A severe case of persistent diarrhoea associated with *Arcobacter cryaerophilus* but attributed to *Campylobacter* sp. and a review of the clinical incidence of *Arcobacter* spp.

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Abstract

Although rarely, *Arcobacter* spp. have been associated with diarrhoea and bacteraemia. We report a persistent case in a healthy 26-year-old Spanish male of bloody diarrhoea, which was attributed to *Campylobacter* but in fact was caused by *Arcobacter cryaerophilus*, as determined by sequencing of the *rpoB* gene. The isolate was re-identified by matrix-assisted laser desorption ionization time of flight (MALDI-TOF) and genotyped for five putative virulence genes and for seven genes included in the *Arcobacter* multilocus sequence typing database. The low score obtained by MALDI-TOF indicates the need to complement the database with more isolates. Only the *ciaB* gene, which encodes for an invasin, was detected. Despite the isolate belonging to a new sequence type, three of the alleles (*glnA*, *pgm* and *tkt*) had been found previously in isolates from faeces of patients with diarrhoea. This study, together with the reviewed literature, indicates that *Arcobacter* can produce bacteraemia and that the isolation from patients with diarrhoea range from 0.11% to 1.25%. This study also demonstrates that *Arcobacter* species are confused with *Campylobacter* spp., as previously suggested. This is one of the factors that leads to underestimation of their incidence together with the use of inappropriate detection and identification methods.

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Introduction

Bacteria of the genus *Arcobacter*, which was created with aerotolerant species previously included in the genus *Campylobacter*, are considered emergent enteropathogens and potential zoonotic agents [1]. The genus currently includes 17 species and some of these species produce abortions, mastitis and gastrointestinal disorders in animals [2–5] and bacteraemia, endocarditis, peritonitis and diarrhoea in humans [6–12].

So far there have been very few human diarrhoea cases reported despite it having been found that *Arcobacter butzleri* was the fourth most common *Campylobacter*-like organism isolated from human stools [1,13,14]. Persistent watery diarrhoea was the main symptom associated with *Arcobacter* species, in contrast to the bloody diarrhoea produced by *Campylobacter jejuni* [1,13]. It has been suggested that *Campylobacter* isolates cover *Arcobacter* spp. [13], which are not routinely studied with the *ad hoc* methods in clinical laboratories. However, the true impact of this confusion is unknown [1].

This study describes in detail the clinical characteristics of an acute case of diarrhoea produced by *A. cryaerophilus*, which was recognized after sequencing of the *rpoB* gene from an isolate biochemically identified as *Campylobacter* sp. The isolate was re-identified with matrix-assisted laser desorption ionization time of flight (MALDI-TOF) and genotyped by multilocus

sequence typing; its putative virulence genotype was screened by PCR. The study intends to alert clinicians to the possible role that this poorly known bacteria genus plays in the development of human disease by showing all known clinical cases.

Case Report

A 26-year-old male with no previous history of disease visited the doctor complaining of bloody watery diarrhoea of 3 weeks duration (with about three liquid depositions a day), with abdominal pain but without fever, nausea or vomiting. The patient had been seen with similar symptoms 4 months before and was diagnosed with acute gastroenteritis. A stringent diet was the recommended treatment but no laboratory testing was made at that time. Considering this previous history, a blood and stool analysis was carried out. The stool sample was examined for parasites and cultured for *Escherichia coli*, *Salmonella* spp., *Shigella* spp., *Yersinia enterocolitica*, *Aeromonas* spp., *Plesiomonas* spp., *Vibrio* spp. and *Campylobacter* spp. Complete blood count was performed and searches were made for hepatitis B antigen, anti-hepatitis C virus antibody and other antibodies against human immunodeficiency virus, cytomegalovirus, adenoviruses and parvovirus B19. The patient was diagnosed with acute gastroenteritis and an empirical antibiotic treatment was initiated with amoxicillin/clavulanic acid.

