Original Article

Clinical Features, Immunological Characteristics, and Treatment Outcomes of *Campylobacter* spp. Infections in Patients With Common Variable Immunodeficiency

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What is already known about this topic? Patients with antibody deficiency syndromes such as common variable immunodeficiency (CVID) can suffer from chronic and relapsing *Campylobacter* spp. infections that may be refractory to treatment.

What does this article add to our knowledge? CVID patients with *Campylobacter* infections exhibited a higher proportion of CD21^{low} B cells versus CVID controls and a decline in lymphocyte counts over time. Antibiotic resistance among *Campylobacter* isolates was common but a novel treatment algorithm was successful.

How does this study impact current management guidelines? The immunological results help to identify patients at risk of *Campylobacter* infection. The treatment algorithm should be evaluated in a larger cohort and then incorporated into guidelines.

BACKGROUND: Campylobacter infection usually causes a self-limited clinical illness lasting 5 to 7 days, resolving without antimicrobial treatment in immunocompetent subjects. However, an inadequate immune response can lead to a prolonged and severe disease requiring antibiotics and more aggressive therapeutic approaches.

OBJECTIVE: To comprehensively describe Campylobacter spp. infections in patients with common variable immunodeficiency (CVID).

METHODS: A retrospective cohort of 14 CVID patients with Campylobacter infection and 95 CVID controls attending the immunology clinic at a large tertiary hospital was assessed. Immunological, clinical, and microbiological parameters were measured with median follow-up over 20 years in both cohorts. Patients were treated according to a novel algorithm for Campylobacter in antibody-deficient patients.

RESULTS: Campylobacter patients had a higher proportion of CD21lowCD38low and transitional B cells (median 38.0% vs 14.2% and 5.4% vs 3.2%) and lower long-term average CD19+ B cells (median 0.06 vs 0.18 × 109/L) and CD4+ T cells (0.41 vs 0.62 × 109/L) in comparison with the controls. Similarly, Campylobacter patients showed a decline in B cells (median 0.02 vs 0.14 × 109/L), CD4+ T cells (0.33 vs 0.59 × 109/L), CD8+ T cells (0.26 vs 0.62 × 109/L), and natural killer cells (0.08 vs 0.18 × 109/L) over time. Antimicrobial resistance, especially to macrolides and fluoroquinolones, was common. Bacterial clearance with associated clinical improvement was obtained after a median of 20 and 113 days for acute Campylobacter (resolution within 3 mo of onset) and chronic Campylobacter (>3 mo) infections, respectively. Seven received first-line treatment (azithromycin or chloramphenicol), 4 second-line (neomycin), and 3 third-line (combination of tigecycline, chloramphenicol, and

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Abbreviations used
ACP- Acute Campylobacter patients
AMR- Antimicrobial resistance
CCP- Chronic Campylobacter patients
CG- Control group
CP- Campylobacter patients
CVID- Common variable immunodeficiency
Ig- Immunoglobulin
IQR- Interquartile range
MLST- Multi-Locus Sequencing Typing
NK- Natural killer
PCR- Polymerase chain reaction
UKHSA- U.K. Health Security Agency
WGS- Whole-genome sequencing

ertapenem; 1 received gentamicin owing to resistance to carbapenems).

CONCLUSIONS: Our study highlights immunological and clinical characteristics of recurrent Campylobacter infections in patients with CVID. Our treatment algorithm was successful and should be evaluated in a larger cohort. © 2023 The Authors. Published by Elsevier Inc. on behalf of the American Academy of Allergy, Asthma & Immunology. This is an open access article under the CC BY license (http://creativecommons.org/licenses/by/4.0/). (J Allergy Clin Immunol Pract 2023;■:■-■)

Key words: Campylobacter; CVID; Common variable immuno-deficiency; Antibiotic treatment

INTRODUCTION

Campylobacter spp. are a broad and diverse group of gram-negative bacteria comprising approximately 26 species, of which at least 10 different species are known to cause human illness. C. jejuni is the most frequently isolated species in human feces, followed by C. coli.[1] Campylobacter spp. are considered one of the leading causes of bacterial diarrhea worldwide[2] and are regarded as the most common cause of food poisoning in the United Kingdom, responsible for illness in 280,000 people per year.[3] The factors responsible for the pathogenesis and susceptibility to Campylobacter are not fully identified; however, the virulence of the strain, number of organisms ingested, and host immunity are known to contribute to illness development.[1]

Campylobacter usually causes a self-limited clinical illness lasting 5 to 7 days, resolving without antimicrobial treatment in immunocompetent subjects.[4,5] However, an inadequate immune response can result in more prolonged and severe disease, requiring antibiotics or more aggressive therapeutic approaches.[6-8] Common variable immunodeficiency (CVID) is characterized by defective immunoglobulin production.[9] It is the most common symptomatic primary immunodeficiency, with a prevalence of approximately 1 case per 30,000 adults worldwide.[10] CVID comprises multiple distinct diseases defined by genetics and immunological characteristics, but the major clinical feature is usually infection in different organ systems.[10,11] Hypogammaglobulinemia has been associated with recurrent, prolonged, and complicated campylobacteriosis,[12] but the available literature is mainly limited to case reports. Dion et al[13] address a similar issue in a cohort of 45 patients with primary antibody deficiency and Campylobacter infection, pointing to a more severe disease phenotype, with more frequent complications and lower levels of immune cells, such as CD4+ T lymphocytes, in those with Campylobacter infection.

Evidence regarding the successful treatment of prolonged or recurrent Campylobacter infection in antibody-deficient patients is limited.

We sought to investigate immunological and bacterial factors of CVID patients with Campylobacter infection and document outcomes from a structured treatment algorithm.

MATERIAL AND METHODS

Study design

This study was a retrospective cohort description of CVID patients with Campylobacter infection attending the immunology clinic at a large tertiary hospital in London, United Kingdom. Subjects were eligible if they were diagnosed with CVID by a consultant immunologist following the International Collaboration in Asthma, Allergy, and Immunology[14] or the European Society for Immunodeficiencies (ESID)[15] definitions and had at least 1 positive stool polymerase chain reaction (PCR) test for Campylobacter spp.

Study methodology

Flow cytometry was used to characterize peripheral blood lymphocyte subsets (frequencies and absolute numbers of CD3+, CD4+, CD8+, CD19+, and CD16+/CD56+ natural killer [NK] cells) and CD19+ B cell phenotype (switched memory [CD27+ IgD− {immunoglobulin D}]) B cells, CD21^{low}CD38^{low} B cells, transitional (IgD+ IgM+ CD27- CD38++ CD24++) B cells, naive (CD27− IgD+) B cells, IgM memory (CD27+ IgD+/ IgM+), and plasmablasts (IgM− IgD− CD27+ CD38++).

Long-term averages were obtained from all available results from 2000 (or date of CVID diagnosis, if later) to 2022. Values reported as less than a limit of detection (eg, <0.1 g/L) were taken as being equal to that limit value for analysis.

Microbiology and genomics

Fecal samples from patients were tested using a commercial enteric bacterial PCR assay for detection of Campylobacter spp. The PCR-positive feces were cultured on Campylobacter selective agar between 37°C and 42°C under microaerophilic conditions. Positive blood cultures were subcultured on blood and chocolate plates. Colonies cultured were further identified as Campylobacter spp. using MALDI-TOF.

Fecal and blood isolates of Campylobacter spp. from patients were referred to the National Campylobacter Reference Laboratory at U.K. Health Security Agency (UKHSA; previously Public Health England). Isolates on Amies charcoal swabs were cultured overnight on 5% Columbia blood agar, incubated at 37°C to 42°C under specialized atmospheric conditions (5% O$_2$, 5% CO$_2$, 3% H$_2$, 87% N$_2$) using a Don Whitley VA500 Microaerophilic Workstation.

