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RESEARCH

Stool Screening for *Campylobacter* Species in Hypogammaglobulinemic Patients Receiving Immunoglobulin Therapy

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Abstract

Hypogammaglobulinemia (HG) predisposes patients to gastrointestinal *Campylobacter* infections. This prospective study determined the prevalence of *Campylobacter* in stool samples from patients with immunoglobulin (Ig)-substituted HG at Bordeaux University Hospital. 73 patients (42 women, median age: 61) receiving Ig substitution therapy were enrolled from July 2022 to July 2024. Stool samples were analysed with culture, PCR, faecal calprotectin levels, and immune profiles were also assessed. A second stool sample was collected from 38 patients after 6–12 months, totalling 111 samples. 53 patients had primary HG (32 common variable immunodeficiency, 7 IgG subclass deficiencies, 4 Bruton's agammaglobulinemias) and 20 had secondary HG (7 drug-induced, 8 lymphoid hemopathy-related, 5 mixed). *Campylobacter* were detected in 11 patients (15.1%), with species identified as *Campylobacter jejuni*, *Campylobacter coli*, and *Aliarcobacter butzleri*. Diarrhea was reported in 42% of Campylobacter-positive patients versus 15% of negative patients. Campylobacter-positive patients exhibited higher median faecal calprotectin levels (255 µg/g vs. 52 µg/g). Among positive patients, 44% (versus 34% in negative patients) had non-infectious complications such as immune complications. Mean residual IgG levels were similar between groups, although IgA and IgM were lower in Campylobacter-positive patients (0 vs. 0.36 g/L and 0.17 vs. 0.40 g/L, respectively). The mean CD4/CD8 ratio was also lower in the positive group (1.71 ± 0.85 vs. 2.06 ± 1.18). This study reveals a high prevalence of *Campylobacter* in HG patients despite receiving Ig therapy. Elevated faecal levels of calprotectin in symptomatic patients suggests active infection. Screening for *Campylobacter* should be considered in HG patients presenting with digestive symptoms.

Keywords Campylobacter · Hypogammaglobulinemia · Immunodeficiency · Immunoglobulin therapy

Introduction

Campylobacter species are gram-negative bacteria with a single polar flagellum, bipolar flagella, or no flagellum, depending on the species. This genus is the leading cause of bacterial diarrhea worldwide. The most identified species is *Campylobacter jejuni* in human faeces, followed by *Campylobacter coli* [1–3]. *Campylobacter* infections are zoonoses. The main reservoir of this genus is the digestive tract of wild or domestic birds. The main route of human contamination is through the ingestion of contaminated food [4].

Although *Campylobacter* infection usually causes self-limited enteritis and requires no medical intervention,

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an impaired immune response can lead to infectious complications such as bacteraemia or secondary localisation, and post-infectious complications such as Guillain–Barré syndrome [2, 5].

Hypogammaglobulinemia (HG), whether primary or secondary, is frequently complicated by infectious diseases, particularly encapsulated bacteria that infect the respiratory tract. However, there are also reports of gastrointestinal bacterial infections, notably by species in the genus *Campylobacter*. Long-term immunoglobulin (Ig) therapy can significantly reduce the incidence of such infections [6], but patients with HG are still prone to contract prolonged, recurrent, and severe *Campylobacter* infections [7] that can lead to complications such as bacteriemia [8]. Nonetheless, the prevalence of *Campylobacter* in HG patients remains unclear. The literature on this subject is limited to retrospective studies on populations with common variable immunodeficiency (CVID) and a few case reports [9–13].

In this study, we investigated the prevalence of *Campylobacter* in the intestines of Ig-substituted HG patients. We also identified the immunological profiles of patients in whom *Campylobacter* was detected, as well as potential risk factors.

Materials and Methods

Study Design and Patients

We conducted a monocentric, prospective, observational study at Bordeaux University Hospital, involving a cohort of patients with primary or secondary HG who were receiving Ig replacement therapy. Stool samples were collected prospectively, from 4 July, 2022, to 31 July, 2024. Eligible patients were those diagnosed with HG and receiving either intravenous or subcutaneous Ig therapy. Patients under 18 years of age were excluded.

Data Collection

Stool and blood samples were collected from patients twice, when feasible, with a minimum interval of 2 months between collections. Prospectively recorded data included demographics, clinical symptoms, underlying immunodeficiency, and antibiotic treatments. At inclusion, calprotectin levels and immunological data were also extracted, including immunoglobulin levels, B and T lymphocyte phenotypes, HLA-DR expression, gamma-delta lymphocytes, regulatory T cells (Tregs), and natural killer (NK) cells.

Definitions

Underlying conditions were classified as either primary or secondary HG, based on the clinician's diagnosis. In cases of secondary HG, a mixed cause was defined as haematological malignancy treated with immunosuppressive drugs. Diarrhea was defined according to the World Health Organization as the passage of three or more loose or watery stools per day.

