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Campylobacter bacteremia in London: A 44-year single-center 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 center 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 bacteremia 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 favored as empirical agents to treat suspected *Campylobacter* enteritis, including cases with associated bacteremia.

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1. Introduction

Campylobacter species are a leading cause of communicable gastrointestinal disease, particularly among patients with immunodeficiency such as HIV infection (Kaakoush et al., 2015). First isolated in stool cultures in 1972 (Dekeyser et al., 1972), *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 (Friedman et al., 2004) although the organism may also be isolated from contaminated water (Denis et al., 2011), cattle (Enokimoto et al., 2007), dogs (Parsons et al., 2010), ducks (Nonga and Muhairwa, 2010), goats (Hutchinson et al., 1985), monkeys (Sestak et al., 2003), sheep (Ertaş et al., 2003), and shellfish (Butzler and Oosterom, 1991). Infection with *Campylobacter jejuni* is most frequently recognized as the pathogen preceding the development of Guillain-Barré syndrome (van Doorn et al., 2008), and is associated with other rare post-infectious complications including reactive arthritis and Miller Fisher Syndrome (Mortensen et al., 2009; Yuki and Kuwabara, 2007).

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 3621 and 6503 laboratory reported cases *per annum* (http://www.hpa.org.uk/Topics/InfectiousDiseases/InfectionsAZ/Campylobacter/EpidemiologicalData/campyDataEw/ (accessed July 19 2016)). St Thomas' 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 1000 residents in Lambeth and 12.2 per 1000 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 diarrhea in humans, (http://www.efsa.europa.eu/en/efsajournal/doc/130r.pdf. Accessed July 19 2016) *Campylobacter* bacteremia is rare and few studies have been published on the topic. The literature features primarily case reports from immunocompetent individuals (Fernández-Cruz et al., 2010; Pigrau et al., 1997; Skirrow et al., 1993), patients with humoral immune deficiency such as hypogammaglobulinaemia or agammaglobulinaemia (Aggarwal et al., 2010; Pereira et al., 2014; van den Bruele et al., 2010; Yamagami et al., 2014), or children (Alnimr, 2014; Ben-Shimol et al., 2013; Tsoni et al., 2012). We present a systematic analysis of all episodes of *Campylobacter* bacteremia recorded at St Thomas' Hospital between 1972 and 2013.

2. Materials and methods

Since 1970, the Department of Infectious Diseases has collected prospective records of all bloodstream infection episodes at St Thomas'

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hospital in London. Since 2004 records from Guy's Hospital, part of the same National Health Service Trust, have been included. We defined a bacteremic 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 bacteremia 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.

3. Results

3.1. 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 (Fig. 1). We identified a total of 41 *Campylobacter* bacteremia 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 (Fig. 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 34 cultures, (Table 1) and the median value was 2 days (interquartile range 2–4 days).

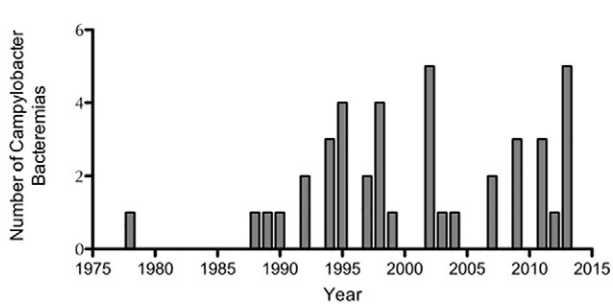

Fig. 1. Number of cases of *Campylobacter* bacteremia, 1975 to 2013.

3.2. 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 diarrheal disease, 14 cases (39%) reported abdominal pain, and two cases underwent emergency appendectomy (5%). Twelve patients (39%) did not have any diarrhea, 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%).

3.3. 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 diarrhea 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.

4. Discussion

This study describes the clinical and epidemiological features of *Campylobacter* bacteremia 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 (Feodoroff et al., 2011; Nielsen et al., 2009). In a single-center study in Madrid, Spain, a total of 15 out of 64 cases (23%) of *Campylobacter* bacteremia were in patients with known HIV infection (Fernández-Cruz et al., 2010). 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 fecal samples were positive for *Campylobacter*, and 394 were associated with bacteremia with a total of 7 deaths (Skirrow et al., 1993). The data highlighted that bacteremia usually followed an acute episode of *Campylobacter* diarrhea and the incidence of bacteremia was highest among the elderly over 65 years with 5.6 per 1000 diarrheal 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 (Poly and Guerry, 2008). Several virulence factors have been identified. Bacterial risk factors for bacteremia include the expression of cytotoxin, flagella and serum resistance although putative virulence genes iam, capA, virB and cdtB are not associated with bacteremia (Louwen et al., 2012; Nielsen et al., 2010). Several species of *Campylobacter* may also circumvent the immune system by, for example preventing effective stimulation of toll-like receptors 5 and 9 (Konkel et al., 1999). Predisposition

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