Campylobacter infection in adult patients with primary antibody deficiency

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Funding. DEFI study was initially supported by public national program for clinical research (PHRC, INSERM RBM0333). The funding source had no role in the present ancillary study.

Potential conflicts of interest. L.B. has received grants for her institution from Allergan, and support for travel/accomodations/meeting expenses from R-Biopharm and Mobidiag. F.M. has received grants from Allergan, and payment for lectures including service on speakers bureaus from Allergan and Takeda. L.Ga. has been consultant for Baxalta, has received payment for development of educational presentations from Amgen, Roche, Janssen Pharmaceuticals, GlaxoSmithKline, Pfizer, Raison et Santé, Baxalta, and support for travel/accomodations/meeting expenses from Janssen Pharmaceuticals, GlaxoSmithKline, and Shire. A.J. has received payment for lectures from Janssen Pharmaceuticals and Abbvie, travel/accomodations/meeting expenses from Janssen Pharmaceuticals, Celgen, Takeda, and Gilead Sciences. E.O. has received personal fees from CSL Behring, Shire, non financial support from Janssen Pharmaceuticals, has served on advisory boards for CSL Behring and Shire. L.Gé. has received support for travel/accomodations/meeting expenses from Janssen Pharmaceuticals and Gilead Sciences.

J.D., M.M., A.W., D.B., V.L.M., P.G., R.N.J.: no conflict

Word count: 987

Clinical implication Box

In patients with severe primary antibody deficiency, Campylobacter infection is a major cause of chronic or recurrent diarrhea. The frequent recurrence with different strains and the high frequency of bacteremia suggest an increased susceptibility to this pathogen in this population.

To the editor:

Primary antibody deficiency (PAD) is characterized by a defective immunoglobulin production and recurrent infections, mostly involving respiratory and gastrointestinal tracts. Chronic or recurrent diarrhea is reported in up to 23% (1). Campylobacter infection is a common cause of infectious diarrhea, reported in 1.2 to 7.5% of patients with common variable immunodeficiency (CVID), the most frequent PAD (1-3). The aim of this study was to describe Campylobacter infection in patients with PAD included in a large nationwide study and analyze factors associated with susceptibility to this pathogen.

The DEFI (DEFicit Immunitaire) study is an ongoing large cross-sectional French multicentric study of adults with PAD, with retrospective collection of clinical data (2). All patients with a history of bacteriologically documented Campylobacter infection were identified, and clinical data were collected for each episode. Factors associated with recurrent infection were assessed as odds ratio (OR) and 95% confidence interval (CI), calculated by means of simple regression analysis. In patients with available material, strains of each episode were characterized using molecular analysis and compared (Table E1A in the Online Repository). A comparison of immunodeficiency-related characteristics of patients with and without Campylobacter infection was performed in the homogenous group of CVID patients. The control group included CVID patients from DEFI centers who confirmed that patients did not develop Campylobacter infection after enrollment (Figure E1 in the Online Repository). After correction for multiple comparisons, a $P<0.016$ was considered significant.

Since 2004, 790 patients with PAD were included in the DEFI study, and 51 presented with Campylobacter infection (6.5%). Medical chart was available for review in 45 patients. Characteristics of these patients at the time of enrollment in DEFI are detailed in Table E2 in the Online Repository. A total of 97 episodes were recorded (Table 1). The overall

distribution of *Campylobacter* species was unremarkable. Antimicrobial susceptibility testing revealed a higher resistance rate than in the general population for each antibiotic tested (See Figure E2 in the Online Repository). A comorbidity was present in 55% of Campylobacter episodes, and a coinfection by other enteropathogens in 10%. Most patients were receiving concomitant therapy at the time of episode. One patient with end-stage cirrhosis died with Campylobacter bacteremia. Overall, bacteremia was observed in 24 episodes (13 patients), and was associated with extra-intestinal complication in 10 episodes.

Nineteen patients (42%) presented with recurrent (2 to 11) episodes. Factors associated with recurrent episodes were the presence of comorbidity (OR, 3.7 [95%CI, 1.1-13.1]), and undetectable serum IgA (OR, 8.6 [95%CI, 1.1-21.2]). None of these factors remain significant in multivariate analysis. Molecular study of a subset of 18 strains from five patients with recurrent infections demonstrated that all strains were different, even when the antimicrobial susceptibility testing was similar and when the episodes occurred closely over time (Table E1B in the Online Repository). Compared to 288 CVID patients without Campylobacter infection, CVID patients with Campylobacter infection presented a higher prevalence of consanguinity and a more severe CVID phenotype, with more frequent disease-related complications, lower serum immunoglobulin levels, lower B and NK cells, and a trend for lower naive CD4+T cell at the time of enrollment in the DEFI study (Table 2).

