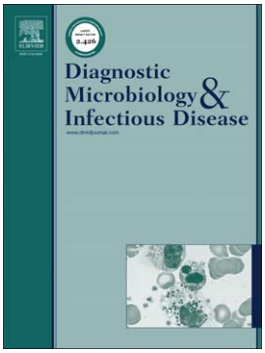

Campylobacter bacteraemia in London: a 44-year single centre study

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Campylobacter bacteraemia in London: a 44-year single centre study

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Abstract

Purpose *Campylobacter* species are a well recognized but rare cause of bloodstream infection.

Methods Here we reviewed 41 cases of *Campylobacter* bloodstream infection occurring at a single centre in London over 44 years, comprising 0.2% of all recorded episodes during this time period.

Results Patients had a mean age of 46 years and, contrasting with previous reports, nearly 50% of our patients did not have significant comorbidities. Ciprofloxacin resistance increased over the study period with 35% of isolates overall being resistant compared with only 3% exhibiting macrolide resistance. Despite a minority of patients receiving appropriate empirical antibiotic therapy, overall mortality was only 7%.

Conclusion *Campylobacter* bacteraemia remains a rare but significant cause of morbidity with a low associated mortality. Underlying immunosuppressive conditions are common but by no means universal. In our setting, macrolides would be favoured as empirical agents to treat suspected *Campylobacter* enteritis, including cases with associated bacteraemia.

Key Words: Campylobacter, bacteraemia, food poisoning, gastroenteritis

Introduction

Campylobacter species are a leading cause of communicable gastrointestinal disease, particularly among patients with immunodeficiency such as HIV infection[1]. First isolated in stool cultures in 1972, [2] *Campylobacter* is a motile, S-shaped, microaerophilic gram-negative bacillus with several important virulence factors including flagella, adhesins and production of enterotoxin. In most cases, *Campylobacter* infection causes a self-limiting enteritis, however severe or extraintestinal infection does occur rarely. Poultry is the major source of zoonotic infection [3] although the organism may also be isolated from contaminated water, [4] cattle,[5] dogs,[6] ducks,[7] goats,[8] monkeys, [9] sheep,[10] and shellfish [11]. Infection with *Campylobacter jejuni* is most frequently recognised as the pathogen preceding the development of Guillain-Barré syndrome, [12] and is associated with other rare post-infectious complications including reactive arthritis and Miller Fisher Syndrome [13,14].

From 2000 to 2012, there were 698,122 laboratory reports of Campylobacter to the Health Protection Agency (now Public Health England) in England and Wales alone. London accounted for between 3,621 and 6,503 laboratory reported cases per annum (http://www.hpa.org.uk/Topics/InfectiousDiseases/InfectionsAZ/Campylobacter/EpidemiologicalData/campyDataEw/ (accessed July 19 2016)). St Thomas's Hospital is a large central London teaching hospital providing care to the boroughs of Lambeth, Southwark, and Lewisham. These boroughs represent greatest number of people living with HIV in the United Kingdom, with a diagnosed HIV prevalence of 14.4 per 1,000 residents in Lambeth and 12.2 per 1,000 residents in Southwark (http://www.hpa.org.uk/webc/HPAwebFile/HPAweb_C/1317139920150. (Accessed July 19 2016)).

Despite Campylobacter species being the most common cause of bacterial diarrhoea in humans, (http://www.efsa.europa.eu/en/efsajournal/doc/130r.pdf. Accessed July 19 2016) *Campylobacter* bacteraemia is rare and few studies

have been published on the topic. The literature features primarily case reports from immunocompetent individuals,[15-17] patients with humoral immune deficiency such as hypogammaglobulinaemia or agammaglobulinaemia, [18-21] or children [22-24]. We present a systematic analysis of all episodes of *Campylobacter* bacteraemia recorded at St Thomas' Hospital between 1972 and 2013.

Materials and methods

Since 1970, the Department of Infectious Diseases has collected prospective records of all bloodstream infection episodes at St Thomas' hospital in London. Since 2004 records from Guy's Hospital, part of the same National Health Service Trust, have been included. We defined a bacteraemic episode as a hospital attendance with at least one positive blood culture for *Campylobacter* species and a compatible clinical illness. The records are kept in an electronic database.