Genomic DNA was extracted from bacterial cultures using a QIAGEN QIAsymphony, fragmented and tagged for multiplexing with Nextera XT DNA Sample Preparation Kits, followed by rapid-run paired-end sequencing on an Illumina High-Seq 2500 platform to produce 100 bp reads. The 7-loci Multi-Locus Sequencing Typing (MLST) was determined from whole-genome sequencing (WGS) data using Metric Oriented Sequence Typer, a modified MLST typing tool based on short-read sequencing. Sequences were assembled using the SPAdes genome assembler in the UKHSA pipeline.[16]

Single nucleotide polymorphisms were identified based on ST-complex specific reference mapping, and cluster detection was

TABLE I. Clinical characteristics of patients with CVID and *Campylobacter* spp. infections

Patient demographic and medical history									**Treatment and infection duration**						**Symptoms**									
Patient ID	Age (y)	Sex	Immunoglobulin treatment	Follow-up duration (y)*	History of immunosuppression	Autoimmunity†	Solid organ neoplasm	Chest infection	Prophylactic antibiotics	Antibiotic regimen‡	*Campylobacter* fecal/blood PCR positive	*Campylobacter* fecal/blood PCR negative	Days	Days total	Diarrhea	Nausea	Weight loss	vomiting	PR bleeding	Fever	Bloating	Cramping	Incontinence	Other diagnosis
A	49	F	IVIg	7	Y	N	N	Y	Co-trim	1	23/9/16	7/3/17	165	202	Y	N	N	N	N	N	N	N	N	Heterogeneous mutation for hemochromatosis
											18/12/18	24/1/19	37											
B	72	F	IVIg	37	Y	Y	Y	Y	Cipro	1	21/1/13	30/1/13	9	98	Y	N	Y	N	N	N	N	N	N	T-cell lymphoma
											25/11/15	8/1/16	44											Total gastrectomy
											23/10/19	7/12/19	45											Pernicious anemia
																								G6PD mutation
C	44	M	SCIg	22	Y	Y	N	Y	Azithro	3	11/12/15	NA	NA	113	Y	N	Y	N	N	N	Y	N	N	Autoimmune phenomena (autoimmune neutropenia and autoimmune thrombocytopenia)
											12/9/16	3/1/17	113											
D	74	M	SCIg	44	N	Y	N	Y	Azithro	2	23/2/03	NA	NA	405	Y	N	Y	N	N	N	N	N	N	Mild thrombocytopenia
											29/11/17	8/2/18	71											
											31/5/18	30/4/19	334											
E	46	M	SCIg	14	N	N	N	Y	Co-amox	3	29/3/17	14/9/17	169	169	Y	N	N	N	N	N	N	N	N	Recurrent isolation of rhinovirus and *Hemophilus influenzae*
F	54	F	SCIg	13	N	Y	N	Y	Azithro	2	9/11/15	NA	NA	145	Y	N	N	N	N	N	N	N	N	Pancytopenia
											24/1/19	18/6/19	145											
G	32	M	SCIg	7	Y	Y	N	Y	Azithro	3	13/2/18	NA	NA	224	Y	N	N	N	N	N	N	N	Y	Thrombocytopenia
											6/9/21	18/4/22	224											
H	53	M	SCIg	17	N	N	Y	Y	Doxy	2	5/5/06	17/10/06	165	1595	Y	N	N	N	N	N	N	N	N	Diffuse large B lymphoma
											27/4/10	19/11/10	206											
											13/9/13	NA	NA											
											10/1/19	Still positive	NA											
											15/1/20	Still positive	370											
											18/5/22	Still positive	854											
I§	47	M	IVIg	26	Y	Y	N	Y	Co-trim	2	18/2/04	11/6/04	114	199	Y	N	N	N	N	N	N	Y	N	Juvenile chronic arthritis
											5/4/05	NA	NA											Pernicious anemia
											21/2/12	24/4/12	63											
											25/5/19	16/6/19	22											
J	70	F	IVIg	32	Y	N	N	Y	Doxy	1	21/8/02	NA	NA	78	Y	Y	N	N	N	N	N	N	N	*Mycobacterium intracellulare* isolated in sputum
											7/9/05	NA	NA											
											26/1/17	14/4/17	78											
K	35	F	SCIg	19	N	N	N	Y	Nil	1	1/8/16	19/8/16	18	18	Y	N	N	N	N	N	N	N	N	Fecal incontinence
L	72	F	SCIg	22	Y	Y	N	Y	Co-trim	1	19/9/16	NA	NA	NA	Y	N	N	N	N	N	N	N	N	Autoimmune hypothyroidism
M	50	M	IVIg	18	Y	N	N	N	Co-trim	1	4/10/16	NA	NA	NA	Y	N	N	N	N	N	N	N	N	Ground-glass changes on chest CT
N	76	F	IVIg	29	Y	N	Y	Y	Cipro	1	22/6/20	13/7/20	21	21	Y	N	Y	N	N	N	N	N	N	CA breast

Azithro, Azithromycin; *CA,* cancer; *Co-trim,* cotrimoxazole; *Cipro,* ciprofloxacin; *Co-amox,* co-amoxiclav; *CT,* computed tomography; *Doxy,* doxycycline; *G6PD,* glucose-6-phosphate dehydrogenase; *ID,* identification; *IVIg,* intravenous immunoglobulin; *NA,* not available; *Nil,* no antibiotics; *SCIg,* subcutaneous immunoglobulin.

*Follow-up duration since CVID diagnosis, expressed in y.

†Autoimmunity refers to autoimmune phenomena (eg, autoimmune neutropenia, idiopathic thrombocytopenic purpura) collected in the clinical history of the patients.

‡Antibiotic regimen received by the patient for *Campylobacter*, 1, first-line; 2, second line; and 3, third line.

§Patient [I] still positive after second line of treatment. Third line needs to be considered.

TABLE II. Demographic and laboratory parameters in the different groups*

Parameters	*Campylobacter* patients (n = 14)	Controls (n = 95)	P value
Demographic characteristics			
Age (y), median IQR)	52 (46−72)	60 (48−71)	NS
Female, n (%)	7 (50)	55 (57.89)	NS
Follow-up duration (y), median (IQR)	21 (15−28)	24 (17−32)	NS
History of immunosuppression (n, %)	9 (64.3)	41 (43.16)	NS
History of autoimmunity (n, %)	9 (64.3)	30 (31.58)	.03
History of solid organ neoplasm (n, %)	3 (21.43)	4 (4.21)	.04
History of chest infection, n (%)	14 (100)	65 (68.42)	.01
History of prophylactic antibiotic use, n (%)	13 (92.8)	75 (78.9)	NS
Immunological parameters, median (IQR)			
Lymphocytes			
Absolute lymphocyte count LTA ($\times10^9$/L)	0.99 (0.75−1.46)	1.33 (0.97−1.86)	NS
CD3+ lymphocyte LTA ($\times10^9$/L)	0.72 (0.59−1.16)	1.15 (0.80−1.50)	NS
Most recent absolute CD4+ lymphocyte count ($\times10^9$/L)	0.33 (0.23−0.43)	0.58 (0.39−0.82)	.001
Oldest absolute CD4+ lymphocyte count ($\times10^9$/L)	0.59 (0.41−0.71)	0.65 (0.45−0.89)	NS
CD4+ lymphocyte count LTA ($\times10^9$/L)	0.41 (0.29−0.59)	0.62 (0.46−0.55)	.009
Most recent absolute CD8+ lymphocyte count ($\times10^9$/L)	0.26 (0.14−0.69)	0.39 (0.25−0.59)	NS
Oldest absolute CD8+ lymphocyte count ($\times10^9$/L)	0.62 (0.27−83)	0.42 (0.28−0.60)	NS
CD8+ Lymphocyte count LTA ($\times10^9$/L)	0.31 (0.17−0.75)	0.40 (0.26−0.60)	NS
Most recent absolute CD19+ lymphocyte count ($\times10^9$/L)	0.02 (0.01−0.11)	0.16 (0.06−0.28)	.001
Oldest absolute CD19+ lymphocyte count ($\times10^9$/L)	0.14 (0.07−0.21)	0.17 (0.08−0.28)	NS
CD19+ Lymphocyte count LTA ($\times10^9$/L)	0.06 (0.02−0.16)	0.18 (0.09−0.30)	.008
Most recent absolute NK lymphocyte count ($\times10^9$/L)	0.08 (0.05−0.18)	0.13 (0.07−0.20)	NS
Oldest absolute NK lymphocyte count ($\times10^9$/L)	0.18 (0.15−0.30)	0.15 (0.10−0.25)	NS
NK Lymphocyte count LTA ($\times10^9$/L)	0.14 (0.07−0.17)	0.14 (0.09−0.22)	NS
Immunoglobulins			
IgG LTA (g/L)	9.26 (7.36−10.77)	8.75 (7.83−10.7)	NS
IgA LTA (g/L)	0 (0.00−0.00)	0 (0.00−0.00)	NS
IgM LTA (g/L)	0.16 (0.00−0.17)	0.15 (0.10−0.30)	NS
B-cell phenotype			
Switched memory B cells (%) (CD27+ IgD−)	0.49, n = 7 (0.41−3.29)	2.60, n = 65 (1.20−5.70)	NS
CD21^{low}CD38^{low} (%)	38.00, n = 7 (18.86−42.26)	14.21, n = 68 (7.62−31.01)	.04
Transitional B cells (%) (IgD+ IgM+ CD27− CD38++ CD24++)	5.38, n = 6 (4.26−9.76)	3.20, n = 64 (1.41−5.73)	.03
Naive B cells (%) (CD27− IgD+)	82.13, n = 5 (80.13−87.90)	79.29, n = 65 (67.68−86.00)	NS
IgM memory (%) (CD27+ IgD+/IgM+)	12.57, n = 5 (5.29−16.71)	11.36, n = 65 (5.60−21.10)	NS
Plasmablasts (%) (IgM− IgD− CD27+ CD38++)	2.27, n = 5 (0.07−4.38)	0.30, n = 64 (0.08−0.84)	NS

