

Campylobacter bacteremia in children

Bacteriemias por *Campylobacter* spp en niños

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What do we know about the subject matter of this study?

Bacteremia due to *Campylobacter* spp is very rare and occurs especially in patients with some comorbidity or immunocompromise or at extreme ages of life. The gastrointestinal focus is the most frequent.

What does this study contribute to what is already known?

This study provides data on the clinical microbiological characteristics of *Campylobacter* spp bacteremia in pediatrics as well as its evolution and the local sensitivity patterns in order to be able to establish a timely treatment.

Abstract

Campylobacter spp. is a common cause of gastroenteritis in children. Bacteremia represents < 1% of all infections and occurs in immunocompromised patients and at extreme ages. **Objective:** To describe the epidemiological, clinical, and microbiological characteristics of children with *Campylobacter* spp. bacteremia. **Patients and Method:** Observational retrospective study that included patients aged from 0 to 16 years hospitalized between January 2015 and February 2022, due to bacteremia with at least one blood culture with isolation of *Campylobacter* spp. The following variables were analyzed: age, sex, underlying disease, symptoms, site of acquisition of the infection, clinical focus of infection, presence of neutropenia and hypogammaglobulinemia, typing and sensitivity of the isolated microorganism, isolation in other sites, initial and definitive treatment, complications, and evolution. Bacterial identification was performed by mass spectrometry and sensitivity was determined by the agar disk diffusion method. **Results:** 30 patients were included, median age 54 months (IQR 23-100 months). 86.6% presented an underlying disease and 70% had compromised immunity. The main clinical focus was gastrointestinal (70%). The species identified were *C jejuni* (n:24, 77.4%), *C upsalsensis* (n:3, 10%), *C coli* (n:2, 6.6%), and *C ureolyticus* (n:1, 3.3%). The sensitivity to meropenem was determined in 27 isolates that were 100% susceptible. Susceptibility to ciprofloxacin and erythromycin was 15% and 91%, respectively. One patient died because of an infection (3%). **Conclusion:** *Campylobacter* spp. bacteremia is more frequent in immunocompromised patients. *C jejuni* was the most frequently isolated species. Sensitivity to carbapenems was 100%. Mortality was low in this clinical series.

Keywords:

Campylobacter spp;
Bacteremia;
Opportunistic
Infections;
Immunocompromise

Introduction

Bacteria of the genus *Campylobacter* are a common cause of gastroenteritis in children and young adults and represent one of the main causes of foodborne infections^{1,2}. Occasionally, it has been documented as an etiologic agent in invasive infections such as cellulitis, septic arthritis, meningitis, endocarditis, pericarditis, cholecystitis, pancreatitis, hepatitis, thrombophlebitis, or respiratory infections³. In addition, *Campylobacter* infection, especially *C. jejuni*, has been reported as a probable trigger of Guillain-Barre syndrome and hemolytic uremic syndrome⁴.

However, bacteremia due to *Campylobacter* spp. is very rare; it represents < 1% of all infections caused by this microorganism and occurs especially in patients with some comorbidity or immunocompromise or at extreme ages of life⁵. There are few studies describing the characteristics of patients with *Campylobacter* spp bacteremia, especially in pediatrics, and none (to our knowledge) carried out in Latin America. In 2021, the Microbiology Service of our institution published a paper describing the fundamental microbiological characteristics of 21 patients with isolation of *Campylobacter* spp in blood cultures between January 2014 and September 2020⁶.

The objective of this work is to describe the microbiological and clinical characteristics of children with *Campylobacter* spp bacteremia, with an in-depth study of the clinical aspects, laboratory findings, and the therapeutic strategy used.

Patients and Method

Study design

Observational, descriptive, and retrospective study which included all patients with bacteremia due to *Campylobacter* spp. The study was carried out in a third-level pediatric hospital located in Buenos Aires (Argentina). It has more than 600 inpatient beds, 5 intensive care units (ICU), and 1 neonatal ICU. Children are admitted from the Emergency Service and the Out-patient Offices, where patients concur spontaneously or are referred from other institutions from all over the country.

The inclusion criteria were age between 0 and 16 years, having a hospital admission between January 2015 and February 2022 due to an infection with at least one blood culture with isolation of *Campylobacter* spp.

