1)	3 (7.7)	9 (20)	.15[d]
Chronic renal failure	118 (20.2)	42 (16.6)	63 (25.6)	6 (15)	7 (15.9)	.054[d]
Hematologic cancer[f]	151 (25.9)	84 (33.5)	43 (17.3)	15 (37.5)	8 (18.2)	<.001[c,d]
Solid neoplasm[g]	135 (23)	40 (15.8)	70 (28.2)	6 (15)	19 (43.2)	<.001[c,d]
Immunodeficiency	257 (43.4)	133 (52.4)	86 (34.1)	20 (50)	17 (38.6)	.001[c,d]
Hypogammaglobulinemia	81 (14.3)	42 (17)	22 (9.4)	16 (42.1)	1 (2.4)	<.001[c,e]
Organ transplantation[h]	26 (4.4)	15 (6)	10 (4)	1 (2.5)	0	.34[e]
HSC transplantation	20 (3.4)	13 (5.2)	1 (0.4)	4 (10)	2 (4.5)	<.001[c,e]
Steroid therapy	112 (19.3)	66 (26.3)	31 (12.8)	8 (20)	6 (13.6)	.002[c,d]
Immunosuppressive therapy	176 (30.2)	97 (38.5)	55 (22.5)	12 (30)	11 (25.6)	.001[c,d]
Splenectomy	15 (2.6)	10 (4)	2 (0.8)	1 (2.5)	1 (2.3)	.10[e]
HIV infection	3 (0.5)	2 (0.8)	1 (0.4)	0	0	>.99[e]
Clinical manifestation						
Fever	426 (75.3)	182 (74.9)	186 (77.5)	28 (71.8)	30 (69.8)	.66[d]
Septic chock	43 (7.6)	20 (8.2)	18 (7.5)	3 (7.7)	2 (4.7)	.94[d]
Diarrhea	233 (41.5)	137 (57)	65 (27.1)	18 (47.4)	12 (27.9)	<.001[c,d]
Gastrointestinal bleeding	18 (3.3)	6 (2.6)	11 (4.7)	0	1 (2.6)	.49[e]
Abdominal pain	112 (58.6)	61 (70.9)	33 (41.3)	8 (80)	10 (66.7)	<.001[c,d]
Ascites	28 (4.9)	13 (5.3)	10 (4)	2 (5)	3 (6.8)	.75[e]
Cellulitis	50 (8.9)	13 (5.4)	33 (13.6)	2 (5.2)	2 (4.7)	.01[c,e]
Secondary localizations[i]	80 (13.5)	11 (4.3)	61 (24.2)	4 (10)	4 (9)	<.001[c,d]
Endovascular infection	38 (6.6)	5 (2.1)	29 (11.5)	0	4 (9)	<.001[c,e]
Endocarditis	12 (2.1)	1 (0.4)	11 (4.4)	0	0	.01[c,e]
Bone and joint infection	24 (4.2)	5 (2)	18 (7.2)	1 (2.5)	0	.02[c,e]
Ascites liquid infection	9 (1.5)	1 (0.2)	6 (1)	2 (0.3)	0	>.99[e]
Meningitis	2 (0.3)	0	1 (0.2)	1 (0.2)	0	>.99[e]
Death within 30 d	69 (11.7)	28 (11)	29 (11.5)	1 (2.5)	11 (25)	.02[c,e]

Abbreviations: HSC, hematopoietic stem cell; HIV, human immunodeficiency virus; IQR, interquartile range.

[a]Data represent no. (%) of patients unless otherwise specified.

[b]*P* value based on Kruskal-Wallis test.

[c]Significant at $P < .05$.

[d]*P* value based on Pearson χ^2 test.

[e]*P* value based on Fisher exact test for count data.

[f]Including 67 lymphomas, 27 acute leukemias, and 11 myelomas.

[g]Including 20 digestive tumors, 18 hepatocellular carcinomas, and 5 pancreatobiliary tumors.

[h]Including 18 kidney, 3 liver, 2 heart, and 2 lung transplants.

[i]Three patients had concurrent bone and joint and endovascular localization, 1 had endocarditis associated with ascitic fluid infection, and 1 had bone, joint, and ascitic fluid infections.