The laboratory evaluation showed an almost normal complete blood count, except for a slight relative reduction in neutrophils (37%) and an increase in lymphocytes (51.2%). The blood culture was negative but the stool sample showed a positive culture in Campylosel medium (BioMérieux, Marcy l'Etoile, France) after 3 days of incubation at 42°C, under microaerobic conditions. The colonies were identified as *Campylobacter* sp. based on phenotypic tests (Gram stain, hippurate hydrolysis and resistance to cephalothin). By disc diffusion, the isolate was susceptible to amoxicillin/clavulanic acid and to gentamicin, but was resistant to ciprofloxacin and erythromycin. Considering these results and the good evolution of the patient, the empirical treatment was maintained for 8 days, after which time he had recovered completely with no more diarrhoea episodes. The isolate was sent to the Unit of Microbiology at the University Rovira i Virgili for re-identification using the sequences of the *rpoB*, as was done routinely for all isolates identified as *Campylobacter* at the hospital. The DNA extraction, amplification and sequencing were performed using primers and conditions previously described [15]. A BlastN analysis with the obtained *rpoB* sequence revealed a 99% similarity with the strain of *A. cryaerophilus*

(Strain of subgroup 1B, LMG 10229, accession number EU669900), followed by a 95% similarity with the sequence of the type strain of *A. cryaerophilus* (Strain of subgroup 1A, LMG 9904^T, accession number EU669899), and only 90% similarity with a strain of the next most similar species, *A. butzleri* (Strain ED-1, accession number AP012047). Therefore, the isolate was identified as being *A. cryaerophilus*.

Considering the rarity of the recovered bacterium, the patient was contacted again to obtain additional information. He indicated that he regularly eats raw meat and fish, and also had a dog at home and a group of laying hens fenced in the garden. Despite the patient indicating that he had not had any other episodes of diarrhoea, a new stool sample was taken to evaluate his possible carrier state. Rectal samples from the dog and cloacal swab samples from three of the six laying hens he had at that time, as well as two samples of their faeces collected from the ground, were taken for microbiological examination using molecular detection and culture, as described in a previous study [16]. However, all of these samples were negative for *Arcobacter*.

To our knowledge, only three cases of *A. cryaerophilus* infection have so far been reported [6,17,18]. Those cases, together with the few available for the other species of the genus, are summarized in Tables 1 and 2. The first and only case of diarrhoea due to *A. cryaerophilus* dates back to 1988 when it was still included in the genus *Campylobacter* with the name *Campylobacter cryaerophila*. The 35-year-old homosexual man with this infection showed intermittent diarrhoea of 4–6 months duration with abdominal pain [17]. The other two are cases of bacteraemia, one in Taiwan that involved an immunocompromised 72-year-old woman with uraemia who showed a haematogenous pneumonia [18], and the other in a 7-year-old boy from China who had fallen into a mud pool while driving a mini motorcycle and suffocated [6]. As seen in Tables 1 and 2, a few other cases of diarrhoea and bacteraemia have been linked to *A. butzleri* [4,7,19–23] and, more rarely, to *Arcobacter skirrowii* [24]. For instance, a case of acute diarrhoea caused by *A. butzleri* in a 30-year-old healthy man was reported from Turkey; it was cured with treatment with ciprofloxacin [23]. A recent case of peritonitis due to *Arcobacter* sp. has been reported in a peritoneal dialysis patient whose catheter was repositioned [25]. Despite intravenous cefazolin and oral levofloxacin being given as a prophylaxis, the patient only responded after intravenous ticarcillin–clavulanate treatment for 2 weeks, with no need for the catheter to be removed.

The majority of these case studies underline the difficulty in recognizing or identifying these bacteria because they grew slowly and their identification required sequencing of the 16S rRNA gene [6,7,21] or the use of specific multiplex PCR methods [22–24,26]. Considering that several hospitals

TABLE 1. Cases of intestinal infections associated with *Arcobacter* spp.