LTA, Long-term average; *NS,* not significant.

*For categorical variables, Fisher exact test was used, results are reported as the number of patients (n) and percentage (%). For comparison of 2 noncategorical variables, Mann-Whitney test was used; median and IQR are shown. *P* value < .05 was considered statistically significant.

performed across the most prevalent ST-complexes. Antimicrobial resistance (AMR) was predicted from the WGS data using a validated in-house bioinformatics pipeline in UKHSA to detect AMR determinants[17] conferring reduced susceptibility to the following antibiotics/classes: erythromycin (macrolide), ciprofloxacin (fluoroquinolone), gentamicin and streptomycin (aminoglycosides) as well as tetracycline.

Phenotypic antimicrobial susceptibility tests were performed by disc diffusion and E-test according to the European Committee on Antimicrobial Susceptibility Testing (EUCAST) recommendations.

Participants

A total of 14 patients with CVID followed for a median of 21 years (interquartile range [IQR] 15−28 y), and a compatible clinical history of *Campylobacter* infection with a positive fecal or blood PCR and/or culture were included. We classified *Campylobacter* infections as either acute (ACP; total illness duration < 3 mo and resolving

with first-line treatment) or chronic/relapsing (CCP). A control group (CG) was also identified, comprising 95 CVID patients with no history of *Campylobacter* or norovirus infection followed for a median of 24.0 years (IQR 17−32 y). Clinical features, immunological parameters over time, and comorbidities were assessed and reported. Treatment and microbiological results for *Campylobacter* spp. were collected for all patients from the first positive PCR or culture until clinical improvement and microbiological clearance. All patients provided written, informed consent for the collection and reporting of their clinical data under a protocol approved by a National Health Service Research Ethics Committee (04/Q0501/119).

Statistical analysis

Statistical analysis was performed using GraphPad Prism software versions 6.0 and later (GraphPad Software, La Jolla, Calif). For categorical variables Fisher exact test was used; results are reported as the number of patients (n) and percentage (%). For comparison of 2
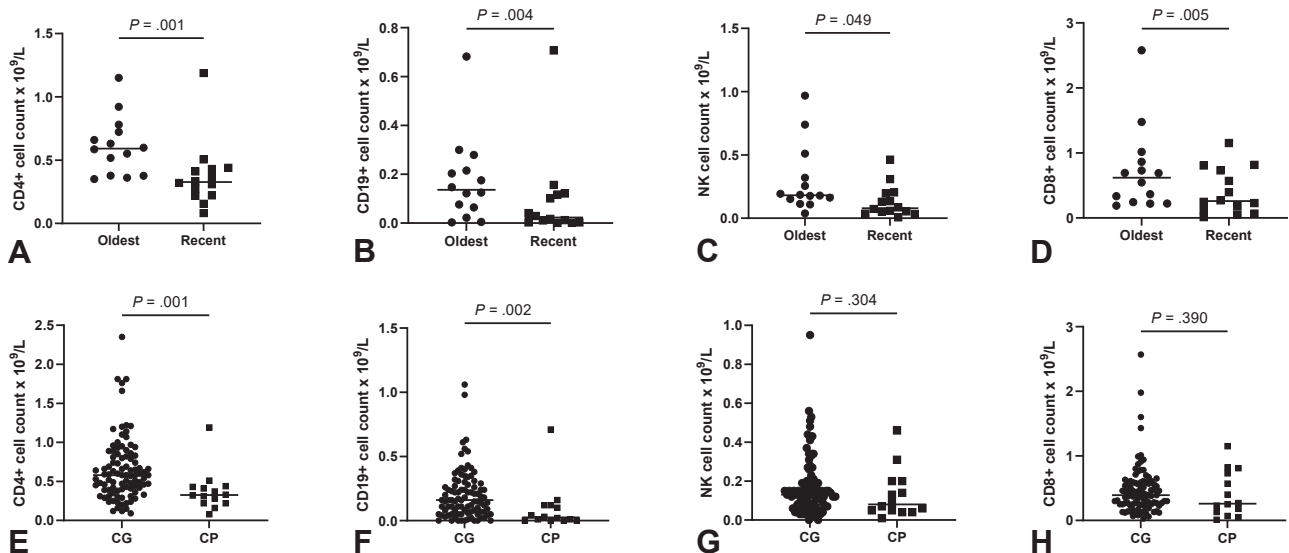
FIGURE 1. Immunological parameters of *Campylobacter* patients (CPs) and the control group (CG). (A—D) Oldest available and most recent absolute lymphocyte counts for CPs: (A) CD4+ T-cell count; (B) CD19+ B-cell count; (C) NK-cell count; (D) CD8+ T-cell count; n = 14. (E—H) Most recent absolute lymphocyte counts for the CG versus the CPs: (E) CD4+ T-cell count; (F) CD19+ B-cell count; (G) NK-cell count; (H) CD8+ cell count; n = 95 and 14 for CG and CPs, respectively. Lines represent medians. *P* values were obtained using Wilcoxon or Mann-Whitney tests.

noncategorical variables, Mann-Whitney test was used (or Wilcoxon test for paired values), whereas for comparison of more than 2 groups, Kruskal-Wallis was implemented, reporting the results as median and IQR. A 2-sided *P* value less than .05 was considered statistically significant.

RESULTS
Clinical characteristics of CVID patients with *Campylobacter* infection and the control group

The overall median age of patients with *Campylobacter* infections (CPs) was 52 years (IQR 46—72 y) and an equal male-to-female distribution was observed. All CPs received immunoglobulin replacement therapy as a treatment for CVID, 8 of 14 subcutaneously (SCIg) and 6 of 14 intravenously (IVIg).

All but 1 patient were on prophylactic antibiotic therapy, 4 of 13 on azithromycin, 4 of 13 on cotrimoxazole, 2 of 13 on doxycycline, 2 of 13 on ciprofloxacin, and 1 of 13 on co-amoxiclav.

All CPs reported a history of diarrhea and weight loss was reported in 4 of 14. Other symptoms including abdominal cramping, bloating, incontinence, and nausea were only reported by a minority (1 of 14 patients for each symptom). Common comorbidities were autoimmune phenomena (50.0%), and we noted a history of iatrogenic immune suppression in 9 of 14 patients. Clinical details are provided in Table I.

Regarding the control group (CG), the overall median age was 60 years (IQR 48—71 y) with a slightly higher proportion of females (57.9%). All patients were on immunoglobulin replacement therapy as a treatment for CVID, 28 of 95 SCIg and 67 of 95 IVIg.