All bacteraemia episodes are classified as either community or hospital-acquired. Episodes were judged to be community acquired if the illness started while the patient was in the community. Hospital acquired episodes had their onset after admission, with positive blood cultures being drawn more than 48 hours after admission. Information gathered included organism species, antibiotic susceptibility, antibiotic treatment, demographic information, major comorbidities, clinical outcomes and focus of infection. Antibiotic therapy was deemed appropriate if the organism was susceptible to the agent *in vitro.*

A manual broth-based system was used from 1970 until 1982. Since then several automated systems have been used, the current system being BacT/ALERT 3D (BioMerieux). Organisms were identified based on a typical colonial appearance, Gram stain morphology and a positive oxidase test. Identification to the species level, where available, was performed by the

national reference laboratory (Public Health England, Colindale, UK). Susceptibility to antibiotics was determined using disc diffusion.

Results

Case series

Between 1970 and 2013 a total of 19,161 bloodstream infections were recorded on our database. Of these, 45% were community acquired and 55% hospital acquired. *Campylobacter* species was first identified in blood cultures from our institution in 1978 (figure 1). We identified a total of 41 *Campylobacter* bacteraemia episodes (table 1) in 41 patients. Twenty-seven patients (66%) were men, and 14 patients were women. The mean age of our cohort was 46 years (standard deviation ± 20.9) and median age was 42 years (interquartile range 30 to 63 years). All cases were community acquired.

There were six species of *Campylobacter* accounting for the majority of cases (table 2). *C. jejuni* accounted for 20 (48.8%) of the total cases. Further species included *C. fetus* (n=2, 4.9%), *C. coli* (n=3, 7.3%), *C. hyointestinalis* (n=1, 2.4%), *C. upsaliensis* (n=1, 2.4%), and *C. ureolyticus* (n=1, 2.4%). Thirteen (31.7%) organisms were not speciated.

The focus of infection in the majority of cases (70.7%) was the gastrointestinal tract (figure 2). We also identified one case of endocarditis, one case of biliary sepsis, and one case of septic thrombophlebitis in an intravenous drug abuser. A clear focus of infection could not be identified in nine cases (22%). Time to blood culture positivity was recorded for thirty-four cultures, (Table 1) and the median value was 2 days (interquartile range 2-4 days).

Clinical and laboratory features

Clinical and laboratory feature are shown in Table 3. All 41 cases documented (100%) had experienced a temperature greater than 38°C, 16 cases (44%) reported diarrhoeal disease, 14 cases (39%) reported abdominal pain, and two cases underwent emergency appendicectomy (5%). Twelve patients (39%) did not have any diarrhoea, vomiting or abdominal pain.

From our cohort, three patients required treatment in the intensive care unit (8%) and the overall mortality was 4.9% (2 of 41). Four patients (11%) were known to be infected with HIV (table 4). Of these, one patient had a CD4 lymphocyte count of 287 cells/mm^3 on admission and three patients had a count less than 10 cells/mm^3. Other underlying illnesses included malignancy in three patients (8%), alcoholic liver disease in three patients (8%) and diabetes mellitus in three patients (8%).

Antibiotic susceptibility and empirical therapy

Data on empirical antibiotic use were available in 29 patients. Eight received no antibiotics, five were treated with empirical ciprofloxacin (3/5 had diarrhoea and 2/5 had presumed biliary infection), four patients received cefuroxime and metronidazole; the remaining 12 patients received co-amoxiclav, clarithromycin, gentamicin, amoxicillin and flucloxacillin in different combinations. Empirical antibiotic therapy was appropriate in only seven of the 29 patients (24%).

Erythromycin susceptibility was demonstrated for 29 of 30 isolates tested (97%). By contrast, only 17 of 26 isolates (65%) tested were susceptible to ciprofloxacin. Notably ciprofloxacin resistance was not detected before 1999 (nine isolates). However, since 1999 just over 50% of *Campylobacter* isolates from blood exhibited ciprofloxacin resistance. In 2013 our laboratory isolated *Campylobacter* species from stool specimens collected from 290 patients. Of these only 53% were susceptible to ciprofloxacin but 98% were susceptible to erythromycin.