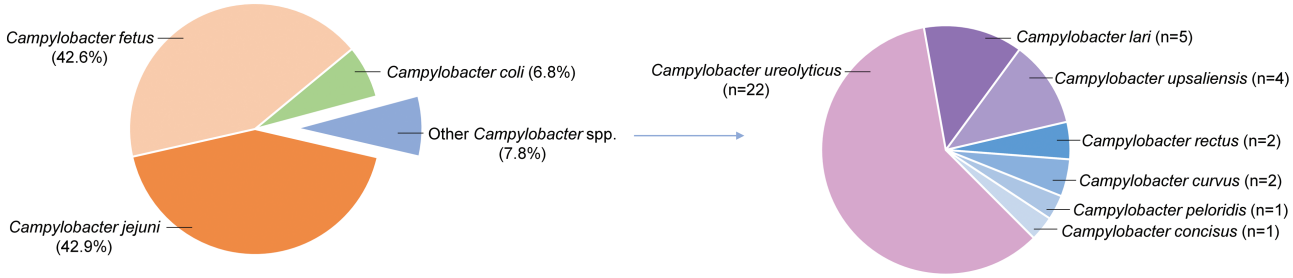

Figure 1. Distribution of *Campylobacter* species among 592 patients with bacteremia.

(Table 3). The median delay (IQR) before the onset of effective therapy was quite short (2 [0–4] days) and was not significantly associated with 30-day mortality (OR, 1 [95% CI, .99–1.01]; $P = .78$). Inefficient empirical treatment was mostly due to cephalosporin and piperacillin-tazobactam prescriptions, in 141 and 46 cases, respectively. In 48 cases (27.6%), the empirical regimen was efficient only because of the inclusion of an aminoglycoside.

Male sex and decompensation of an underlying liver disease (OR, 6.32 [95% CI, 1.96–22.05]; $P < .001$) were also independent mortality risk factors after multivariate analysis (Table 3). Univariate analysis showed an increasing severity from *C. coli,* to *C. jejuni* and *C. fetus,* to other *Campylobacter* spp. bacteremia, but this increase was not confirmed after multivariate analysis ($P = .27$). The median duration of antibiotic therapy (IQR) was 10 (5–15) days, prolonged to 41.5 days (17–46) days when a secondary localization was diagnosed.

The outcomes in 426 patients who benefited from appropriate antibiotic therapy were further analyzed (Table 4). Monotherapy was administered to 293 patients (68.8%), and 31.2% received bitherapy. Among patients with secondary localizations, 36 (49.3%) received dual therapy. Most patients received β-lactam therapy, either amoxicillin, amoxicillin-clavulanate, or carbapenem (74.4%), and 51 patients received macrolide monotherapy. Compared with other patients, they were younger (median age, 60.5 vs 68.5 years; $P = .04$), more frequently had diarrhea (70% vs 38.7%; $P < .001$), and had shorter hospitalizations (8 vs 10 days; $P = .01$) and duration of antibiotic treatment (8 vs 14 days; $P = .004$). Interestingly, macrolide monotherapy was associated with better 30-day survival with univariate but not with after multivariate analysis (Table 3).

DISCUSSION

The present study, conducted in 592 patients with *Campylobacter* bacteremia, aimed to evaluate the impact of the delay to initiation of effective antibiotic therapy, which was not significantly associated with 30-day mortality rate. However, the median delay was rather short in this study (2 days), which corresponded to the median time of blood culture positivity and thus bacterial identification. This could explain the nonsignificant result. Indeed, the prescription of an appropriate antibiotic treatment was independently associated with survival at 30 days.

Consistent with previous studies, 22.1% of patients did not receive any adequate antibiotic therapy [2, 10]. This could be explained both by high rates of acquired resistance to amoxicillin and fluoroquinolone and by the fact that many patients were treated with cephalosporin or piperacillin-tazobactam, which has been associated with therapeutic failure in previous studies [3, 8, 10]. Interestingly, almost 80% of patients who did not receive appropriate treatment had a favorable outcome. In a