Seventy-five of 95 in the CG were on prophylactic antibiotics (33 on azithromycin, 12 on cotrimoxazole, 11 on doxycycline, 9 on ciprofloxacin, 7 on co-amoxiclav, 2 on clarithromycin and 1

on penicillin), showing a similar distribution and type of prophylactic regimen compared with the CPs.

The CG had a trend toward a lower history of immunosuppression (43.2% vs 64.3%; *P* = .16), and had less autoimmunity (31.6% vs 64.3%; *P* = .03), solid organ neoplasm (4.2% vs 21.4%; *P* = .04) and history of chest infection (68.4% vs 100.0%; *P* = .01) than the CPs.

Notably, 12 of 95 CG patients had a history of *Giardia,* 1 *Helicobacter pylori* and esophageal candidiasis. Demographic and clinical characteristic of both groups are provided in Table II.

Immunological parameters of CVID patients with *Campylobacter* infection

All CPs had low or undetectable IgA and 5 of 14 had long-term IgG below our usual trough target of 8 g/L. However, no differences in the immunoglobulin levels between the groups were observed (Table E1; available in this article's Online Repository at www.jaci-inpractice.org; and Table II). In 4 patients, at least 1 *Campylobacter* infection coincided with low IgG levels (Figure E1; available in this article's Online Repository at www.jaci-inpractice.org), but in all other cases, IgG was above the target trough concentration at the time of positive tests.

Comparing the most recently available with the first available recorded lymphocyte counts (Figure 1, *A—D*), CPs demonstrated a decrease over time in the absolute number of CD4+ T cells (median 0.33 vs 0.59 × 10^9/L; *P* = .001), CD8+ T cells (median 0.26 vs 0.62 × 10^9/L; *P* = .005), CD19+ B cells (median 0.02 vs 0.14 × 10^9/L; *P* = .004) and NK cells (median 0.08 vs 0.18 × 10^9/L; *P* = .049); these differences were not observed in the CG.

A possible temporal relationship between the decrease in cell counts and the timing of *Campylobacter* infection may be observed in some patients, and iatrogenic immunosuppression was common (Figure E1).
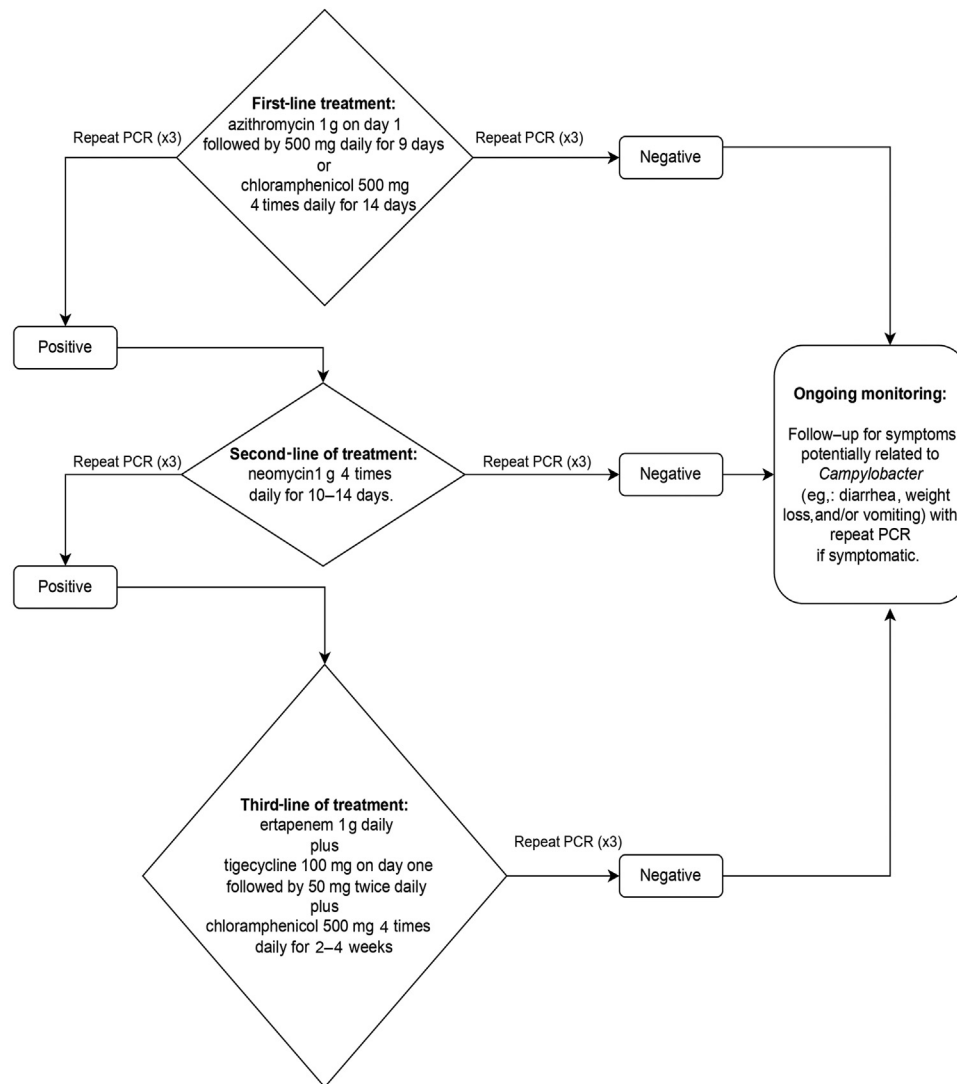
FIGURE 2. Treatment algorithm for fecal *Campylobacter* spp. PCR or culture-positive antibody-deficient patients. (Note: applicable only for isolated colitis, not for bloodstream infection, which should be managed with third-line treatment.)

When comparing the most recent values of CD19+ and CD4+ T lymphocytes between groups, CPs showed lower numbers than controls (median 0.03 vs 0.16 × 109/L; P = .001; and 0.31 vs 0.58 × 109/L; P = .001) (Figure 1, E–H).

We also compared long-term average immunological parameters between CPs and controls and observed that CPs had significantly lower average CD19+ and CD4+ T cell numbers (median 0.06 vs 0.18 × 10^9/L; $P = .008$; and 0.41 vs 0.62 × 10^9/L; $P = .009$) (Figure E2; available in this article's Online Repository at www.jaci-inpractice.org)

Finally, the CD21^{low}CD38^{low} B-cell and transitional B-cells percentages were significantly elevated in the CP group (median 38.0% vs 14.2%; $P = .04$; and 5.4% vs 3.2%; $P = .03$, respectively) (Figure E2).
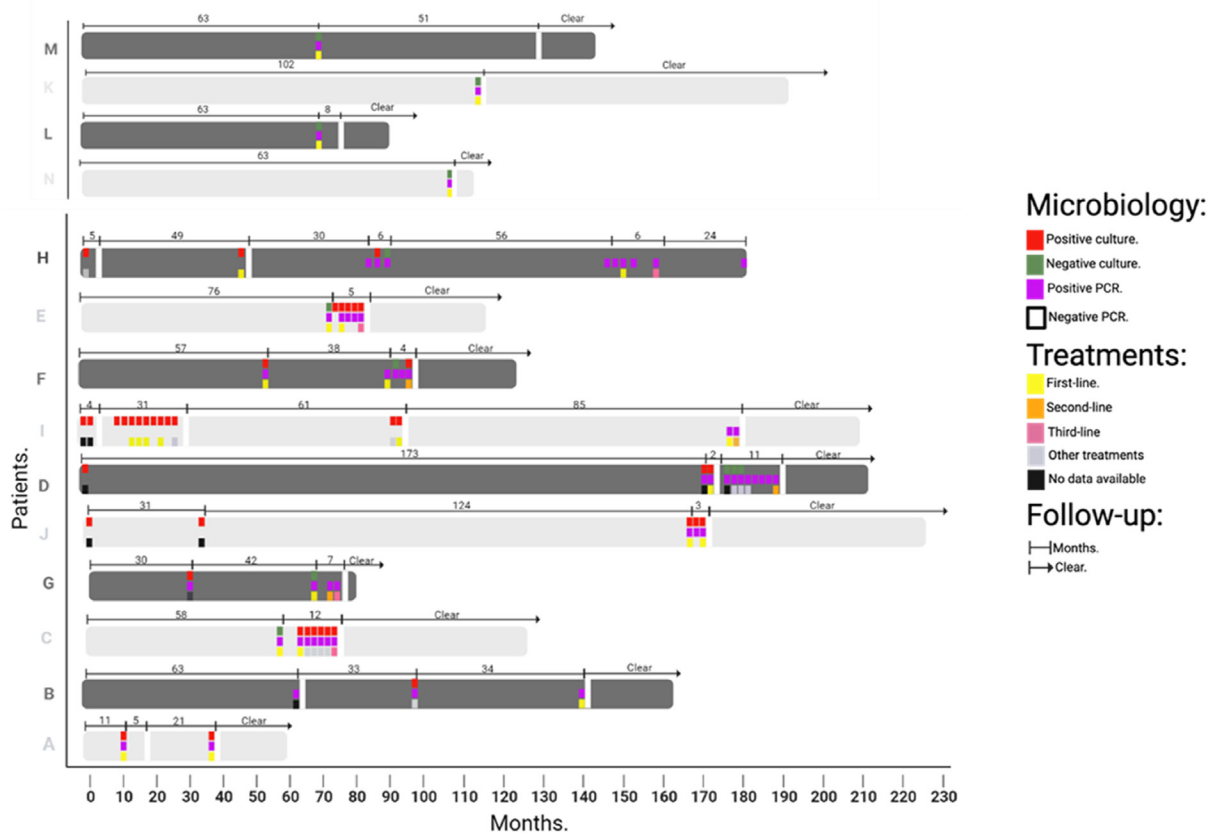
Duration of *Campylobacter* infection