A stool sample was considered *Campylobacter*-positive if either stool culture or polymerase chain reaction (PCR) detected any *Campylobacter* species. Patients were classified as positive if at least one stool sample tested positive during the study. Antibiotic treatment was deemed appropriate if the isolated strain was susceptible to at least one of the prescribed antibiotics.

Microbiology and Genomics

All faecal samples were either brought to the hospital by the patient with instructions for storage at a low temperature of 2–8 °C, or directly collected at the hospital by the care team. All samples were sent to the Centre national de référence des campylobacters et hélicobacters (CNRCH). Cultures were performed on Campylosel medium (bioMérieux, Marcy-l'Étoile, France) and incubated in a microaerobic atmosphere at 35 °C. Bacteria were identified via matrix-assisted laser desorption ionisation-time of flight mass spectrometry [14]. PCR tests were performed on 50-µL stool samples using the RIDA Gene bacterial stool panel (R-Biopharm AG, Darmstadt, Germany). This kit allows the detection of *Campylobacter*, *Salmonella*, and *Yersinia enterocolitica*. Susceptibility testing was performed using the disk diffusion method according to the Antibiogram Committee of the French Society of Microbiology and European Committee on Antimicrobial Susceptibility Testing 2023 recommendations.

Whole-Genome Sequencing (WGS) and Assembly of Campylobacter Isolates

WGS was performed from previously prepared pure cultures of each *Campylobacter* isolate. DNA was extracted using the MagNA Pure 6 DNA and viral NA SV kit, which uses bacterial lysis and the MagNA Pure 96 system (Roche Applied Science, Manheim, Germany). Paired-end sequencing was performed using NovaSeq 6000 Illumina technology. Raw sequencing data (.fastq) were cleaned using Sickle v1.33 (https://github.com/najoshi/sickle) and genomes were *de novo* assembled using SKESA v2.5.1 [15].

Species were confirmed using the molecular average nucleotide identity method with FastANI v1.33 [16] based on a threshold of ≥ 95% for validating species. Sequence types (STs), clonal complexes (CCs), and core-genome multilocus sequence types (MLSTs) were identified using PubMLST (cgMLST *Campylobacter* scheme v2.0) [17]. Mechanisms associated with antimicrobial resistance were determined using Blastn command line tool v2.15.0+ [18] combined with multiple databases of genes, proteins, and mutations including the National Center for Biotechnology Information, Comprehensive Antibiotic Resistance Database, and ResFinder databases, as well as an in-house CNRCH *Campylobacter* resistance database. To understand where *C. jejuni* and *C. coli* bacteria might have come from, we used STRUCTURE [19]. This method, combined with information about genes that tend to be specific to certain animal hosts [20, 21] and how the bacteria change over time (mutation analysis) [22], allowed us to estimate the likely sources of contamination. For *C. jejuni*, we considered chicken, ruminants, and the general environment as potential sources. For *C. coli*, we considered chicken, ruminants, and pigs. We also analysed the genetic makeup of any *Campylobacter* bacteria that we found, using Prokka v1.14.5 [23] to identify the genes within the bacterial DNA. Then, we used RFPlasmid v1.0 [24] to predict whether the bacteria contained plasmid DNA.

Immunology

Flow cytometry was used to characterise T lymphocyte subsets in peripheral blood (including central memory T cells CD27+or CCR7+and CD45RA–, naïve T cells CD27+or CCR7+and CD45RA+, effector memory T cells CD27– or CCR7– and CD45RA–, and TEMRA CD27– or CCR7– and CD45RA+) and B cell phenotypes (percentages of naïve B cells CD27– and IgD+, unswitched memory B cells CD27+and IgD+, switched memory B cells CD27+and IgD–, transitional B cells CD24++and CD38++, and plasmablasts CD24– and CD38++).

Flow cytometry analyses were run within 24 h following blood sampling. Unless specified, all monoclonal antibodies (mAbs) were purchased from BD Biosciences (Franklin Lakes, NJ, USA).

Outcomes

The primary outcome was to determine the prevalence of *Campylobacter*-positive stool samples in patients with substituted HG. Secondary outcomes were to compare immunological and clinical characteristics of *Campylobacter*-positive and *Campylobacter*-negative patients, as well as to identify potential risk factors associated with *Campylobacter* infection. Additionally, we investigated the diversity of *Campylobacter* species in our cohort as well as their antibiotic resistance profiles.

Ethical Approval

This study was conducted as a part of routine patient care and falls under the framework of an MR004 study. Under these circumstances, French law does not require formal Ethics Committee approval or informed consent for retrospective data collection (https://www.legifrance.gouv.fr/loda/id/JORFTEXT000000886460/); however, all patients were provided with information regarding the study and did not explicitly object to the use of the data for research purposes.