Patients' sex/age	Country	Presentation	Species	Outcome	Underlying conditions	Reference
M/35 years	Australia	Chronic diarrhoea (6 months)	*A. cryaerophilus*[1]	NS	Homosexual with history of anxiety and repeated sexual exposure	[17]
3–7 years[2]	Italy	No diarrhoea, abdominal pain, occasional vomiting or fever	*A. butzleri*	Recovered 7–10 days after no specific treatment	None	[4]
1. M/48 years 2. F/52 years	Germany	1. Acute watery diarrhoea (15 days) and abdominal cramps 2. Chronic diarrhoea (3 weeks) and abdominal cramps	*A. butzleri*	1. Recovered 3 days after treatment with ofloxacin 2. Recovered 2 days after treatment with doxycycline	1. Type 1 diabetes mellitus 2. Hyperuricaemia and alcohol abuse	[19]
1. M/2 years 2. F/1 years	Chile	1. Acute mucous diarrhoea and vomiting 2. Chronic diarrhoea (4 months) with abdominal cramps and pain	*A. butzleri*	1. Recovered in 2 days with parenteral fluid therapy, restricted diet but without antimicrobial treatment 2. Recovered 10 days after treatment with erythromycin	None	[22]
M/73 years	Belgium	Chronic diarrhoea (2 months)	*A. skirrowii*	Recovered 10 days after no specific treatment	Prosthetic aortic heart valve	[24]
M/30 years	Turkey	Acute watery diarrhoea, abdominal pain, nausea and sweating	*A. butzleri*	Recovered 2 days after treatment with ciprofloxacin	None	[23]
M/26 years	Spain	Persistent bloody and watery diarrhoea (3 weeks)	*A. cryaerophilus*	Recovered 8 days after treatment with amoxicillin/clavulanic acid	Acute gastroenteritis 4 months earlier	Current study

NS, not specified.
[1]Originally described as *Campylobacter cryaerophila.*
[2]Four males and six females between 3 and 7 years old.

TABLE 2. Extra-intestinal infections associated with *Arcobacter* spp.

Patients sex/age	Country	Presentation	Species	Outcome	Underlying disease	Reference
Neonate	UK	Bacteraemia with hypotension, hypothermia and hypoglycaemia	*A. butzleri*	Recovered 6 days after penicillin and cefotaxime treatment	Mother had prenatal bleeding due to placenta praevia. Delivery at 26 weeks of gestation	[20]
M/72 years	Taiwan	Bacteraemia and haematogenous pneumonia	*A. cryaerophilus*	Recovered 2 weeks after ceftizoxime and tobramycin treatment	Chronic renal failure, haemodialysis with arteriovenous fistula. Two months of fever and progressive cough with purulent sputum. She also had a 1-month history of anorexia and frequent loose stool 2 months before admission	[18]
M/60 years	Taiwan	Bacteraemia with fever and haematemesis	*A. butzleri*	Recovered 4 days after cefuroxime treatment	Chronic hepatitis B carrier, liver cirrhosis	[21]
F/69 years	Hong Kong	Bacteraemia with fever and lower quadrant pain	*A. butzleri*	Recovered 3 days after cefuroxime and metronidazole treatment	Gangrenous appendicitis	[7]
F/63 years	China	Peritonitis after repositioning of catheter with fever and abdominal pain	*Arcobacter* sp.	Recovered 2 weeks after treatment with ticarcillin-clavulanate	End-stage renal failure of unknown cause	[25]

NS, not specified.

now use the MALDI-TOF identification technique for such fastidious, slow-growing microbes, we have re-identified our *A. cryaerophilus* isolate using that method [27]. The isolate was studied with the Ultraflex TOF/TOF MALDI-TOF instrument, that uses the MALDI BIOTYPER 2.0 software (Bruker Daltonics, Bremen, Germany) after spotting a fresh colony directly on to the target plate and the addition of 1 μL of the matrix, cinaminic acid, as described by the manufacturer. The type strain of *A. cryaerophilus* (LMG 9904[T]) was used in parallel as a control. The MALDI BIOTYPER output for our clinical strain scored 1.493 with the strain *A. cryaerophilus* T277 CPB. A score of <1.7 normally indicates an unconfident identification, between 1.7 and 1.99 indicates a genus-level identification, and a score ≥2 indicates a species-level identification. The second higher score was only 1.42 with a strain of the species