Four patients were included in the ACP group. Clinical response to treatment was measured as a cessation of symptoms or a negative culture/PCR for *Campylobacter*. The median time

of infection, obtained from the sum of days with positive PCR, was 20 days (IQR 18.8−20.3 d). Two patients did not have a follow-up negative PCR or culture for *Campylobacter* but experienced sustained improvement in symptoms after treatment. Notably, comparing the immunological parameters of the ACP group with the CGs, no significant differences were obtained.

The CCP group comprised 10 patients. The median time of infection, obtained from the sum of days with positive PCR, was 113 days (IQR 54−167 d).

Antimicrobial sensitivity of *Campylobacter* isolates

Table E2 (available in this article's Online Repository at www.jaci-inpractice.org) presents the results of antimicrobial sensitivity tests for *Campylobacter* isolates from our patients, available in 7 of 14. Macrolide and fluoroquinolone resistance were common, whereas chloramphenicol and aminoglycoside resistance were rarely seen. Of note, treatment-emergent resistance to carbapenems was seen in 1 patient.

FIGURE 3. Treatment and follow-up. Fourteen patients with *Campylobacter* infection are represented in the graph. Four patients had ACP (patients M, K, L and N) and all responded to first-line treatment; the other 10 patients had chronic infection or relapse. Patients are organized from highest to lowest number of CD21^{low}CD38^{low} B cells in each group. A, B, and J were treated successfully with first-line therapy. Patients D, F, H, and I were eventually treated successfully with second-line therapy. Finally, patients C, E, and G were successfully treated with third-line treatment. All patients are currently clear from *Campylobacter,* except patient H is still positive after second-line treatment, so third-line treatment will be considered.

Treatment response of *Campylobacter* infections

Wherever feasible, patients with *Campylobacter* colitis received treatment according to our novel treatment algorithm described in Figure 2. CVID patients with *Campylobacter* bacteremia were treated with third-line treatment (combination treatment with parenteral antibiotics). Patients treated historically were given treatment according to best practice at the time. In Figure 3, we describe the treatment response of each patient included in the cohort.

First-line treatment.
A total of 7 patients responded to the first-line treatment for *Campylobacte*r spp. Four belonged to the ACP group and received azithromycin 1 g on day 1 followed by 500 mg daily for 9 days. The remaining 3 patients were in the CCP group. Of these, 2 (A and B) received azithromycin and 1 patient (J) received chloramphenicol 500 mg 4 times daily for 14 days. This group experienced prolonged improvement in symptoms and consecutive negative fecal *Campylobacter* PCR results after a median of 78 days (IQR 21–98 d).

Second-line treatment.
A total of 4 patients (D, F, H, and I) belonging to the CCP group responded to second-line treatment for Campylobacteriosis with neomycin 1 g 4 times daily for

10 to 14 days. All subjects had received first-line and/or other treatment with no definitive improvement. Prolonged improvement of the symptoms and consecutive negative fecal PCRs were obtained after a median of 302 days (IQR 185.5–702.5 d) in patients D, F, and I. Patient H continues to be positive despite treatment with second-line therapy, and a therapeutic approach with third-line needs to be considered.

Third-line treatment.
Finally, 3 patients (C, E, and G) received third-line treatment. The first case (D) developed *C. jejuni* invasive infection after failing first-line treatment for colitis. He had recurrent positive blood and fecal cultures. He was started on third-line treatment but continued to be bacteremic despite combination treatment that included 8 weeks of carbapenems. The WGS confirmed persistence of infection with the same strain. He finally successfully cleared the infection with a combination of gentamicin (10 d), tigecycline (7 wk) and oral chloramphenicol (6 wk). The other 2 patients, F and H, had persistent *C. jejuni* colitis and were treated with the third-line regimen described in the treatment algorithm. Resolution of symptoms and consecutive negative fecal PCRs were obtained after a median of 169 days (IQR 141–196.5 d).

DISCUSSION

Campylobacter infections are well recognized in patients with antibody deficiency syndromes, including CVID,[8,13,18] and are known to impair quality of life. Although infections can be mild and self-limiting, they can also become chronic or have severe complications including bacteremia, endocarditis, and metastatic infection.

Similar to a previous case series,[13] patients in our study all suffered diarrhea and experienced a range of other gastrointestinal symptoms. Of note, we also observed weight loss in 4 of 14 patients. In contrast to Dion et al,[13] fever was not seen, and bacteremia was rare in our cohort. This may have related to the inclusion of adults only in our cohort. Surprisingly, we observed a high rate of chronic or relapsing infection (71.4%) in comparison with Dion et al (42%)[13] and the general population (1.2%).[19]

Immunologically, all patients had reduced or undetectable IgA and we observed long-term average IgG levels below our center's target of 8g/L in 5 of 14 patients. This may have related to treatment adherence or potentially to gastrointestinal protein loss. Dion et al[13] also noted lower baseline IgA and IgG in patients with *Campylobacter* than in immune-deficient controls. van der Hilst et al[20] also studied a similar cohort of 15 and 34 patients with X-linked agammaglobulinemia and CVID, respectively, describing that approximately 40% of X-linked agammaglobulinemia and 15% of CVID patients suffered from chronic or recurrent gastroenteritis secondary to *C. jejuni*. The authors suggested that patients with undetectable levels of IgA are at a higher risk of developing *Campylobacter*.[20] Nevertheless, 14.2% of CPs in our cohort showed reduced, but detectable levels of IgA. These findings do not contradict the role of IgA in the control of gastrointestinal infections, but suggest that other mechanisms are also important. The IgM levels tended to be higher than IgA and there was no difference between CPs and control patients. Owing to the availability of historical data, we did not compare baseline cell counts, but we observed a decrease in CD4+ T-cell, CD8+ T-cell, B-cell, and NK-cell numbers over time, with a possible temporal relationship to the *Campylobacter* infection and iatrogenic immunosuppression. This is reminiscent of our previous findings in chronic norovirus infection.[21] We also observed a higher percentage of CD21^{low} B cells with both infections, a hallmark of chronic immune activation.[22] Furthermore, in common with our description of chronic norovirus and in the French *Campylobacter* cohort, use of immunosuppression was frequent (9 of 14 patients) and may have contributed to the decline in cell counts over time and potentially susceptibility to infection.