Statistical Analysis

Descriptive statistics are presented as percentages for categorical variables and as means with standard deviations or medians with interquartile ranges (IQRs) for continuous variables. R Studio (R Core Team, Vienna, Austria) was used to analyse descriptive statistics and GraphPad Prism v9.4.1 (GraphPad Software, La Jolla, CA, USA) was utilised for comparative analyses. Significance was evaluated at a threshold of $p < 0.05$.

Demographic data, underlying conditions, clinical and biological characteristics, and immunological profiles were compared between patients with positive and negative *Campylobacter* test results (both samples and patients). Categorical variables were compared using Fisher's exact test, and noncategorical variables were compared using the Mann–Whitney test.

Results

Characteristics of the Study Population

In total, 73 adult patients were included in the study (Table 1). Among these, 38 (52.1%) had a second stool collection, on average 234 ± 164 days later, resulting in 111 stool samples collected over 2 years. At baseline, the mean age of the patients was 58 years, and the female/male sex ratio was 1.35.

Among the 73 patients, 53 (72.6%) exhibited primary immunodeficiency, 32 with CVID (43.8%), 7 with IgG subclass deficiency (9.6%), 4 with Bruton's agammaglobulinemia (5.5%), and 10 with other diagnoses (13.7%). The mean age of these 53 patients was 53 ± 16 years, and the sex ratio was 1.17. Twenty patients (27.4%) had secondary HG, 7 with medication-related HG (9.5%), 8 with

Table 1 Clinical characteristics of the study population at baseline

Characteristics *n* (%)	Total patients *n* = 73
Demographic characteristics	
Age, median (IQR)	61 (48–71)
Female sex	42 (57.5)
Underlying condition	
Primary HG	**53 (72.6)**
CVID	32 (43.8)
Isolated IgG subclass deficiency	7 (9.6)
Bruton agammaglobulinemia	4 (5.5)
CTLA4 deficiency	2 (2.7)
Cellular and humoral immunodeficiency	4 (5.5)
Others	4 (5.5)
Secondary HG	**20 (27.4)**
Medication-related	7 (9.6)
Myeloma	5 (6.8)
CLL	2 (2.7)
Lymphoma	1 (1.4)
Mixed	5 (6.8)
Clinical manifestations	
Diarrhea	17 (23.3)
Abdominal pain	8 (11.0)
Nausea	3 (4.1)
Vomiting	2 (2.7)
Weight loss	3 (4.1)
Asymptomatic	52 (71.2)
Treatments	
IVIG (vs. SCIG)	48 (67.6)
Antibiotic use ≥ 3 (< 1 year)	6 (8.3)

CLL chronic lymphocytic leukemia; IVIG Intravenous immunoglobulin; SCIG Subcutaneous immunoglobulin

haematological malignancies (10.8%), and 5 with mixed-cause HG (6.8%). For these patients, the mean age at baseline was higher at 73 ± 9 years, and the sex ratio was 0.67 (supplementary Table S1).

Seventeen patients (23.3%) had diarrhea at baseline. The median faecal level of calprotectin in our 73 patients was 72 µg/g (IQR: 23–209). At the time of sample collection, the mean gammaglobulin level among the 73 patients was 10 ± 5.86 g/L, and 8.3% had received antibiotics for at least three infectious episodes in the past year.

Immunological Characteristics

The mean IgG, IgA, and IgM levels at the time of immunodeficiency diagnosis for the 73 patients were 4.47 ± 2.43, 0.80 ± 0.75, and 0.58 ± 0.69 g/L, respectively. Among the 53 patients with primary HG, the mean IgG level at diagnosis was 4.42 ± 2.58 g/L, the mean B lymphocyte count was 0.169 ± 0.159 G/L (representing 11.1 ± 8.5% of lymphocytes), and the mean percentage of switched memory B cells (MBCs) was 7.7 ± 8.6%. For the 20 patients with secondary HG, the mean IgG level at diagnosis was 4.58 ± 2.11 g/L, the mean B lymphocyte count was 0.170 ± 0.302 G/L (11.5 ± 15.0%), and the mean percentage of MBCs was 6.3 ± 5.1%. Undetectable IgA and IgM levels were more frequent in primary immunodeficiencies, with 15.1% of these patients showing both, compared to none in secondary immunodeficiencies. Additional immunological characteristics with the median values are provided in supplementary Tables S1–S5.