Discussion

This study describes the clinical and epidemiological features of *Campylobacter* bacteraemia in an urban setting in the United Kingdom (UK). We found that *C. jejuni* was the commonest species implicated and although underlying immunosuppressive diseases were common, approximately half of the patients had no underlying conditions. Predisposing host risk factors described in the literature include male gender and the host immune status prior to bacterial exposure [25,26]. In a single centre study in Madrid, Spain, a total of 15 out of 64 cases (23%) of *Campylobacter* bacteraemia were in patients with known HIV infection [15]. Previous work in the UK by the Public Health Laboratory Service (PHLS) and the Communicable Disease Surveillance Centre (CDSC) studied the laboratory reports of *Campylobacter* in England from 1981 to 1991. A total of 267,565 faecal samples were positive for *Campylobacter*, and 394 were associated with bacteraemia with a total of 7 deaths [16]. The data highlighted that bacteraemia usually followed an acute episode of *Campylobacter* diarrhoea and the incidence of bacteraemia was highest among the elderly over 65 years with 5.6 per 1000 diarrhoeal cases, compared with 0.3 per 1000 cases among children aged 1 to 4 years.

The pathogenesis of *Campylobacter* infection remains poorly understood, in part due to the lack of an animal model that mimics human gastrointestinal disease and identify correlates of virulence [27]. Several virulence factors have been identified. Bacterial risk factors for bacteraemia include the expression of cytotoxin, flagella and serum resistance although putative virulence genes iam, capA, virB and cdtB are not associated with bacteremia [28,29]. Several species of *Campylobacter* may also circumvent the immune system by, for example preventing effective stimulation of toll-like receptors 5 and 9 [30]. Predisposition of patients with HIV/AIDS for opportunistic infection with *Campylobacter* species suggests a role for cell-mediated immunity. It is notable that three of the four patients infected with HIV presented in the first half of our study, suggesting that the advent of antiretroviral therapy in 1996 might reduce the susceptibility to *Campylobacter* bacteraemia.

Mortality may appear high but it is important to note this represents a snapshot at a single centre. Data from pre-1990 suggests an overall mortality of 1.77% in the UK associated with *Campylobacter* blood stream infections however it is recognized that immunocompromise is a risk factor for death. Indeed one case series from Barcelona reported a *Campylobacter jejuni* bactereamia mortality rate of 11.5%, significantly associated with HIV infection.

Nationally and internationally the proportion of *Campylobacter* isolates exhibiting ciprofloxacin resistance has been increasing since the late 1990's, in human stool samples (30-90% isolates resistant), isolates from blood cultures (62.5%) and broiler chicken carcasses (80%) with rates steadily increasing [31-34], which mirrors our experience. Erythromycin resistance remains relatively rare; though a prolonged outbreak of multidrug resistant *C. jejuni* occurred in Canada between 2003-2013 amongst men who have sex with men [35]. With such high rates of resistance, ciprofloxacin is no longer a suitable first line antibiotic for patients with suspected Campylobacter enteritis or bacteraemia. Although data are scarce to guide empirical treatment, macrolides or carbapenems would be favoured agents.

We were unable to estimate the incidence of the *Campylobacter* bacteraemia as our study was hospital-based in a single centre. However our findings are consistent with studies published in the literature, in particular the predisposition among men, for those with HIV, a high proportion of extraintestinal or unknown foci of infection, and the predominance of *C. jejuni* bacteraemia [17]. Furthermore, studies from France and Israel highlighted the higher proportion of *Campylobacter* bacteraemia among patients with malignancy and liver disease, which is consistent with our findings [36,37]. *Campylobacter* enteritis is often associated with systemic upset and fever, and it is possible that transient bacteraemia occurs as part of this illness but in immunocompetent individuals is rapidly extinguished by the immune

response. Notably a recent Swedish study reported an upswing in the incidence of *Campylobacter* bacteraemia in 2014 [38]. Careful investigation revealed it was temporally related to changes in detection methods: BacT/Alert Plus bottles containing combination of O2, CO2 and N2 replacing O2 containing BACTEC bottles. In addition, apparent differences in incidence over time or between countries may reflect different thresholds for blood culture collection or different duration of incubation of blood culture bottles, rather than true variation in incidence. The advent of molecular diagnostic techniques means speciation is becoming easier and faster with newer species of *Campylobacter* being detected in blood cultures [39,40]. It is notable that the mortality from this infection in our study (4.9%) was low, despite the use of frequently inactive empirical antimicrobials, suggesting that the organism has intrinsically low virulence.