In the healthy host, epithelial cells respond to *Campylobacter* with the release of chemokines, predominantly interleukin-8 that recruits neutrophils.[23] Phagocytosis and intracellular killing by neutrophils are also accompanied by the extracellular release of granule proteins. Subsequent cellular signaling by resident or recruited mononuclear phagocytes[23] shapes the adaptive immune response, predominantly characterized by cytokine production from CD4+ T cells (with both Th1 and Th17 differentiation) and antibody production from B cells.[23] NK cells are also implicated.[23] Failure of these mechanisms is consistent with our findings of lower T-cell and B-cell counts in the CPs compared with the CG (and a reduction over time in numbers of T cells, B cells, and NK cells) and a low long-term average IgG level in some cases.[24,25]

Previous studies have demonstrated evolution of AMR on treatment, making this a particularly challenging infection to treat effectively.[26] Although first-line treatment options are well recognized, they are limited by high rates of antibiotic resistance (especially for fluroquinolones and tetracycline). At population level, macrolide resistance remains low in the United Kingdom (<2% in *C. jejuni*, up to 20% in *C. coli*), as does aminoglycoside resistance (<1%) [UKHSA, unpublished data, 2019]). However, most CVID patients are on prophylactic antibiotics, increasing the selection pressure on gut microbiota contributing to persistent carriage and emergence of drug resistant strains.[26] Multidrug-resistant strains severely limit treatment options and have been known to cause veterinary and human outbreaks.[27-29]

Although in most cases *Campylobacter* disease is self-limiting, a recent analysis suggests that up to 80% of individuals in the community received an oral antibiotic such as a fluoroquinolone or macrolide.[30] The high prevalence of fluoroquinolone resistance (~75%–90% in some regions) in *Campylobacter* strains has led to a change in treatment, making macrolides first line. However, the recent increase of macrolide resistance in *Campylobacter* spp. is concerning.[31-33]

A relatively recent review published by Dai et al[30] discussed the issue of novel and alternative strategies to prevent, control, and treat antibiotic resistant *Campylobacter,* including prebiotics, probiotics, bacteriocins, bacteriophages, immunization, and antibiotic adjuvants.

In this study, although we did not have the extended panel of antibiotic susceptibilities available for all isolates, we saw frequent resistance to macrolides and fluoroquinolones. For both of these antibiotic classes, initial results demonstrated susceptibility in 3 patients and resistance in 4, presumably relating in large part to the use of antibiotic prophylaxis. Prophylaxis with antibiotics in antibody deficiency is predominantly aimed at reducing respiratory tract infection, where the intervention has evidence of efficacy.[34] However, clinicians should be aware of the risk of resistance with breakthrough infections, including *Campylobacter*. In those with baseline susceptibility who submitted serial samples, intermediate sensitivity or resistance was inevitably seen. We also saw emergence of resistance to carbapenems on treatments, particularly in 1 patient with bacteremia. Conversely, resistance to chloramphenicol and aminoglycosides was rare.

We used oral neomycin as second-line treatment in patients with uncomplicated gastroenteritis who failed first-line treatment with chloramphenicol or macrolides (the latter for patients not on macrolide prophylaxis). Although this was only used in 4 patients, 2 responded, making it a viable option for treatment. The third-line regimen is used in those failing oral neomycin or patients with complicated or invasive infections. This includes a combination of 3 agents (2 parenteral) to avoid emergence of resistance on treatment. We propose this novel pathway as a possible solution for management of *Campylobacter* infections in the immunocompromised.

Our study has limitations. The data reflect real-world clinical and laboratory practice rather than a formal clinical trial. As such, not all data are available for all patients and, despite the treatment protocol, therapy was based on individual clinical decisions and did not always strictly adhere to the guidance (especially in historically treated patients). Some data, for example on symptoms, may not have been captured fully in case notes, and not all microbiological samples were cultured and subjected to antibiotic

sensitivity testing. It would have been interesting to compare baseline immunological parameters at the time of diagnosis, but these were not available for all patients and we made a pragmatic decision to collect data from 2000 onward. The division into ACP versus CCP infection was arbitrary, but we felt this was useful to describe different clinical phenotypes.

In summary, we have demonstrated that *Campylobacter* infections in patients with CVID can be prolonged or recurrent and that weight loss is relatively common in our adult cohort. Patients with *Campylobacter* infections often experience a decline in B- and T-cell counts over time, which may be a predisposing factor for infection (eg, when secondary to immune suppression) or a consequence of the infection itself. Antibiotic resistance was very common, especially to macrolides and fluoroquinolones, with concerning treatment-emergent resistance to carbapenems. We propose our treatment protocol as a rational approach that aims to avoid hospital admission and intravenous treatment where possible but uses combination therapy to prevent the appearance of multidrug-resistance in refractory cases.

CONCLUSIONS

Our study highlights immunological and clinical characteristics of chronic and recurrent *Campylobacter* infections in patients with CVID. We have developed a treatment algorithm that has shown successful outcomes in a cohort of patients with CVID. Emergence of antibiotic resistance and failure of standard treatment regimens are high. Early involvement of infection specialists at the reference laboratory, susceptibility testing for extended panel of antibiotics, and strain typing are extremely useful to manage these difficult-to-treat infections. The treatment regimen should be evaluated in a larger cohort of patients.