Pseudomonas proteolytica. Despite the unconfident identification the first match was with an *A. cryaerophilus* and among the following bacteria listed there was no *Campylobacter* spp. The type strain of *A. cryaerophilus* (LMG 9904[T]) used as control was correctly identified despite it showing a low score (1.885). Clinicians should be aware that in the case of a strain showing this behaviour with MALDI-TOF it is worth confirming its identity by sequencing the *rpoB* gene, so that the true incidence of these bacteria can be established. The inconclusive results obtained with MALDI-TOF could be explained by the fact that a correct identification with this method depends on the number of bacteria strains included in the database [27]. The BIOTYPER database has only 13 *Arcobacter* strains and only four of them belong to the species *A. cryaerophilus*. However, the capacity of this method to separate strains belonging to all

Arcobacter spp. has been recently demonstrated [2,28], therefore, it is possible that the inclusion of more strains in the BIOTYPER database will allow their correct identification, and this will contribute to clarify the clinical importance of this genus.

The seven housekeeping genes (*aspA*, *atpA*, *glnA*, *gltA*, *glyA*, *pgm* and *tkt*) included in the *Arcobacter* multilocus sequence typing database created by Miller *et al.* [29] were sequenced from our isolate of *A. cryaerophilus* using the primers described by these authors. New alleles were obtained for four genes (i.e. *aspA-215*, *atpA-152*, *gltA-149* and *glyA-473*), while the sequences of the *glnA* (codifying for glutamine synthetase), *pgm* (phosphoglucomutase) and *tkt* (transketolase) genes corresponded to the already known alleles 59, 133 and 115, respectively. Therefore, this new clinical isolate

(strain 609) belonged to a new sequence type (ST) named ST-392. Interestingly, the allele glnA-59 and the pgm-133 had been obtained from strain 276, which was isolated from the faeces of a patient with gastroenteritis in France in 2004, while the allele tkt-115 had been obtained from strain 305, which was also obtained from faeces of a patient with gastroenteritis in the USA in 2009. Apart from strains 276 and 305, the database includes only two other isolates of *A. cryaerophilus* recovered from human samples, i.e. strains 281 (from gastroenteritis) and 285 (from human blood), and both isolates share the ST-201. The few available human pathogenic strains in the database do not allow a relationship to be established between the presence of certain alleles, or STs, and virulence. Therefore, it is important that more strains isolated from human infections are included in the
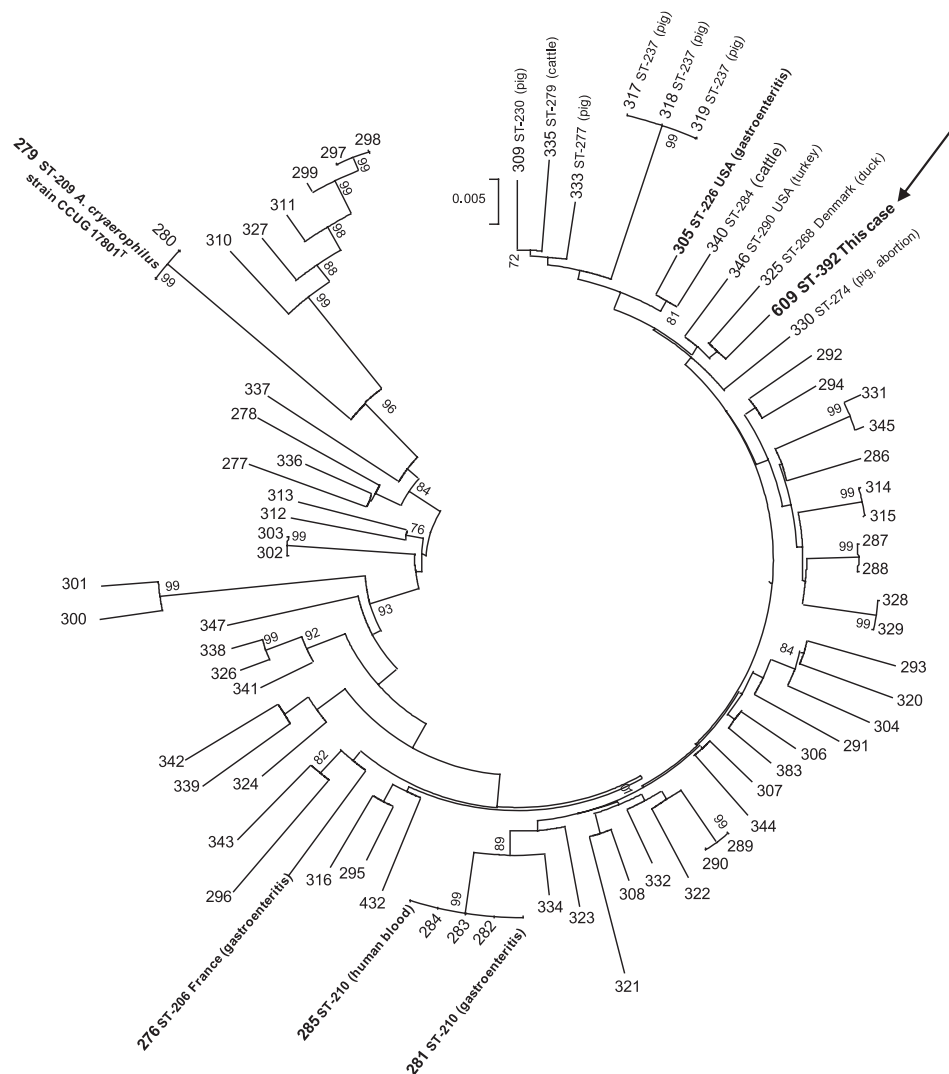

