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1           **Campylobacter infection in adult patients with primary antibody deficiency**

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35

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50

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52

53 **Clinical implication Box**

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

57

58 **To the editor:**

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

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

78 Since 2004, 790 patients with PAD were included in the DEFI study, and 51 presented with  
79 Campylobacter infection (6.5%). Medical chart was available for review in 45 patients.

80 Characteristics of these patients at the time of enrollment in DEFI are detailed in Table E2 in  
81 the Online Repository. A total of 97 episodes were recorded (Table 1). The overall

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

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

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

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

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

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

138



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164 Exclusion of Patients with a Severe T-Cell Defect Improves the Definition of Common  
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166

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

<b>Characteristics</b>	<b>No. or median</b>	<b>% or IQR</b>
<b>Clinical features</b>		
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 <sup>a</sup>	17/84	20
Comorbidity <sup>b</sup>	53	55
<b>Complications</b>		
Hospitalisation	33/85	39
Duration, days	7	3-14
Late complications <sup>c</sup>	9/97	9
<b>Current therapy at <i>Campylobacter</i> diagnosis</b>		
Immunosuppressive drugs <sup>d</sup>	35/88	40
Proton pump inhibitors	41/81	51
Ig replacement therapy	79/90	87
Antibiotic prophylaxis	30/84	35
<b>Serum Ig levels, g/L</b>		
	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
<b><i>Campylobacter</i> species</b>		
	n=97	
<i>Campylobacter jejuni</i>	55	56
<i>Campylobacter coli</i>	19	20
Other <i>Campylobacter</i> species	4	4
Unspecified	19	20

169 Abbreviations: Ig, immunoglobulin; IQR, interquartile range.

170 <sup>a</sup> Digestive infection in 10 cases: *Helicobacter pylori* gastritis (n=4), lambliaiasis (n=2),

171 *Clostridium difficile* colitis (n=3), cytomegalovirus colitis (n=2); urinary infection in 4 cases;

172 respiratory infection in 3 cases.

173 <sup>b</sup> Diabetes (n=2 patients), chronic liver disease (n=13 patients), blood neoplasia (n=3  
174 patients), or transplantation (n=1 patient).

175 <sup>c</sup> Reactive arthritis (n=8), relapsing erythema nodosum (n=1).

176 <sup>d</sup> Prednisone(n=9), budesonide (n=18), TNF $\alpha$  (tumor necrosis factor alpha)-blocker (n=2),  
177 methotrexate (n=7), mycophenolate (n=2).

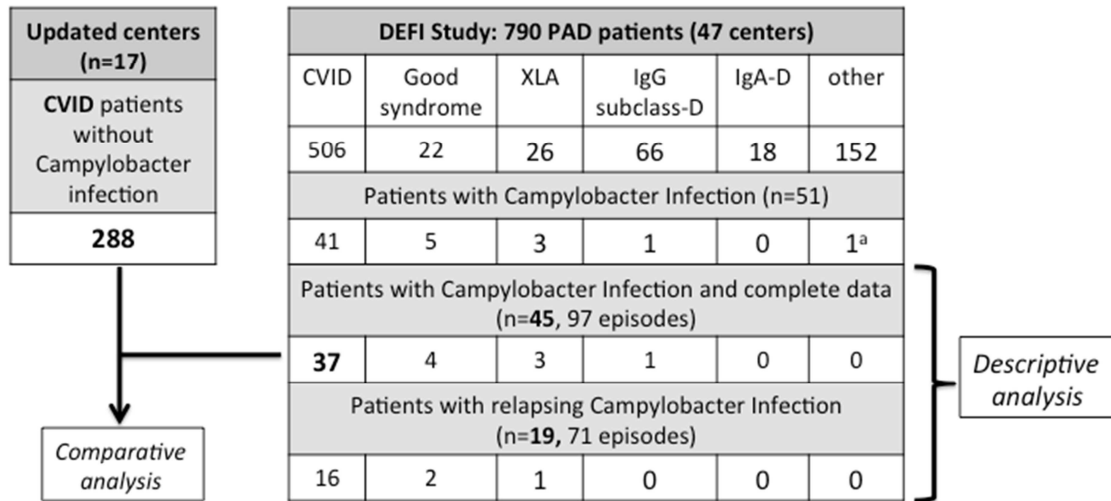
178

179 **Table 2.** Comparison between common variable immunodeficiency (CVID) patients with  
 180 Campylobacter infection (Campylo pos) and without Campylobacter infection (Campylo neg)  
 181 at enrollment in the DEFI study. Results are expressed as median (IQR) or number (%).  
 182