This study is the first description of a large series of patients with PAD and Campylobacter infection. The 6.5% prevalence was probably underestimated due to the retrospective nature of the clinical data collection. In this population symptoms were mostly restricted to an isolated, frequently severe, chronic watery diarrhea, with associated malnutrition, leading to repeated hospitalizations and impaired quality of life. Other digestive symptoms and fever were less frequent than those observed in the general population (4). In contrast, bacteremia as well as extra-digestive localizations were more frequent (25% versus 0.15-2%, and 22%

versus 7%, respectively) (5). Despite frequent hospitalizations, the overall prognosis was good. Recurrence rate was high (42%) compared to 1.2% in the general population (6), and was associated with extra-intestinal comorbidity and undetectable IgA level in univariate analysis. Although limited by the number of available strains, molecular profile of strains from patients with recurrent infections were all different. Thus, we could hypothesize that reinfection is more likely than persistent colonization, although colonization with multiple strains cannot be excluded.

Conditions associated with the occurrence of Campylobacter infection were described in an analysis restricted to a large homogenous group of 325 CVID patients. The present data suggest that hypochlorydria, either PPI-induced or associated with autoimmune gastritis, might play an important role in the pathogenesis of this infection. Almost all CVID-associated complications, particularly liver and gastrointestinal disease, were more frequent in patients with Campylobacter infection. A more severe immune deficiency at CVID diagnosis, with lower serum immunoglobulin level was also observed. Even in patients with immunoglobulin replacement therapy, IgM and IgA levels remain very low. IgA and IgM, almost absent in immunoglobulin batches, are more important than IgG in Campylobacter immunity (7). B-cell and specifically switch memory B cell deficiency was also more severe in CVID patients with Campylobacter infection than in patients without. This is in line with the high prevalence of Campylobacter infection observed in Good syndrome and XLA, two conditions associated with no circulating B cells (Figure E1 in the Online Repository). B-cells are also known to be important for the dialogue between immune system and gut microbiota, whose composition is important for Campylobacter immunity (8). T-cells may also play an important role, with a trend for decreased naive T-cells. Indeed, fifteen patients (40%) presented with a severe associated T-cell defect and could be considered as Late Onset Combined Immunodeficiency (data not shown) (9).

In patients with PAD, Campylobacter infection is quite frequent and seems to be related to various factors adding up together: severity of the immune deficiency, PAD complication, and associated antibiotics, immunosuppressive therapies and PPI. It is characterized by a high frequency of recurrence and bacteremia. Recurrence is associated with the presence of comorbidity and IgA defect, and turned out to be due to reinfection more than to persistent colonization, suggesting a specific susceptibility despite immunoglobulin substitution.

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Table 1. Description of 97 Campylobacter episodes in 45 patients included in the DEFI study. Results are expressed as median (IQR), or number/number of episode with available data (%).

Characteristics	No. or median	% or IQR
Clinical features		
Digestive symptoms	81/87	93
Diarrhea	79	91
Chronic diarrhea	39	45
Abdominal pain	15	17
Vomiting	3	3
Fever	21/84	25
Bacteremia	24/97	25
Extra-intestinal symptoms	18/83	22
Respiratory	7	8
Osteo-articular	5	6
Urinary	2	2
Cutaneous	5	6
Concomitant infection[a]	17/84	20
Comorbidity[b]	53	55
Complications		
Hospitalisation	33/85	39
Duration, days	7	3-14
Late complications[c]	9/97	9
Current therapy at Campylobacter diagnosis		
Immunosuppressive drugs[d]	35/88	40
Proton pump inhibitors	41/81	51
Ig replacement therapy	79/90	87
Antibiotic prophylaxis	30/84	35
Serum Ig levels, g/L	n=37	
IgG	6.5	03-09
IgA	0.05	0-0.3
Undetectable IgA level	31	83
IgM	0.12	0.05-0.6
Undetectable IgM level	20	57
***Campylobacter* species**	n=97	
Campylobacter jejuni	55	56
Campylobacter coli	19	20
Other *Campylobacter species*	4	4
Unspecified	19	20

Abbreviations: Ig, immunoglobulin; IQR, interquartile range.