Two recently reported outbreaks of campylobacteriosis have been linked to commercial catering serving chicken livers leading to a novel theory linking modern restaurant cooking styles with outbreaks of *Campylobacter* [41,42]. The increasing popularity of chicken livers, particularly served pink or made into pate leading to estimations that 19%–52% of livers served commercially in the United Kingdom fail to reach 70°C and that predicted *Campylobacter* survival rates are 48%–98%[43] .

Ongoing surveillance would be prudent to ensure the incidence of bacteraemia remains low, in particular considering the widespread nature of *Campylobacter* among human and animal hosts and the existing burden of gastrointestinal disease.

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Declaration of interest

Dr O'Hara has been awarded grants from the British Infection Association and the Academy of Medical Sciences UK.

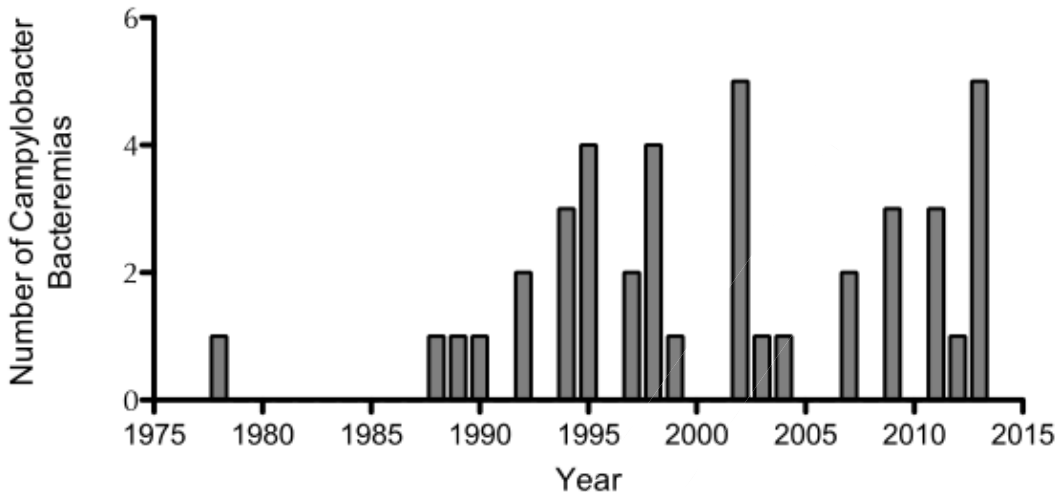

Figure 1. Number of cases of *Campylobacter* bacteraemia, 1975 to 2013

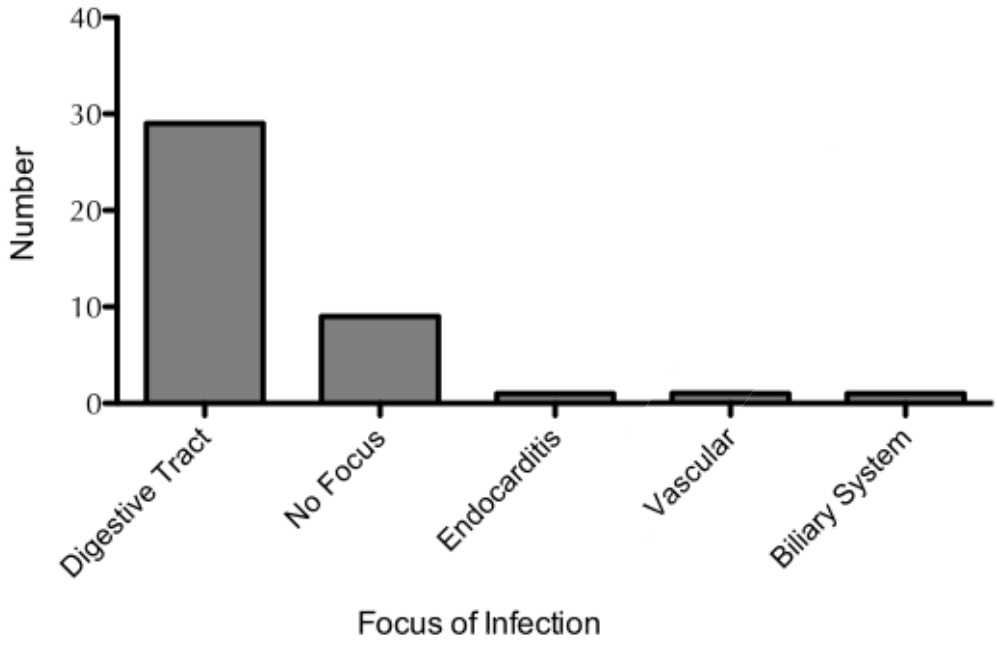

Figure 2. Focus of infection for *Campylobacter* bacteraemia

CASE	YEAR	AGE	SEX	OUTCOME	ORGANISM	FOCUS	GI SYMPTOMS	UNDERLYING CONDITION	TIME TO POSITIVITY(DAYS)