The medical records were reviewed, and the following data were recorded: age, sex, baseline disease, symptoms, source of infection, clinical focus of infection, presence of neutropenia and hypogammaglobu-

linemia, typing and sensitivity of the isolated microorganism, isolation in other sites, initial and definitive treatment, complications, and evolution.

Bacteremia due to *Campylobacter* spp was defined as the isolation in one or more blood cultures of a microorganism belonging to the *Campylobacter* genus, with a maximum incubation period of 5 days. Regarding the source of infection, out-of-hospital infection was considered the one present at hospital admission or that manifested itself up to the first 48 hours of hospitalization, and in-hospital infection was considered the one whose clinical manifestations appeared after 48 hours of hospitalization. The clinical focus of infection was established by the presence of local signs and symptoms of infection and/or by the isolation of the same microorganism in blood cultures and at the site of infection. Primary bacteremia was assumed in the absence of another source of infection.

A patient was considered to have received effective initial treatment after empirical antibiotic treatment with adequate sensitivity of the isolated microorganism, according to antibiotic susceptibility tests. Recurrence of bacteremia was defined as the isolation of the same microorganism in new blood cultures, detected at least 1 month after the resolution of the initial episode.

Death attributed to infection was assumed to be death in a patient with persistent signs and symptoms caused by *Campylobacter* spp bacteremia and in the absence of another cause with or without persistent positive blood cultures.

Microbiological aspects

Bacterial identification was performed by mass spectrometry (MALDI-TOF MS) with Vitek MS® (Biomérieux Argentina) and sensitivity was determined by the disk diffusion method using Mueller-Hinton agar with 5% sheep blood; the Clinical and Laboratory Standards Institute (CLSI) cut-off points of erythromycin and ciprofloxacin for *Campylobacter* and meropenem for Enterobacteriaceae were considered⁷.

Statistical analysis

For the descriptive analysis, categorical variables were expressed as percentages and continuous variables as median and interquartile range (IQR). Microsoft Excel, version 2019, was used.

Ethical considerations

This study was approved by the Ethics Committee of the institution. The research was subject to current regulations and the data were analyzed anonymously and confidentially.

Results

During the study period, 30 patients with *Campylobacter* spp bacteremia were identified, representing 0.9% of the positive blood cultures. Of these, 19 (63.3%) were male. The median age was 54 months (IQR: 23 -100 months). 26 patients (86.6%) had some underlying pathology: leukemia (n = 11, 36.6%), non-oncologic liver disease (n = 5, 16.6%), solid organ transplantation (n=4, 13.3%), solid organ tumor (n = 2, 6.6%), primary immunodeficiency (n = 1, 3.3%), chronic kidney disease (n = 1, 3.3%), and chronic non-progressive encephalopathy (n = 1, 3.3%). Four patients had no comorbidity. Of these, 3 were younger than 6 months so their age may have been a determining factor in the severity of infection. The remaining patient was 6 years old, presented with fever and gastrointestinal focus, and blood cultures were negative before starting antibiotic treatment. The presence of an associated immunological disease was ruled out.

Infection acquisition was out-of-hospital in 27 patients (90%) and in-hospital in 3 patients. Although in-hospital cases were few, no differences in antibiotic sensitivity or severity were observed in this group compared to out-of-hospital cases. 21 patients (70%) regularly attended the hospital for treatment of chronic pathologies. 15 patients (50%) had a central venous catheter, but no device-associated bacteremia was observed.

The main symptoms on admission were fever (n = 29, 96.6%), abdominal pain (n = 15, 30%), non-bloody diarrhea (n = 13, 43.3%), bloody diarrhea (n = 5, 16.6%), and vomiting (n = 4, 13.3%). The main clinical focus was gastrointestinal in 21 patients (70%). One patient with chronic liver disease presented edematous-ascitic syndrome. 7 patients (23.3%) had no evident clinical focus, and primary bacteremia was assumed (table 1). Of these, 6 were immunosuppressed patients and the remaining one was neonate.

9 patients (30%) presented neutropenia at the time of diagnosis. Gamma globulin concentrations were evaluated in 17 patients, of whom 7 (40%) had hypogammaglobulinemia.