Table 2. Antimicrobial Resistance by Species

	Antimicrobial Sensitivity by Campylobacter Species, No. (%) of Infections				
Antimicrobial	All Species	*C. jejuni*	*C. coli*	*C. fetus*	*P* Value[a]
Amoxicillin	131 (25.4)	85 (38.5)	21 (60)	17 (7.2)	<.001
Amoxicillin-clavulanate	2 (0.6)	2 (0.8)	0	0	.49
Ciprofloxacin	249 (45.8)	146 (58.6)	22 (57.9)	68 (29.4)	<.001
Erythromycin	22 (4)	6 (2.4)	9 (23.7)	4 (1.7)	<.001
Tetracycline	167 (33.7)	108 (49.5)	23 (63.9)	33 (15.2)	<.001
Gentamicin[b]	3 (0.6)	1 (0.4)	0	2 (0.9)	.69
Imipenem[c]	0	0	0	0	…

[a] *P* value for antimicrobial resistance by species (Fisher exact test for count data).

[b] Strains susceptible to gentamicin were assumed to be susceptible to amikacin.

[c] Only 16.4% of strains were tested.

Table 3. Risk Factors Associated With 30-day Mortality Rate (N = 505)

	Univariate Analysis		Multivariate Analysis[a]	
Risk Factor	OR (95% CI)	*P* Value	OR (95% CI)	*P* Value
Age (as median [IQR])	1.02 (1–1.03)	.01	1.02 (1–1.04)	.06
Female sex (as %)	0.52 (.27–.94)	.03[b]	0.45 (.21–.92)	.03[b]
Underlying condition (as no. [%])				
Chronic liver disease	2.63 (1.37–4.84)	<.001	0.84 (.28–2.16)	.73
Diabetes	1.38 (.73–2.5)	.42	…	…
Chronic renal failure	1.39 (.74–2.5)	.30	…	…
Solid neoplasm	1.80 (1.02–3.1)	.04	1.58 (.79–3.08)	.19
Immunodeficiency[c]	1.32 (.79–2.2)	.29	…	…
Clinical manifestation (as no. [%])				
Hemorrhagic shock	4.53 (1.16–15.43)	.03	2.91 (.59–12.97)	.18
Septic shock	1.95 (.8–4.23)	.13	…	…
Gastrointestinal symptoms (diarrhea or abdominal pain)	0.72 (.43–1.21)	.22	…	…
Liver decompensation	5.92 (2.57–13.18)	<.001[b]	6.32 (1.96–22.05)	<.001[b]
Cellulitis	1.29 (.51–2.83)	.57	…	…
Secondary localization	0.63 (.24–1.41)	.28	…	…
Appropriate antimicrobial treatment	0.41 (.23–0.72)	<.001[b]	0.47 (.24–.93)	.03[b]
Time to appropriate antibiotic introduction (in days)	1 (.99–1.01)	.78		
Macrolide monotherapy	0.30 (.05–0.98)	.05	0.6 (.09–2.24)	.49
Campylobacter species				
C. fetus	1 (Reference standard)	.01	1	.27
C. jejuni	0.98 (.55–1.72)		1.09 (.55–2.14)	
C. coli	0.21 (.01–1.02)		0.29 (.02–1.59)	
Other *Campylobacter* species	2.70 (1.19–5.86)		1.87 (.67–4.84)	

Abbreviations: CI, confidence interval; IQR, interquartile range; OR, odds ratio.

[a]The multivariate model was adjusted for all variables associated with a fatal outcome within 30 days with a significance of $P < .05$ in univariate analysis. Adjusted ORs calculated from the multivariable model after imputation of missing data.

[b]Significant at $P < .05$ in both univariate and multivariate analysis.

[c]Immunodeficiency included hypogammaglobulinemia, organ transplantation, hematopoietic stem cell transplantation, steroid or immunosuppressive therapy, splenectomy, and hematologic cancers.

Finnish nationwide retrospective study, similar outcomes were reported, regardless of antimicrobial treatment for *C. jejuni* and *C. coli* bacteremia [2]. Indeed, *Campylobacter* bacteremia might be transient, particularly in immunocompetent young patients. This might not be applicable to *C. fetus* and needs further evaluation.

The secondary objectives were to describe patients and infection characteristics according to species. *Campylobacter* bacteremia was more likely to affect elderly male patients, in contrast to *Campylobacter* overall infections which mainly occur before 30 years of age [4]. Moreover, secondary localizations were significantly associated with *C. fetus,* while *C. jejuni* and *C. coli* affected immunocompromised patients with digestive presentation.