[a] Digestive infection in 10 cases: *Helicobacter pylori* gastritis (n=4), lambliasis (n=2), *Clostridium difficile* colitis (n=3), cytomegalovirus colitis (n=2); urinary infection in 4 cases; respiratory infection in 3 cases.

[b] Diabetes (n=2 patients), chronic liver disease (n=13 patients), blood neoplasia (n=3 patients), or transplantation (n=1 patient).

[c] Reactive arthritis (n=8), relapsing erythema nodosum (n=1).

[d] Prednisone(n=9), budenoside (n=18), TNFα (tumor necrosis factor alpha)-blocker (n=2), methotrexate (n=7), mycophenolate (n=2).

Table 2. Comparison between common variable immunodeficiency (CVID) patients with Campylobacter infection (Campylo pos) and without Campylobacter infection (Campylo neg) at enrollment in the DEFI study. Results are expressed as median (IQR) or number (%).

Characteristics	**Campylo pos** (n=37)	**Campylo neg** (n=288)	**P**
Population			
Female	22 (59)	172 (58)	0.98
Consanguinity	10 (27)	27 (10)	0.002*
Age at CVID diagnosis	32 (25-44)	37 (26-50)	0.17
Clinical complications			
Infection only	10 (27)	167 (58)	$<10^{-3}$*
Disease-Related Complication[a]	27 (73)	104 (36)	$<10^{-3}$*
Lymphoid proliferation	20 (54)	75 (26)	$<10^{-3}$*
Granulomatosis	11 (30)	39 (13)	0.01*
Autoimmune cytopenia	8 (22)	48 (17)	0.45
Opportunistic infection	10 (27)	22 (8)	0.001*
Chronic liver disease[b]	15 (40)	42 (15)	$<10^{-3}$*
Gastrointestinal complication	31 (84)	117 (41)	$<10^{-3}$*
Pernicious anemia	5 (13)	4 (1)	0.001*
Villous atrophy	8 (22)	15 (5)	0.002*
IBD	4 (11)	11 (4)	0.07
Digestive granuloma	3 (8)	6 (2)	0.07
Other GI tract infection[c]	16 (43)	43 (15)	$<10^{-3}$*
Acute recurrent diarrhea	12 (32)	27 (9)	0.01*
Chronic diarrhea	23 (62)	56 (19)	$<10^{-3}$*
Biology at CVID diagnosis			
Serum Ig level, g/L			
IgG	1.7 (0.84-2.8)	3.0 (1.3-4.3)	0.005*
IgA	0.07 (0.06-0.32)	0.25 (0.07-0.46)	0.008*
IgM	0.19 (0.06-0.42)	0.22 (0.11-0.50)	0.05
Blood cell count			
Hemoglobin level, g/dL	13 (11-14)	14 (13-15)	0.44
Platelet count, $x10^9$/L	202 (109-274)	209 (167-260)	0.16
Neutrophil count, $x10^6$/L	4000 (2850-5760)	3700 (2850-5470)	0.60
Lymphocyte count, $x10^6$/L	1406 (662-1918)	1371 (1025-1866)	0.44
CD3+ T cells	1107 (563-1658)	1063 (789-1426)	0.95
CD4+	555 (305-743)	561 (398-833)	0.35
Naive CD4+[d]	63 (16-213)	125 (48-271)	0.02
CD19+ B cells	51 (13-149)	101 (49-173)	0.03
<1%	9 (25)	26 (9)	0.008*
SMB cells[e]	0.3 (0.1-2.5)	2.7 (0.8-7.5)	$<10^{-3}$*
NK cells	71 (37-122)	106 (62-195)	0.008*

Abbreviations: CVID, common variable immunodeficiency; IBD, inflammatory bowel disease; GI, gastrointestinal; Ig, immunoglobulin; SMB, switch memory B cells

* Significant P value (<0.016), after correction for multiple comparisons

[a] Disease-Related Complication: lymphoid proliferation including granuloma, autoimmune cytopenia or enteropathy with villous atrophy (3)