Microbiological Characteristics

During the study, 11 of 73 patients (15.1%) had at least one *Campylobacter*-positive stool sample. Of 111 samples collected, 12 (10.8%) were *Campylobacter*-positive. Among these 12 samples, 7 were culture-positive (58.3%) and 10 were PCR-positive. *Campylobacter jejuni* was the most identified species with 4 positive cultures (57.1%), followed by *C. coli* with 2 positive cultures (28.6%), and *Aliarcobacter butzleri* with 1 positive culture (14.3%). The identified *Campylobacter* species exhibited an expected antibiotic resistance profile in accordance with their resistome identified by next-generation sequencing. Genomic sequencing also revealed significant diversity among the *C. jejuni* and *C. coli* isolates in terms of clonal complexes, sequence types, cgMLST profiles, source attribution markers, and resistome (supplementary Table S6). Most patients were untreated, and all four patients who received antibiotic treatment were prescribed appropriate antibiotherapy (Table 2).

Comparison Between Campylobacter-Positive and Campylobacter-Negative Patients

Among the 11 *Campylobacter*-positive patients, 81.8% ($n = 9$) had primary immunodeficiency, compared to 71.0% ($n = 44$) in the *Campylobacter*-negative group. Of the positive patients, 54.5% ($n = 6$) had CVID, versus 41.9% in the negative group ($p = 0.518$). In addition, three (27.3%) of the positive patients had Bruton's agammaglobulinemia, compared to only one (1.6%) in the negative group ($p = 0.010$). The median age was similar in both groups; however, the sex ratio was 0.38 in the positive group versus 1.70 in the negative group (Fig. 1 and supplementary Table S7).

For patients with primary immunodeficiency, we collected data on non-infectious complications. Among *Campylobacter*-positive patients, 44.4% ($n = 4$) had such complications, including gastrointestinal disease, granulomatous disease, immune thrombocytopenia, and nodular regenerative hyperplasia. In comparison, 34.1% ($n = 15$) of negative patients had such complications, including granulomatous disease, autoimmunity, gastrointestinal disease, nodular regenerative hyperplasia, and lymphoid malignancy.

Table 2 Microbiological characteristics of the *Campylobacter*-positive samples

Parameters *n* (%)	Total samples (*n* = 12)	NA
Tests		
Faecal culture positive	7 (58.3)	0
Faecal PCR positive	10 (100.0)	2
Species identification		
Campylobacter jejuni	4 (57.1)	
Campylobacter coli	2 (28.6)	
Aliarcobacter butzleri	1 (14.2)	
Antimicrobial resistance		
Ampicillin	4 (57.1)	0
Amoxicillin-clavulanic acid	0 (0)	0
Gentamicin	0 (0)	0
Erythromycin	1 (16.7)	1
Ciprofloxacin	6 (85.7)	0
Tetracyclin	4 (66.7)	1
Antibiotic use		
Azithromycin 500 mg daily for 3 days	2 (16.7)	0
Amoxicillin-clavulanic acid for 3 weeks followed by Fosfomycin for 3 months	1 (8.3)	0
Spiramycin 3 M I.U. three times daily for 5 days	1 (8.3)	0
Untreated	8 (66.7)	0

M I.U. million international unit; NA indicates samples for which data are not available

The mean IgG, IgA, and IgM levels at the time of immunodeficiency diagnosis for the 63 negative patients were 4.63 ± 2.39 g/L, 0.83 ± 0.75 g/L, and 0.58 ± 0.69 g/L, respectively. For the 11 *Campylobacter*-positive patients, the mean levels tend to be lower (3.14 ± 2.68 g/L, 0.59 ± 0.70 g/L, and 0.57 ± 0.81 g/L, respectively). The differences were not statistically significant.

Regarding B lymphocyte subsets, the only value statistically significant was the mean percentage of transitional B cells significantly lower in the positive group versus the negative group (0.6 ± 0.5% vs. 3.4 ± 5.8%, $p < 0.05$). The mean percentage of naive B lymphocytes tended to be higher (78.3 ± 10.2% versus 69.1 ± 21.3%), whereas the mean percentage of unswitched and switched MBCs tended to be lower in the positive group versus the negative group (12.8 ± 9.8% versus 18.8 ± 18.7%, 4.0 ± 2.6% versus 8.1 ± 8.8%, respectively).

Regarding T lymphocyte subsets, the positive group was characterized with a higher mean percentage of naive CD4 + T cells (40.5 ± 19.0% vs. 29.3 ± 20.1%, not statistically significant), and effector memory CD8 + T cells (17.8 ± 11.0% vs. 5.8 ± 4.6%, $p < 0.05$) and a lower mean percentage of effector memory CD4 + T cells and naive CD8 + T cells (8.7 ± 6.7% vs. 13.7 ± 12.1% and 31.6 ± 12.0% vs. 41.1 ± 19.5%, respectively, not statistically significant). Additional data are provided in supplementary Tables S8–S10.