Regarding this clinical variability, we tried to identify patients at risk of severe forms. Patients with chronic liver disease seemed to be more vulnerable, but this was not confirmed in multivariate analysis. However, liver decompensation was an independent risk factor for 30 day-mortality. In previous series, 5%–39% of patients with *Campylobacter* bacteremia presented with chronic liver disease [2, 3, 8, 10], and patients with chronic hepatitis or cirrhosis were more likely to present with an increased relative abundance of *Campylobacter* in gut microbiota [15]. Regarding the risk of gut translocation among patients with severe liver disease and portal hypertension [16], digestive colonization by *Campylobacter* could explain this increased risk of ascitic fluid infection and bacteremia.

Surprisingly, *C. jejuni* was the most frequently involved species, confirming the epidemiological change reported by recent NRCCH data, as *C. fetus* was found to be responsible for the majority of bacteremia in France before 2017 [3, 4]. However, *C. fetus* remains the most invasive species, mainly responsible for secondary localizations, due to the presence of a protein capsule called the S-layer, which impairs complement activation by a lack of C3b binding [17].

Several hypotheses have been proposed about the recent increase in *C. jejuni* bacteremia. Variability in clinical expression may be related to bacterial genetic diversity, but to our knowledge, the virulence factors that have been described thus far allow only for the discrimination between colonizing and infective strains, but no chromosomal or mobile genetic elements responsible for virulence have been identified so far [18].

A study on reservoirs to invasive infections described a higher proportion of chicken-attributed isolates in invasive

Table 4. Thirty-day Clinical Outcomes According to Antibiotic Treatment in Patients With Bacteremia, With or Without Secondary Localization (N = 426)

Treatment by Bacteremia Group	Patient Outcome, No. (%)	
	Death	Relapse
Uncomplicated bacteremia (n = 353)		
β-Lactam monotherapy (n = 165)	10 (6.1)	5 (3)
Amoxicillin (n = 33)	1 (3)	0
Amoxicillin-clavulanate (n = 110)	9 (8.2)	4 (3.6)
Carbapenem (n = 22)	0	1 (4.5)
Macrolide monotherapy (n = 50)	3 (6)	0
Fluoroquinolone monotherapy (n = 22)	2 (9.1)	0
Tetracycline monotherapy (n = 4)	0	2 (50)
Aminoglycoside monotherapy (n = 15)	6 (40)	1 (7.1)
β-Lactam bitherapy (n = 85)	11 (12.9)	2 (2.4)
+Aminoglycoside (n = 59)	6 (10.2)	2 (3.4)
+Macrolide (n = 15)	0	0
+Fluoroquinolone (n = 11)	5 (45.5)	0
Macrolide + aminoglycoside (n = 5)	1 (20)	0
Macrolide + fluoroquinolone (n = 4)	1 (25)	0
Fluoroquinolone + aminoglycoside (n = 3)	1 (33.3)	0
Bacteremia with secondary localization (n = 73)		
β-Lactam monotherapy (n = 33)	2 (6.1)[a]	3 (9.1)[b]
Amoxicillin (n = 11)	0	2 (18.2)
Amoxicillin-clavulanate (n = 15)	0	1 (6.7)
Carbapenem (n = 7)	2 (28.6)	0
Macrolide monotherapy (n = 1)	0	0
Fluoroquinolone monotherapy (n = 1)	0	0
Tetracycline monotherapy (n = 1)	0	0
Aminoglycoside monotherapy (n = 1)	0	0
β-Lactam bitherapy (n = 34)	2 (5.9)[c]	3 (8.8)[d]
+Aminoglycoside (n = 12)	2 (18.2)	1 (8.3)
+Macrolide (n = 5)	0	2 (40)
+Fluoroquinolone (n = 17)	0	0
Fluoroquinolone + aminoglycoside (n = 2)	0	0

[a]Carbapenem monotherapy for vascular localizations.

[b]Amoxicillin for 1 patient with shoulder arthritis and 1 patient with vascular prosthesis infection and spondylodiscitis and amoxicillin-clavulanate for 1 vascular localization.