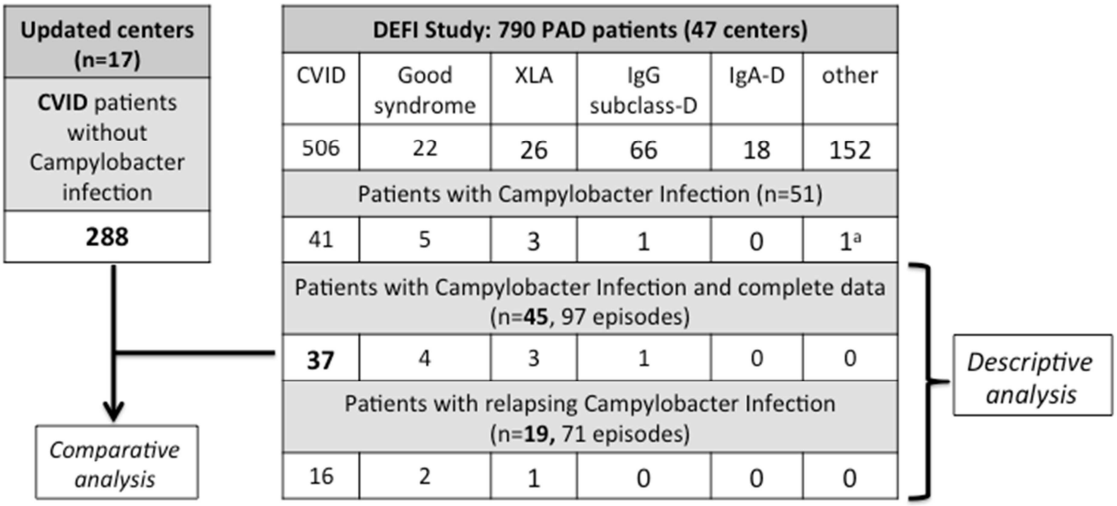
[b] Chronic liver disease in patients with CVID and Campylobacter infections was portal hypertension (n=4), nodular regenerative hyperplasia (n=3), granulomatosis (n=6), lymphoid hyperplasia (n=5), cholangitis (n=1) and other (n=8)

[c] Excluding Campylobacter

[d] Naive CD4+ T cells CD4+CD45RA+CCR7+

[e] Switch memory B cells CD19+IgD-CD27+

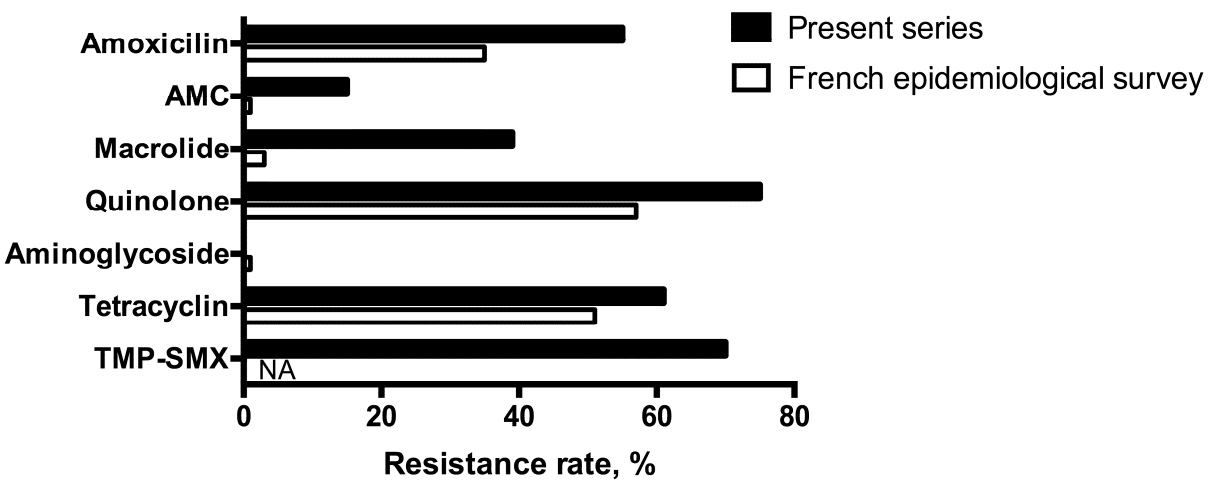
Figure E1.



Abbreviations: PAD, primary antibody deficiency; CVID, common variable immunodeficiency; XLA, X-linked agammablobulinemia, D, deficiency.

[a] Patient with CD40 ligand deficiency

Figure E2.



Abbreviation: AMC : Amoxicillin-Clavulanate; TMP-SMX, trimetoprim-sulfametoxazol; NA, not available.