Comparison Between Campylobacter-Positive and Campylobacter-Negative Samples

The clinical characteristics and immunological parameters at the time of collection were compared between positive ($n = 12$) and negative ($n = 99$) samples (Table 3). At the time of collection, 41.7% ($n = 5$) of positive patients had

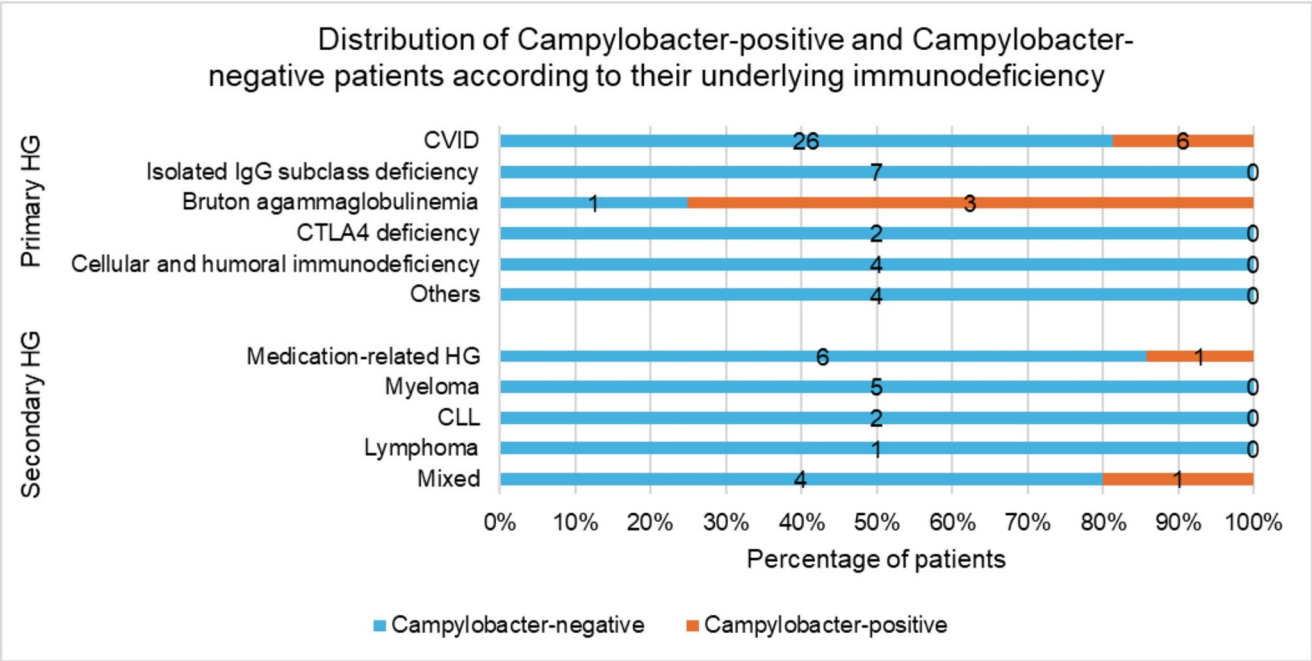

Fig. 1 Distribution of Campylobacter-positive and Campylobacter-negative patients according to their underlying immunodeficiency