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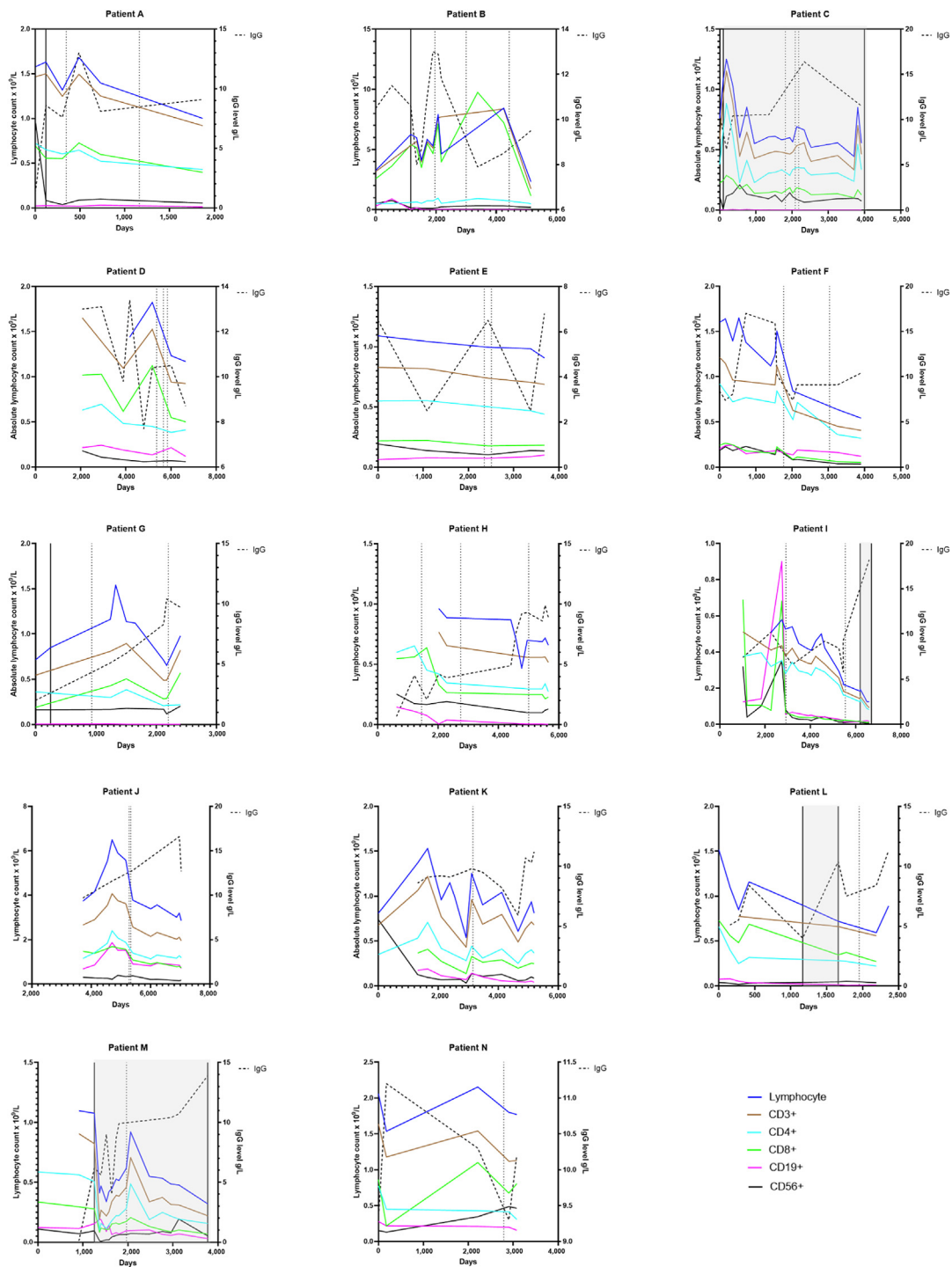
FIGURE E1. Graphic representation of lymphocyte subset results obtained during patients' follow-up (from date of common variable immunodeficiency [CVID] diagnosis [or most recent result after diagnosis, if applicable] to 2022). Dark blue line, absolute lymphocyte count ($\times 10^9$/L). Brown line, absolute CD3+ lymphocyte count ($\times 10^9$/L). Light blue line, absolute CD4+ lymphocyte count ($\times 10^9$/L). Green line, absolute CD8+ lymphocyte count ($\times 10^9$/L). Pink line, absolute CD19+ lymphocyte count ($\times 10^9$/L). Black line, absolute CD56+ natural killer–cell lymphocyte count ($\times 10^9$/L). Dotted black line, immunoglobulin (Ig) G level (g/L). Dotted vertical lines represent the dates of positive culture or/and PCR for *Campylobacter.* One solid vertical line represents the time of any single immunosuppressive regimen; shaded areas represent the time interval during which the patient received a prolonged immunosuppressive regimen. During follow-up, patients A, D, K, Q, H, and O received prednisolone. Patients H and O also received rituximab and mycophenolate mofetil, respectively. Similarly, patients J and N received tofacitinib and infliximab, respectively. Finally, patient B was diagnosed with a T-cell lymphoma circa 2010, no treatment needed. *PCR,* Polymerase chain reaction.
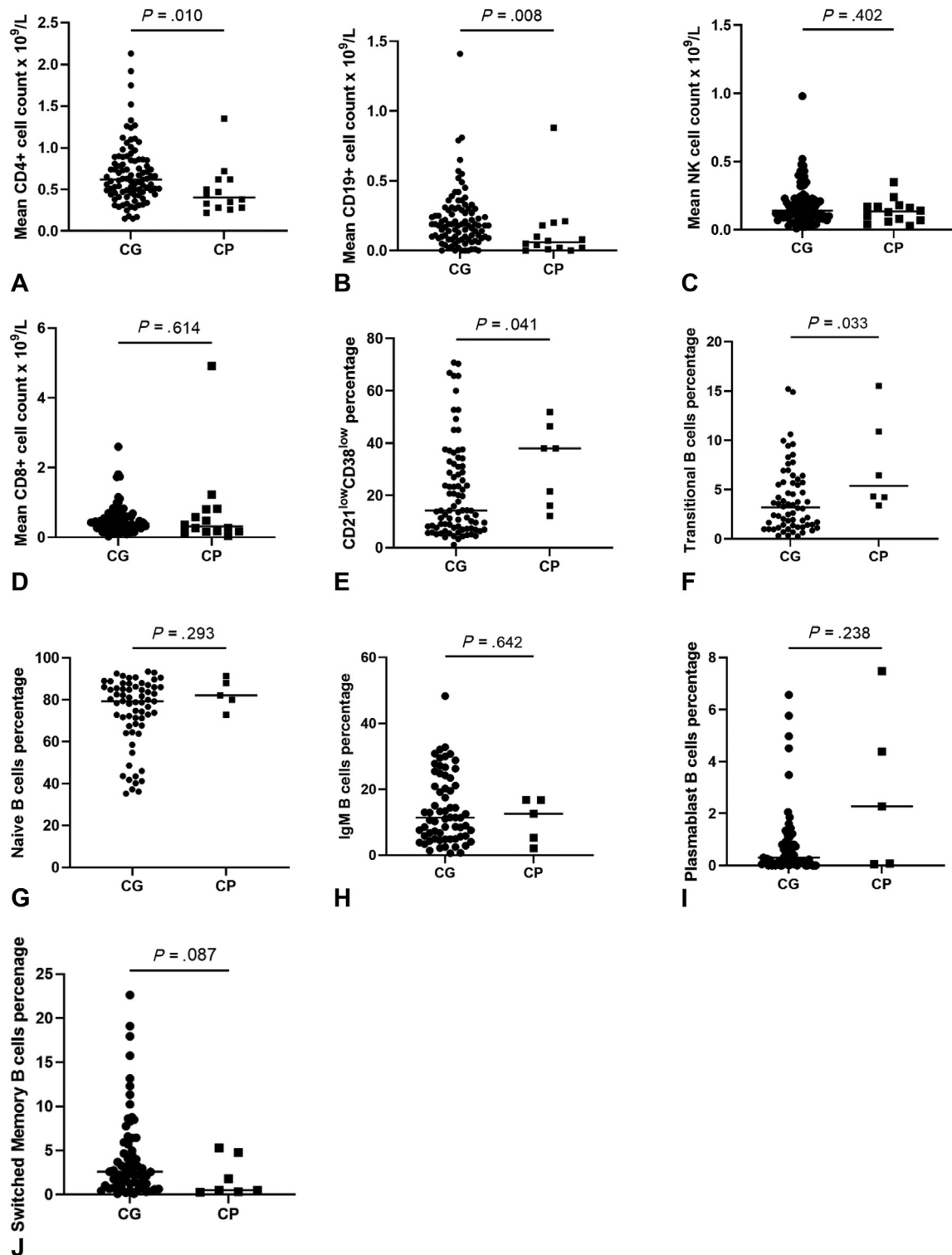
FIGURE E2. Long-term average lymphocyte counts or percentage of cell subpopulations for the control group (CG) versus *Campylobacter* patients (CP). Values for the long-term average: (**A**) CD4+ T cell count (CG n = 95 vs CP n = 14); (**B**) CD19+ B cell count (CG n = 95 vs CP n = 14); (**C**) natural killer (NK) cell count (CG n = 95 vs CP n = 14); (**D**) CD8+ cell count (CG n = 65 vs CP n = 14); (**E**) CD21low CD38low percentage (CG n = 84 vs CP n = 7); (**F**) transitional B cells percentage (CG n = 64 vs CP n = 6); (**G**) naive B cells percentage (CG n = 65 vs CP n = 5); (**H**) immunoglobulin (Ig) M memory B cells percentage (CG n = 65 vs CP n = 5); (**I**) plasmablast B cells percentage (CG n = 64 vs CP n = 5); (**J**) switched memory B cells percentage (CG n = 65 vs CP n = 7). Lines represent medians. *P* values were obtained using Mann-Whitney tests.