1	1978	23	M	S	*Campylobacter* spp.	DIGESTIVE TRACT	NR	RENAL FAILURE	4
2	1988	48	F	S	*C. jejuni*	DIGESTIVE TRACT	NONE	LIVER CIRRHOSIS	4
3	1989	32	M	S	*C. jejuni*	DIGESTIVE TRACT	NR	DIABETES RENAL FAILURE TRANSPLANT - RENAL	4
4	1990	80	M	S	*C. jejuni*	DIGESTIVE TRACT	NONE	MALIGNANCY	4
5	1992	76	F	S	*C. fetus*	ENDOCARDITIS	NONE	OTHER	NR
6	1992	30	M	S	*Campylobacter* spp.	DIGESTIVE TRACT	DIARRHOEA	NONE	4
7	1994	42	M	S	*C. jejuni*	NO FOCUS	NONE	HIV/AIDS	3
8	1994	28	M	S	*C. jejuni*	DIGESTIVE TRACT	DIARRHOEA	NONE	2
9	1994	38	M	S	*C. jejuni*	DIGESTIVE TRACT	ABDOMINAL PAIN	HIV/AIDS	4
10	1995	38	M	S	*C. jejuni*	DIGESTIVE TRACT	DIARRHOEA	NONE	3
11	1995	30	F	S	*C. jejuni*	DIGESTIVE TRACT	DIARRHOEA	PREGNANCY	6
12	1995	40	M	D	*Campylobacter* spp.	NO FOCUS	DIARRHOEA	HIV/AIDS	4
13	1995	64	M	S	*C. jejuni*	DIGESTIVE TRACT	NONE	NONE	2
14	1997	45	M	S	*C. jejuni*	DIGESTIVE TRACT	ABDOMINAL PAIN DIARRHOEA	LIVER CIRRHOSIS	1
15	1997	23	F	S	*C. jejuni*	DIGESTIVE TRACT	ABDOMINAL PAIN FEVER DIARRHOEA	OTHER	3
16	1998	85	M	D	*C. jejuni*	DIGESTIVE TRACT	DIARRHOEA	NONE	2
17	1998	52	F	S	*Campylobacter* spp.	DIGESTIVE TRACT	ABDOMINAL PAIN DIARRHOEA	NONE	2
18	1998	28	M	S	*C. jejuni*	DIGESTIVE TRACT	ABDOMINAL PAIN FEVER DIARRHOEA	NONE	2