Table 3 Demographic, clinical and biological parameters in the different groups

Parameters	***Campylobacter*** -negative samples ($n=99$)	NA	***Campylobacter*** -positive samples ($n=12$)	NA	p value
Demographic characteristics					
Age, median (IQR)	63 (51–71)	0	60 (41–69)	0	NS
Female sex, n (%)	62 (62.6)	0	3 (25.0)	0	**<0.05**
Digestive symptoms, n (%)	18 (19.4)	6	6 (50.0)		**<0.05**
Diarrhea	14 (14.7)	4	5 (41.7)	0	**<0.05**
Abdominal pain	8 (8.5)	5	2 (16.7)	0	NS
Nausea	3 (3.2)	5	0	0	NS
Vomiting	2 (2.1)	5	0	0	NS
Weight loss	3 (3.2)	5	1 (8.3)	0	NS
Faecal calprotectin (µg/g), median (IQR)	52 (10–209.25.25)	5	255 (149–677.75.75)	2	**<0.05**
Underlying condition, n (%)					
Primary HG	**70 (70.7)**		**10 (83.3)**		NS
CVID	42 (42.4)	0	6 (50.0)	0	NS
Isolated IgG subclass deficiency	10 (10.1)	0	0	0	NS
Bruton agammaglobulinemia	2 (2.0)	0	4 (33.3)	0	**<0.05**
CTLA4 deficiency	3 (3.0)	0	0	0	NS
Cellular and humoral immunodeficiency	6 (6.1)	0	0	0	NS
Others	7 (7.1)	0	0	0	NS
Secondary HG	**29 (29.3)**		**2 (16.7)**	0	NS
Medication-related HG	10 (10.1)	0	1 (8.3)	0	NS
Myeloma	9 (9.1)	0	0	0	NS
CLL	2 (2.0)	0	0	0	NS
Lymphoma	1 (1.0)	0	0	0	NS
Mixed (medication on hematological malignancy)	7 (7.1)	0	1 (8.3)	0	NS
IVIG	68 (70.1)	2	5 (45.5)	1	NS
Antibiotic use≥3 (<1 year)	10 (10.3)	2	1 (9.1)	1	NS
Biology at the time of collection, median (IQR)					
Lymphocytes count (G/L)	1.42 (0.91–1.98)	7	0.96 (0.82–1.58)	1	NS
Neutrophils count (G/L)	3.71 (2.79–4.98)	7	3.79 (3.12–4.40)	1	NS
CRP (mg/L)	2.5 (1.2–7.0.2.0)	5	3.10 (2.25–16.03)	2	NS
Gammaglobulin count (g/L)	8.4 (7.0–10.7.0.7)	10	8.8 (7.5–10.8)	1	NS
IgG (g/L)	9.170 (7.785–11.865)	8	10.460 (9.250–11.795.250.795)	1	NS
IgA (g/L)	0.360 (0–1.040.040)	10	0 (0–0.719.719)	1	NS
IgM (g/L)	0.400 (0.170–0.830)	10	0.170 (0–0.510.510)	1	NS
TL CD4 (G/L)	0.555 (0.399–0.921)	10	0.505 (0.358–0.906)	0	NS
TL CD8 (G/L)	0.343-0.198.343.198-0.554)	10	0.354 (0.278–0.539)	0	NS
BL (G/L)	0.131 (0.029–0.275)	12	0.034 (0–0.155.155)	1	NS
CD4/CD8	1.739 (1.236–2.629)	10	1.646 (1.083–2.341)	0	NS

BL B lymphocytes; CLL chronic lymphocytic leukemia; IVIG Intravenous immunoglobulin; NA not available; NS not significant; TL T lymphocytes

diarrhea compared to 14.7% ($n=14$) in the negative group. The median faecal level of calprotectin was 255 µg/g (IQR: 149–678) in the positive group, significantly higher than the 52 µg/g (IQR: 10–209, close to the normal value of <50 µg/g) observed in the negative group. The infection rate over the prior year was similar between the two groups, with 9.1% ($n=1$, with 1 missing information) of the positive group having used antibiotics more than three times, compared to 10.3% ($n=10$) of the negative group.

The two groups had similar immunoglobulin trough levels with a median of 8.80 (IQR: 7.50–10.75) g/L in the positive group versus 8.40 (IQR: 7.00–10.70) g/L in the negative group. The median (IQR) B lymphocytes count was 0.034 (0-0.155) G/L in the *Campylobacter*-positive group, versus 0.131 (0.029–0.275) G/L in the *Campylobacter*-negative group. The median T CD4+lymphocyte count also differed slightly between the two groups with the CD4/CD8 ratio being 1.71±0.85 in the positive group versus 2.06±1.18 in the negative group.

Interestingly, the IgA and IgM levels at inclusion showed some variation between the two groups, although not significantly. The median IgA level was 0.36 (0-1.04) g/L in the negative group, compared to 0 (0-0.72) g/L in the positive group ($p=0.207$). Similarly, the median IgM level was 0.38 (0.17–0.81) g/L in the negative group, and 0.17 (0-0.51) g/L in the positive group ($p=0.092$).

Clinical Characteristics of the Campylobacter-Positive Patients

The data are presented in Table 4. Digestive evaluations were performed for the 11 *Campylobacter*-positive patients. Six of these patients had recently undergone colonoscopy (with or without gastroscopy). In four cases, macroscopic findings were normal, while the other two showed signs of ileitis or mucosal oedema. Biopsies revealed signs of colitis in two patients, while the results were normal in the remaining cases. These patients primarily had a history of recurrent infections, particularly pulmonary and digestive. Five had post-infectious bronchiectasis; two of these were chronically colonised by *Haemophilus influenzae*, and one by *Pseudomonas aeruginosa*. One patient experienced severe non-infectious complications of CVID, including hepatic nodular regenerative hyperplasia and immune thrombocytopenia.

Discussion

Campylobacter infections are common digestive infections, particularly in patients with humoral immunodeficiencies. Although usually self-limiting, they can be recurrent [7] and severe in patients with HG, leading to bacteraemia [25, 26], endocarditis [27], or osteomyelitis [12].