TABLE E1. Immunological parameters of *Campylobacter* patients

Patient ID	Lymphocytes (1.1–1.4 X10⁹/L) Long-term average	CD3+ cells (NR 0.60–3.0 × 10⁹/L) Most recent result	First available result	Long-term average	CD4+ cells (NR 0.43–1.82 × 10⁹/L) Most recent result	First available result	Long-term average	CD8+ cells (NR 0.25–1.20 × 10⁹/L) Most recent result	First available result	Long-term average	CD19+ cells (NR 0.12–0.67 × 10⁹/L) Most recent result	First available result	Long-term average	NK cells (NR 0.09–0.60 × 10⁹/L) Most recent result	First available result	Long-term average	Immunoglobulins long-term average IgG (6.60–15.9 g/L)	IgA (0.60–5.0 g/L)	IgM (0.53–2.47g/L)
A	1.49	0.92	1.47	1.36	0.43	0.72	0.62	0.40	0.69	0.58	0.01	0.02	0.02	0.05	0.97	0.08	8.46	0.11	0.16
B	5.57	1.75	3.18	5.40	0.51	0.52	0.62	1.15	2.58	4.91	0.00	0.30	0.02	0.20	0.51	0.18	10.59	<0.10	<0.10
C	0.60	0.46	0.59	0.48	0.33	0.38	0.33	0.13	0.22	0.16	0.00	0.00	0.00	0.07	0.11	0.13	10.94	<0.10	<0.10
D	1.34	1.09	1.65	1.09	0.41	0.63	0.47	0.82	1.02	0.82	0.12	0.22	0.20	0.06	0.18	0.07	10.83	<0.10	0.19
E	1.00	0.69	0.83	0.74	0.44	0.55	0.50	0.18	0.22	0.18	0.10	0.06	0.08	0.14	0.19	0.14	6.54	<0.10	<0.10
F	1.38	0.41	1.21	0.94	0.32	0.92	0.72	0.05	0.24	0.17	0.12	0.20	0.18	0.04	0.19	0.16	10.30	<0.10	0.29
G	0.98	0.82	0.55	0.68	0.22	0.36	0.26	0.57	0.19	0.36	0.00	0.01	0.00	0.20	0.16	0.17	7.20	<0.10	0.16
H	0.70	0.52	0.77	0.56	0.28	0.60	0.35	0.23	0.55	0.27	0.00	0.15	0.01	0.13	0.26	0.17	5.56	<0.10	<0.10
I	0.42	0.09	0.51	0.33	0.08	0.38	0.28	0.01	0.69	0.04	0.02	0.13	0.05	0.01	0.32	0.03	9.26	<0.10	0.14
J	3.78	1.95	2.66	2.62	1.19	1.15	1.35	0.73	1.48	1.23	0.71	0.68	0.88	0.31	0.18	0.24	13.28	<0.10	<0.10
K	0.96	0.68	0.67	0.70	0.37	0.35	0.38	0.25	0.37	0.27	0.04	0.18	0.07	0.09	0.74	0.10	9.27	<0.10	<0.10
L	0.90	0.56	0.78	0.66	0.22	0.66	0.28	0.27	0.73	0.48	0.01	0.08	0.04	0.04	0.04	0.04	6.92	<0.10	<0.10
M	0.50	0.22	0.91	0.34	0.16	0.59	0.22	0.07	0.34	0.13	0.03	0.12	0.10	0.05	0.11	0.06	7.85	<0.10	0.20
N	1.80	1.13	1.64	1.18	0.31	0.78	0.43	0.81	0.86	0.81	0.16	0.28	0.21	0.46	0.15	0.35	10.89	<0.10	<0.10

ID, Identification; *Ig,* immunoglobulin; *NK,* natural killer; *NR,* normal range.

TABLE E2. Antimicrobial susceptibility testing and strain characterization*

Patient	Biological sample	*Campylobacter* spp./type (clonal complex)	Isolation date	Treatment	Ery	Cip	Tet	Co-amox	Ert	Mer	Tig	Gen	Col	Fos	Co-trim	Rif	Chl	Min
A	F		18/12/2018	Azi	S	S	S	NT	NT	NT	NT	NT	NT	NT	NT	NT	NT	NT
C	F	*C. jejuni* ST 1233 (ST 353)	12/09/2016	Azi	R	R	R	X (16)	X (0.5)	NT	NT	NT	NT	NT	NT	NT	NT	NT
	B	*C. jejuni* ST 1233 (ST 353)	02/11/2016	Cip	R	R	R	NT	X (1)	X (0.25)	X (0.032)	X (0.5)	NT	NT	X (>32)	NT	X (2)	NT
	B	*C. jejuni* ST 1233 (ST 353)	18/11/2016	Ert	R	R	R	NT	X (>32)	X (16)	NT	X (0.125)	NT	NT	X (>32)	NT	X (3)	NT
	B	*C. jejuni* ST 1233 (ST 353)	30/11/2016	Mer	R	R	R	X (16)	X (>32)	X (8)	X (0.032)	X (0.125)	X (8)	NT	X (>32)	X (>32)	X (3)	NT
	B	*C. jejuni* ST 1233 (ST 353)	14/12/2016	Mer+ Tig+ Chl	R	R	R	X (32)	X (>32)	X (>32)	X (0.064)	X (0.25)	NT	X (256)	NT	NT	R	I
D	F		23/02/2003	NA	NT	R	NT	R	S	NT	NT	S	NT	NT	NT	NT	S	NT
E	F	*C. jejuni* ST 5866 (ST 353)	06/05/2017	Chl	R	R	R	NT	X (0.125)	X (0.016)	X (0.064)	X (0.25)	NT	NT	NT	NT	X (4)	NT
	F	*C. jejuni* ST 5866 (ST 353)	04/07/2017	NA	R	R	R	X (1)	X (0.125)	X (1)	X (0.064)	X (0.25)	NT	NT	NT	NT	X (8)	NT
	F	*C. jejuni* ST 5866 (ST 353)	05/09/2017	Ert+ Tig+ Chl	R	R	R	X (1)	X (0.25)	X (0.016)	X (0.016)	X (0.125)	NT	NT	NT	NT	NT	NT
H	F		05/05/2006	Cip	S	R	NT	S	NT	NT	NT	S	NT	NT	NT	NT	S	NT
	F		27/04/2010	Cip+ Azi	R	I	NT	NT	NT	NT	NT	NT	NT	NT	NT	NT	NT	NT
	F		09/11/2013	NA	I	R	NT	NT	NT	NT	NT	NT	NT	NT	NT	NT	NT	NT
I	F		18/02/2004	NA	S	S	NT	S	NT	NT	NT	S	NT	NT	NT	NT	S	NT
	F		14/05/2004	NA	S	R	NT	NT	NT	NT	NT	S	NT	NT	NT	NT	S	NT
	F		05/04/2005	NA	S	R	NT	R	NT	NT	NT	S	NT	NT	NT	NT	S	NT
	F		12/04/2005	NA	S	NT	NT	R	NT	NT	NT	S	NT	NT	NT	NT	S	NT
	F		14/06/2005	Ery	S	R	NT	R	NT	NT	NT	S	NT	NT	NT	NT	R	NT
	F		26/07/2005	Ery	S	R	NT	R	NT	NT	NT	S	NT	NT	NT	NT	S	NT
	F		02/09/2005	Ery	S	I	NT	R	NT	NT	NT	S	NT	NT	NT	NT	NT	NT
	F	*C. jejuni* untypable	23/11/2005	Ery	S	R	NT	R	NT	NT	NT	S	NT	NT	NT	NT	NT	S
	F	*C. jejuni* untypable	24/01/2006	NA	S	S	NT	R	NT	NT	NT	S	NT	NT	NT	NT	S	NT
	F		20/06/2006	Ery	S	S	NT	R	NT	NT	NT	S	NT	NT	NT	NT	S	NT
	F		21/02/2012	Cla	I	R	NT	NT	NT	NT	NT	NT	NT	NT	NT	NT	NT	NT
J	F		21/08/2002	NA	R	S	NT	R	NT	NT	NT	S	NT	NT	NT	NT	S	NT
	F		07/09/2005	NA	R	R	NT	R	NT	NT	NT	S	NT	NT	NT	NT	S	NT
	F	*C. jejuni*	04/02/2017	Azi	R	R	R	X (1)	X (0.032)	NT	NT	NT	NT	NT	NT	NT	NT	X (2)	NT

Azi, Azithromycin; *B,* blood; *Chl,* chloramphenicol; *Cip,* ciprofloxacin; *Cla,* clarithromycin; *Co-amox,* co-amoxiclav; *Col,* colistin; *Co-trim,* co-trimoxazole; *Ert,* ertapenem; *Ery,* erythromycin; *F,* feces; *Fos,* fosfomycin; *Gen,* gentamicin; *I,* intermediate; *Mer,* meropenem; *Min,* minocycline; *NA,* not available; *NT,* not tested; *PCR,* polymerase chain reaction; *R,* resistant; *Rif,* rifampicin; *Tet,* tetracycline; *Tig,* tigecycline; *X,* minimum inhibitory concentration (no European committee on antimicrobial susceptibility testing [EUCAST] breakpoint data available).

*Patients and samples not listed here were positive by PCR for *Campylobacter* spp. but the organism was not cultured.