<b>Characteristics</b>	<b>Campylo pos</b> (n=37)	<b>Campylo neg</b> (n=288)	<b>P</b>
<b>Population</b>			
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
<b>Clinical complications</b>			
Infection only	10 (27)	167 (58)	<10 <sup>-3</sup> *
Disease-Related Complication <sup>a</sup>	27 (73)	104 (36)	<10 <sup>-3</sup> *
Lymphoid proliferation	20 (54)	75 (26)	<10 <sup>-3</sup> *
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 <sup>b</sup>	15 (40)	42 (15)	<10 <sup>-3</sup> *
<b>Gastrointestinal complication</b>	31 (84)	117 (41)	<10 <sup>-3</sup> *
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 <sup>c</sup>	16 (43)	43 (15)	<10 <sup>-3</sup> *
Acute recurrent diarrhea	12 (32)	27 (9)	0.01*
Chronic diarrhea	23 (62)	56 (19)	<10 <sup>-3</sup> *
<b>Biology at CVID diagnosis</b>			
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 <sup>9</sup> /L	202 (109-274)	209 (167-260)	0.16
Neutrophil count, x10 <sup>6</sup> /L	4000 (2850-5760)	3700 (2850-5470)	0.60
Lymphocyte count, x10 <sup>6</sup> /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+ <sup>d</sup>	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 <sup>e</sup>	0.3 (0.1-2.5)	2.7 (0.8-7.5)	<10 <sup>-3</sup> *
NK cells	71 (37-122)	106 (62-195)	0.008*

184 Abbreviations: CVID, common variable immunodeficiency; IBD, inflammatory bowel  
185 disease; GI, gastrointestinal; Ig, immunoglobulin; SMB, switch memory B cells  
186 \* Significant P value (<0.016), after correction for multiple comparisons  
187 <sup>a</sup> Disease-Related Complication: lymphoid proliferation including granuloma, autoimmune  
188 cytopenia or enteropathy with villous atrophy (3)  
189 <sup>b</sup> Chronic liver disease in patients with CVID and Campylobacter infections was portal  
190 hypertension (n=4), nodular regenerative hyperplasia (n=3), granulomatosis (n=6), lymphoid  
191 hyperplasia (n=5), cholangitis (n=1) and other (n=8)  
192 <sup>c</sup> Excluding Campylobacter  
193 <sup>d</sup> Naive CD4<sup>+</sup> T cells CD4<sup>+</sup>CD45RA<sup>+</sup>CCR7<sup>+</sup>  
194 <sup>e</sup> Switch memory B cells CD19<sup>+</sup>IgD<sup>-</sup>CD27<sup>+</sup>

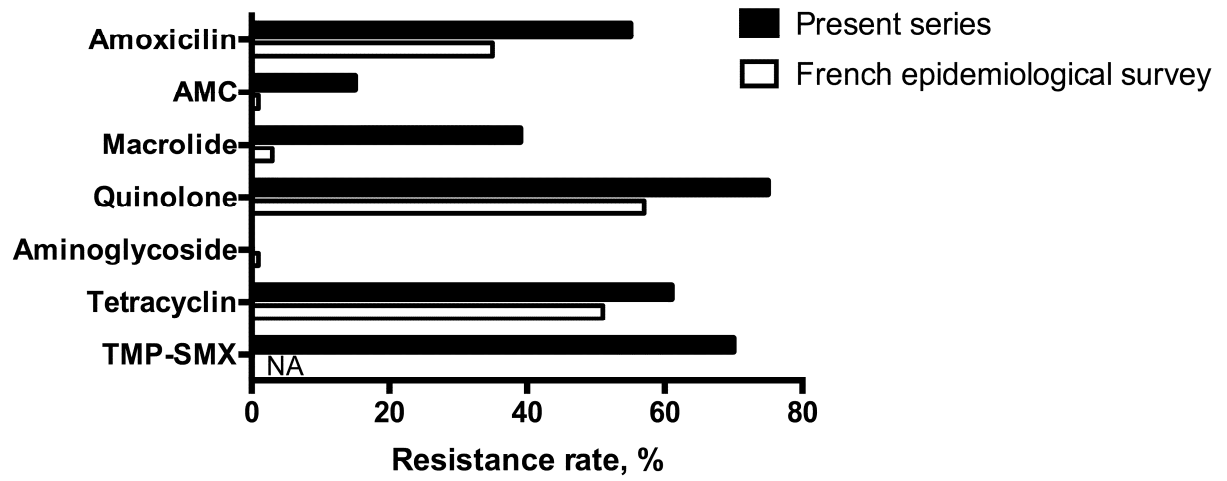
**Figure E1.**



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

<sup>a</sup> Patient with CD40 ligand deficiency

**Figure E2.**



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