This study is the first large prospective cohort to investigate the prevalence of *Campylobacter* in the stool of patients with HG. Previous studies have reported varying rates of *Campylobacter* infection among this patient population. The retrospective French DEFI study, which involved patients with primary immunodeficiency disorders, reported an 8% prevalence of *Campylobacter* infection in those

Table 4 Characteristics of the patients tested positive for *Campylobacter*

N°	Sex	Age	Campylobacter species	Antibiotic treatment	Clinical signs	C-reactive protein (mg/L)	Digestive endoscopies	Faecal calprotectin (µg/g)	Immunodeficiency
11	M	60	Unknown (PCR)			3.5	Colonoscopy (2010): normal.	527	XLA
13	F	78	Unknown (PCR)		Diarrhea	2.1	Colonoscopy (2024): normal.	149	CVID
27	M	49	***C. Coli*(culture and PCR)**		Diarrhea	17.7		1857	XLA
29	M	43	***C. jejuni*(culture)**	Spiramycin	Diarrhea Abdominal pain Weight loss	44.0	Colonoscopy (2023): no ulcerative lesion, chronic colitis, *Giardia*. Gastroscopy (2023): partial small villous atrophy, without intraepithelial lymphocytosis, *Giardia.*	325	CVID
36	M	78	***A. butzleri*(culture)**			2.7		185	SHG (CLL, RTX)
46	F	64	Unknown (PCR)			0.3		149	CVID
53	M	80	***C. coli*(culture and PCR)**	Azithromycin	Diarrhea	111.1			SHG (RTX)
54	F	66	***C. jejuni*(culture and PCR)**			0.2		10	CVID
59	M	36	***C. jejuni*(culture and PCR)**	Azithromycin	Diarrhea	11.0	Colonoscopy (2023): normal. Biopsy: active focal colitis, associated with lymphocytic colitis. Gastroscopy (2023): normal.	728	CVID
61	M	28	Unknown (PCR)				Colonoscopy and gastroscopy (2018): aspecific stenosing ulcerated terminal ileitis, gastritis.	893	XLA
64	M	25	***C. jejuni*(culture and PCR)**	Amox-clav then Fosfomycin	Abdominal pain		Colonoscopy and gastroscopy (2022): normal. Biopsy: reactive lymphoid hyperplasia, no villous atrophy.		CVID

Amox-clav amoxicillin-clavulanic acid, *CLL* chronic lymphocytic leukemia, *CVID* combined variable immunodeficiency, *IVIG* intravenous immunoglobulin, *RTX* rituximab, *SCIG* subcutaneous immunoglobulin, *SHG* secondary hypogammaglobulinemia, *XLA* X-linked agammaglobulinemia

with CVID [6], while another study reported a lower rate of 1.2% among 248 CVID patients [28]. In a cohort study of 55 patients with primary antibody deficiencies, 49% of patients with diarrhea and 17% of asymptomatic patients had *Campylobacter*-positive stool cultures [8]. Despite patients receiving adequate Ig replacement therapy, we observed a relatively high prevalence of *Campylobacter* of 15.1% among 73 patients. However, the actual prevalence of *Campylobacter* infection in the general population is still uncertain, which makes direct comparisons challenging.

In our study, 81.8% of *Campylobacter*-positive patients had primary immunodeficiency. The sex ratios differed between positive and negative patients due to the overrepresentation of X-linked agammaglobulinemia in the positive group (n = 3). In addition, six patients had CVID and two had secondary HG. While prolonged, recurrent, or severe *Campylobacter* infections are well-documented in primary HG, they are less frequently reported in secondary HG. A literature review on recurrent *Campylobacter* enteritis identified 14 cases of primary HG and 1 case of secondary HG related to non-Hodgkin's lymphoma, previous chemotherapy, and maintenance rituximab [7]. We identified two cases of secondary HG with *Campylobacter*: one in a patient with post-rituximab HG and the other in a patient with mixed HG secondary to chronic lymphocytic leukaemia treated with rituximab and chemotherapy.

Immunoglobulin trough levels indicated that our patients were well-substituted, with a median (IQR) gammaglobulin level of 8.80 (7.50–10.75) g/L in positive patients. Interestingly, IgA and IgM levels were slightly lower in the positive group, at 0 (0–0.72) g/L for IgA and 0.17 (0–0.51) g/L for IgM; however, the differences did not reach statistical significance, likely due to an insufficient sample size. Furthermore, the positive population appeared to have more severe underlying immunodeficiencies, with a significantly higher proportion of patients with X-linked agammaglobulinemia. *Campylobacter* infections are more frequent in CVID patients with undetectable IgA levels [6, 9, 10]. However, 40.0% of our positive patients had detectable IgA levels and 60.0% had detectable IgM levels, suggesting that other mechanisms may contribute to susceptibility to this infection. For example, we observed a lower percentage of CD4 + T lymphocytes and a decreased CD4/CD8 ratio in our positive population (1.71 ± 0.85 in the positive group versus 2.06 ± 1.18 in the negative group). Because systemic and recurrent *Campylobacter* infections are also associated with human immunodeficiency virus-related immunodeficiency, a potential role of cellular immunity in these infections cannot be neglected [25].