19	1998	21	M	S	*Campylobacter* spp.	DIGESTIVE TRACT	ABDOMINAL PAIN FEVER DIARRHOEA	NONE	2
20	1999	29	F	S	*C. jejuni*	DIGESTIVE TRACT	ABDOMINAL PAIN FEVER DIARRHOEA	NONE	5
21	2002	37	M	S	*Campylobacter* spp.	DIGESTIVE TRACT	NONE	OTHER	2
22	2002	37	M	S	*Campylobacter* spp.	DIGESTIVE TRACT	ABDOMINAL PAIN FEVER DIARRHOEA	OTHER	3
23	2002	55	M	S	*C. jejuni*	NO FOCUS	NONE	HIV/AIDS	2
24	2002	60	M	S	*C. upsaliensis*	NO FOCUS	NONE	OTHER	2
25	2002	62	M	S	*C. hyointestinalis*	DIGESTIVE TRACT	DIARRHOEA	GALLSTONES LIVER CIRRHOSIS	3
26	2003	1 day	F	S	*C. fetus*	NO FOCUS	NONE	PREMATURE	4
27	2004	74	M	S	*Campylobacter* spp.	DIGESTIVE TRACT	DIARRHOEA FEVER	DIABETES	2
28	2007	65	F	S	*C. jejuni*	NO FOCUS	NONE	DIABETES	2
29	2007	20	F	S	*C. jejuni*	NO FOCUS	NONE	OTHER	NR
30	2009	80	F	S	*C. coli*	BILE (ERCP)	NR	MALIGNANCY	NR
31	2009	46	M	S	*C. coli*	DIGESTIVE TRACT	NR	INTRAVENOUS DRUG USE LIVER CIRRHOSIS	4
32	2009	63	F	S	*Campylobacter* spp.	NO FOCUS	NR	MALIGNANCY	NR
33	2011	38	F	S	*Campylobacter* spp.	DIGESTIVE TRACT	ABDOMINAL PAIN FEVER DIARRHOEA	NONE	2
34	2011	63	M	S	*Campylobacter* spp.	DIGESTIVE TRACT	NR	MALIGNANCY TRANSPLANT - BONE MARROW	NR
35	2011	21	F	S	*Campylobacter* spp.	DIGESTIVE TRACT	ABDOMINAL PAIN FEVER	NONE	1
36	2012	83	F	S	*C. coli*	DIGESTIVE TRACT	ABDOMINAL PAIN DIARRHOEA	NONE	2
37	2013	53	M	S	*Campylobacter* spp.	DIGESTIVE TRACT	DIARRHOEA	DIABETES RENAL FAILURE	2

38	2013	77	M	D	*C. jejuni*	NO FOCUS	NONE	MALIGNANCY	NR
39	2013	42	M	S	*C. ureolyticus*	SEPTIC THROMBOPHLEBITIS	FEVER	INTRAVENOUS DRUG USE	NR
40	2013	35	M	S	*C. jejuni*	DIGESTIVE TRACT	ABDOMINAL PAIN FEVER DIARRHOEA	NONE	NR
41	2013	29	M	S	*C. jejuni*	DIGESTIVE TRACT	FEVER	NONE	2

Table 1. Case series of *Campylobacter* bacteraemia, 1970 to 2013

Time to positivity = time for blood cultures to become positive. S = Survived, D = Died NR = not recorded.

ORGANISM ISOLATED	NUMBER OF PATIENTS (%)	YEAR FIRST ISOLATED
Campylobacter jejuni	20 (48.8)	1989
Campylobacter fetus	2 (4.9)	1992
Campylobacter coli	3 (7.3)	2002
Campylobacter hyointestinalis	1 (2.4)	2002
Campylobacter upsaliensis	1 (2.4)	2002
Campylobacter ureolyticus	1 (2.4)	2013
Campylobacter (unspeciated)	13 (31.7)	1978

Table 2. *Campylobacter* species isolated from blood from 1970 to 2013.

SYMPTOM	NUMBER OF PATIENTS (%)
FEVER	35 (85)
DIARRHOEA	19 (46)
ABDOMINAL PAIN	13 (32)
JOINT PAIN	3 (7)
HEADACHE	4 (10)
VOMITING	2 (5)
WEIGHT LOSS	3(7)

Table 3. Clinical features in patients with *Campylobacter* bacteraemia

UNDERLYING CONDITION	NUMBER (%)
PREMATURITY	1 (2.4)
PREGNANCY	1 (2.4)
INTRAVENOUS DRUG USE	2 (4.9)
RENAL FAILURE	3 (7.3)
DIABETES	4 (9.8)
LIVER FAILURE	4 (9.8)
HIV/AIDS	4 (9.8)
MALIGNANCY	5 (12.2)
NONE	19 (46.3)

Table 4. Underlying conditions of patients with *Campylobacter* bacteraemia.

Compliance with Ethical Standards
Funding: None
Conflict of Interest: None
Ethical approval : Not required
Informed consent: Not required

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