The species identified were *C. jejuni* (n = 24, 77.4%), *C. upsalsensis* (n = 3, 10%), *C. coli* (n = 2, 6.6%), and *C. ureolyticus* (n=1, 3.3%). In one patient, identification to species level was not possible. The median time to isolation was 54 hours (IQR: 39.5-68.75 hours). Sensitivity to meropenem was determined in 27 isolates which were 100% sensitive. Table 2 shows the sensitivity to erythromycin and ciprofloxacin. In 21 patients, a concomitant stool culture was performed simultaneously (up to 5 days after bacteremia) of which 5 (23.8%) were positive for the same agent found in blood cultures.

28 (93.3%) patients received empirical treatment with piperacillin-tazobactam (PTZ) in 20 of them (71.4%), meropenem in 4 (14%), and ceftriaxone in 4 (14%). Only the 4 patients who received carbapenem empirically received effective initial treatment. The median time to indicate effective treatment was 1.5 days (IQR: 1-4.75) and it was meropenem in all cases, which was maintained for a median of 11 days (IQR: 10-14 days).

Four patients (14%) developed septic shock, and one patient developed acute renal failure. No immunoreactive complications (Guillain Barré syndrome, reactive arthritis) were observed. One patient died due to the infection; the patient had leukemia, was admitted with a gastrointestinal focus (without neutropenia or hypogammaglobulinemia), and received treatment with meropenem at the appropriate dose from the time of admission. Blood cultures were confirmed to be negative 48 hours after effective treatment; however, the patient developed septic shock and died 10 days after hospitalization, with no other microbiological isolates documented.

Table 1. Number and percentage of patients presenting each symptom and clinical focus of infection at the time of hospital admission

Symptom, N° (%)	
Fever	29 (96.6)
Abdominal pain	15 (50)
Non-bloody diarrhea	13 (43.3)
Bloody diarrhea	5 (16.6)
Vomiting	4 (13.3)
Clinical focus of infection, N° (%)	
Gastrointestinal	21 (70)
Primary bacteremia	7 (23.3)
Edematous ascitic syndrome	1 (3.3)

Table 2. Number and percentage of isolates that were sensitive and resistant to evaluated antimicrobials

	Number of evaluated isolates	Sensitive, No. (% of evaluated)	Resistant, No. (% of evaluated)
Erythromycin	23	21 (91)	2 (9)
Ciprofloxacin	20	3 (15)	17 (85)
Meropenem	27	27 (100)	0 (0)

Discussion

The *Campylobacter* genus consists of gram-negative, motile, non-spore-forming, curved bacilli whose main reservoir is the digestive tract of birds and mammals. Ingestion of contaminated meat is the main form of human infection, although, in rural environments in underdeveloped countries, it is possible to contract the infection by exposure to chicken feces in the domestic environment¹.

Several studies have demonstrated the higher prevalence of *Campylobacter* spp bacteremia in immunocompromised patients and extreme ages of life^{4,5,8}. In the pre-HAART era, HIV/AIDS was the main risk factor⁹. Currently, it is described especially in patients with liver disease, oncologic disease, humoral immunodeficiency, and solid organ and bone marrow transplantation⁴.

In most series, the main source of infection is the abdominal area, although the respiratory and urinary areas, skin and soft tissue, and intravascular devices have also been described as sources of infection. Up to 25% of the episodes may correspond to primary bacteremia^{4,10}.

In our series, gastrointestinal symptoms were the main clinical focus of infection. The fecal culture was positive in 23.8% of the samples analyzed, a result similar to that reported in other series, which report a positive stool culture in 19-38% of the cases of bacteremia due to *Campylobacter* spp¹⁰⁻¹². The low percentage of isolation in stool culture could be because it is a fastidious microorganism, difficult to grow. Variables such as the administration of antibiotics, the low volume of material submitted, or the time from the onset of symptoms to the collection of the sample could also influence the results found¹³.

A study in Israel compared the characteristics of episodes of *Campylobacter* spp bacteremia in children with and without risk factors¹². They concluded that in healthy hosts it manifests as a single episode, at younger ages, and with gastrointestinal symptoms, while in those with risk factors, it is observed in older patients, often without an evident clinical focus, and there may be infection recurrence.

An association between *Campylobacter* spp bacteremia and humoral immunodeficiency has been described¹⁴. In this study, only one patient had primary immunodeficiency as an underlying disease and hypogammaglobulinemia was found in 17 patients.