For the seven patients who tested positive in bacterial cultures, we performed genomic sequencing to determine the diversity of strains and sources of contamination. For both *C. jejuni* and *C. coli*, there was a large diversity of clonal complexes, sequence types, cgMLSTs, source attribution markers, and antibiotic resistance genes (supplementary Table S6). We were unable to determine whether the detection of *Campylobacter* reflected an acute or chronic infection. However, the significantly elevated faecal levels of calprotectin, the presence of digestive symptoms, and the PCR and culture data indicating a substantial bacterial inoculum suggest that these cases were more likely infectious episodes rather than true chronic, asymptomatic colonisation.

Pikkarainen et al. reported that faecal calprotectin levels were higher in patients classified as "probable CVID" compared to those with "possible CVID" and levels were particularly elevated in patients with very low B-cell counts (< 2% of total lymphocytes). In this CVID cohort, faecal calprotectin was a reliable marker of histological intestinal inflammation, which was associated with various gastrointestinal complications [29].

Indeed, 54.5% (n = 6) of our 11 positive patients had digestive symptoms. Dionisi et al. [8]. described a case of chronic, asymptomatic colonisation by *C. coli* in a patient with X-linked agammaglobulinemia, which eventually resulted in bacteraemia from the same digestive strain 10 years later. The authors proposed that *Campylobacter*should be detected and treated using highly sensitive techniques, even if they are asymptomatic.

We have identified one patient among our 11 positive patients, with severe CVID, who had a medical history of recurrent *Campylobacter* spp. infections, despite antibiotic treatments. After recovering the four bacterial strains from previous episodes of infectious diarrhea (2 *C. jejuni* and 2 *C. coli* isolates), we were able to demonstrate in this patient a chronic carriage of *C. jejuni* whose strain was identical and *C. coli*, with slight variations in MLST profile (supplementary Table S6). This indicates a difficulty in eradicating these infections in the severely immunocompromised patients.

A recent study has shown that among various primary immunodeficiency patients with chronic or recurrent *Campylobacter* infection in the past years in the United Kingdom [13], *Campylobacter* strains can persist for years in the intestinal tract and reinfect the patient, which may play a significant role on morbidity. Eradicating the infection is highly dependent on the patient but also on the strain and mostly requires combined antimicrobial administration and immunoglobulin replacement [7]. The risk of eradication failure is high.

Also, the various antibiotic treatments administered to these patients in an attempt to eliminate all digestive carriage, or in the context of recurrent bacteremia, could not only contribute to dysbiosis, but also to the selection of mutants resistant to the various antibiotics used. Roa-Bautista et al. [10] proposed an algorithm for the management of recurrent *Campylobacter* infections in individuals with CVID but no official guidelines are available.

Our PCR Kit was also able to detect *Salmonella* and *Yersinia*. PCR detected *Yersinia* in two patients but no cases of *Salmonella*. We did not test for any other pathogens, such as *Giardia* or *Norovirus*. Given that these types of infections are common in individuals with HG and can lead to acute infections or chronic enteropathy with severe malabsorption [6, 30], an investigation of the prevalence of these infections in the same patient population would be valuable.

Our study had some limitations. First, not all data were available for every patient, particularly concerning the immunological tests conducted during the diagnosis of patients with long-term follow-up. Additionally, our study population primarily received substitution with intravenous Ig therapy (67.6%), whereas most patients with HG typically receive subcutaneous Ig replacement therapy. This limitation could introduce bias by excluding a portion of patients, particularly those with primary HG. Moreover, the sample size was insufficient for robust statistical analysis, which limited our ability to identify specific risk factors for *Campylobacter* infections and to conduct multivariate or subgroups analyses. Finally, our cohort lacked data on gut microbiota, which has recently emerged as an important factor influencing the immune system in immunodeficient patients. Mucosal IgA deficiency has been linked to duodenal inflammation, while a high dysbiosis index is associated with gut inflammation in patients with CVID [31, 32]. Investigating the association between *Campylobacter* infection and specific gut microbiota profiles could be valuable, as microbiota-targeted therapies may offer potential benefits in such cases.

Conclusion

Our study highlights a significant prevalence of *Campylobacter* in the stool of patients with both primary and secondary HG, despite adequate Ig supplementation. The notable association between digestive symptoms and elevated faecal levels of calprotectin in *Campylobacter*-positive patients indicates active infection rather than chronic, asymptomatic colonisation. Therefore, it is imperative to conduct thorough screenings for *Campylobacter* infections in HG patients presenting with digestive symptoms.

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Declarations

Competing interests The authors declare no competing interests.

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