[c]Amoxicillin + gentamicin for hip prosthesis infection and imipenem + gentamicin for endocarditis.

[d]Amoxicillin-clavulanate + gentamicin for endocarditis, amoxicillin + imipenem for arthritis, and amoxicillin + azithromycin for spondylodiscitis.

strains [19]. Interestingly, bile salt and antimicrobial agent resistance are often mediated by the *Campylobacter* multidrug efflux pump (CME), whose expression is associated with the ability of *C. jejuni* to colonize broilers. Therefore, the intensive use of antibiotics during chicken breeding could lead to invasive strain selection. This could also explain the increasing antimicrobial resistance [18]. However, this needs to be balanced regarding NRCCH data on strain origin evaluation as this trend has reversed since 2015 [4].

Finally, host factors might be responsible for this epidemiological modification. In the current study, immunocompromised patients were more susceptible to *C. jejuni*, consistent with the previous French cohort [3]. In the present study, most patients receiving rituximab, an anti-CD20 monoclonal antibody responsible for profound B lymphocyte depletion, were affected by *C. jejuni*. *C. coli* was also more likely to be isolated in patients with hypogammaglobulinemia. *Campylobacter* is the main agent of infectious diarrhea in patients with agammaglobulinemia, who are also more at risk of invasive infections owing to the lack of campylobacter-specific immunoglobulin, particularly digestive mucosa immunoglobulin A [20].

Finally, our study confirms the vascular tropism of *C. fetus,* already described in large series and case reports [21–25], because *C. fetus* bacteremia is frequently complicated by vascular localizations and endocarditis. The endocarditis incidence has probably been underestimated in the absence of recommendations for systematic transthoracic echocardiography, because 11% of the 99 patients with *C. fetus* bacteremia who underwent echocardiography had endocarditis, close to the rate described in *S. aureus* bacteremia [26]. Moreover, foreign implants seemed to be a risk factor for bacterial grafting as endocarditis, vascular infections, and bone and joint involvement often occurred in preexisting implants. These localizations might also be underdiagnosed because routine culture conditions of vascular and osteoarticular samples are not optimal for *Campylobacter* spp. growth. Therefore, we recommend systematic transthoracic echocardiography in *C. fetus* bacteremia and computed tomographic angiography for patients with vascular grafts.

Despite interesting results, this study has several limitations, notably owing to its retrospective nature. Indeed, the census of *Campylobacter* bacteremia was not exhaustive because there is currently no mandatory declaration of these infections in France, this being responsible for an evident recruitment bias. Moreover, some patients were lost to follow-up and final analysis was performed in the remaining population. Therefore, these limitations do not allow us to reach a conclusion about the optimal treatment of *Campylobacter* bacteremia. It should be evaluated through randomized controlled trials, including the need for dual therapy depending on clinical severity and the presence of secondary localizations. Nevertheless, considering their low resistance rates, amoxicillin-clavulanate and gentamicin appear to be the best empirical therapies. Indeed, only 2 strains were resistant to amoxicillin-clavulanate in the present study, while none were reported by the NRCCH among 5050 strains evaluated in 2019 [4] and only 3 were resistant to aminoglycosides.

Almost half of the strains were resistant to fluoroquinolone, and particular attention should be given to the high level of resistance of *C. coli* to macrolides, which reached 23.7% in this study and 7.3% reported in 2019 by the NRCCH [4]. Therefore, the use of these drugs should be guided by susceptibility testing. Even though the macrolides' bacteriostatic mechanism does not make it a first-choice treatment for bacteremia, this dogma is currently being questioned in other infections [27, 28]. In the present study, univariate analysis

seemed to show a protective role of macrolide monotherapy for 30-day mortality rates, but this needs to be carefully interpreted regarding the younger age in this group, the almost complete absence of secondary localization, and the likely lower infection severity. Therefore, the role of macrolides in bacteremia remains a matter of debate.

In conclusion, *Campylobacter* is an uncommon cause of bloodstream infection occurring mainly in elderly immunocompromised individuals. We found evidence of significantly reduced survival in patients who did not receive appropriate antimicrobial therapy. Moreover, particular attention should be paid to risk factors for secondary localizations when *C. fetus* is isolated in a blood culture.

Supplementary Data

Supplementary materials are available at *Clinical Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

Notes

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