There are more than 25 species within the *Campylobacter* genus. Those usually described in patients with acute gastroenteritis are *C. jejuni* in 95% of the cases and *C. coli* in 4%; the rest of the species together cause 1% of the episodes¹⁵. A classic description from 1978

identified *C. fetus* as responsible for most episodes of bacteremia¹⁶. However, in later series^{4,5,10,17}, including a study in a pediatric population¹², *C. jejuni* predominates, as in this work. This difference could be due to the increase in the immunosuppressed population (which is at risk of bacteremia by less aggressive species) or, as Skirrow et al. stated, to advances in diagnostic methods for *C. jejuni* and *C. coli*¹⁷.

Campylobacter spp has traditionally been resistant to most beta-lactam antibiotics, so macrolides and quinolones were for many years the empirical treatment of choice¹⁸. Since the 1990s, *Campylobacter* spp resistance to fluoroquinolones has increased rapidly in different countries, being recognized as an emerging public health problem¹⁹⁻²¹. This coincided with the approval of the use of fluorinated quinolones in veterinary medicine²². Therefore, quinolones are no longer a therapeutic alternative when *Campylobacter* spp infection is suspected^{1,23,24}. In addition, there is evidence that infections caused by quinolone-resistant strains are more severe and prolonged than those caused by sensitive strains^{21,22,25}.

Although some studies have warned about the increased resistance of *Campylobacter* spp. to macrolides²⁶, in this and other series, sensitive isolates predominated^{10,12}. Therefore, they continue to be a valid alternative as a treatment for gastrointestinal conditions caused by this microorganism, although they would not be the treatment of choice in invasive infections such as bacteremia²⁴.

Studies analyzing the sensitivity of *Campylobacter* spp. to carbapenems in human infections report sensitivity rates close to 100%^{4,10,12}.

Except for carbapenems, most *Campylobacter* spp strains are considered resistant to beta-lactam antibiotics²⁷. The main mechanism involved is the production of a variety of beta-lactamase enzymes, but modification of cell membrane porins and the presence of efflux pumps have also been described²⁸. The efficacy of beta-lactam antibiotics combined with beta-lactamase inhibitors such as piperacillin-tazobactam is still unclear²⁹.

Regarding mortality associated with infection, it varies in different studies between 0% (pediatric cohort only)¹² and 15%⁴. Data regarding the impact of inadequate treatment on mortality are not conclusive; some studies found an association between both variables¹¹, while other publications did not^{4,10,30}. In our series, the low mortality rate (3%) is not consistent with the low percentage of patients with adequate empirical treatment and the high number of immunocompromised patients. However, we must emphasize that most patients received piperacillin-tazobactam as initial treatment. As in other series, the lack of data on susceptibility to this antibiotic makes

it difficult to establish with certainty whether it was effective or not.

The main strength of this study is the methodical recording of clinical and microbiological data in a highly complex hospital, in the study of an entity that has few reports in pediatrics. On the other hand, the weakness is that it was performed in a single center and has a retrospective design which did not allow us to know some epidemiological data and that some of the variables analyzed coincide with those described in the work of García et al⁶, performed in the same institution and published in 2021, which included episodes of bacteremia due to *Campylobacter* spp in the period 2014-2020. However, this study adds more clinical and therapeutic information that is relevant to the management of these patients.

It should be noted that knowing the clinical characteristics and sensitivity patterns in children with *Campylobacter* spp bacteremia allows early suspicion of the diagnosis and appropriate empirical treatment.

In conclusion, *Campylobacter* spp bacteremia is infrequent in pediatrics. In this cohort of children, patients with underlying pathology and immunocompromise predominated. The main clinical picture was gastrointestinal. *C. jejuni* was the most frequently isolated species. All the isolates tested were sensitive to meropenem and mortality was low.

Ethical Responsibilities

Human Beings and animals protection: Disclosure the authors state that the procedures were followed according to the Declaration of Helsinki and the World Medical Association regarding human experimentation developed for the medical community.

Data confidentiality: The authors state that they have followed the protocols of their Center and Local regulations on the publication of patient data.

Rights to privacy and informed consent: This study was approved by the respective Research Ethics Committee, which, according to the study's characteristics, has accepted the non-use of Informed Consent.

Conflicts of Interest

Authors declare no conflict of interest regarding the present study.

Financial Disclosure

Authors state that no economic support has been associated with the present study.

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