FIG. 1. Neighbour joining tree based on the concatenated sequences of *aspA*, *atpA*, *glnA*, *gltA*, *glyA*, *pgm* and *tkt* (3339 bp) showing the position of strain 609 (ST-392) among the 75 strains of *Arcobacter cryaerophilus* included in the *Arcobacter* multilocus sequence typing database. Bootstrap values (≥70%) based on 1000 replications are shown at the nodes.

database as we did. In the tree constructed with the concatenated sequences of the seven genes from each of the 75 *A. cryaerophilus* strains that are currently included in the database (Fig. 1), our strain grouped with two others obtained in Europe from poultry (strain 346, ST-290 and strain 325, ST-268), being therefore the most related strains. However, whether the *A. cryaerophilus* strain was acquired in our patient through consumption of poultry meat could not be demonstrated.

Five putative *Arcobacter* virulence genes (*ciaB*, *cadF*, *cj1349*, *hecA* and *irgA*) were also searched for in our strain using the primers designed by Douidah *et al.* [30]. However, only the presence of the *ciaB* gene was detected, which encodes for an invasion protein in *C. jejuni*. The same result was obtained for five strains of *A. cryaerophilus* recovered from shellfish and from animal faeces in our laboratory [31]. In the study of Douidah *et al.* [30], which included 99 *A. cryaerophilus* strains isolated from human, chicken, pig, cattle, sheep, horse and dog, the *ciaB* gene was present in the majority (92.9%) of the strains, followed by *cj1349* (51.5%), *cadF* (34.3%), *hecA* (4%) and *irgA* (3%).

Among the faecal samples at the *Hospital Universitari Sant Joan de Reus,* where the isolate of *A. cryaerophilus* was obtained, *Campylobacter* was the most commonly isolated enteropathogen, representing 41.4% (65/157) of the positive stools in the last year, followed by *Salmonella* spp. (36.3%), *Aeromonas* spp. (14.6%), *Shigella* spp. (4.4%), *Hafnia alvei* (3.2%) and *Yersinia enterocolitica* (1.3%). Among the *Campylobacter* and *Campylobacter*-like organisms, *C. jejuni* was the most prevalent species (82.7%), followed by *Campylobacter coli* (16.4%), while *A. cryaerophilus* was in third place (0.9%), which agrees with previous studies [13,14].

A summarized revision of studies on *Arcobacter*, including those comparing patients with and without diarrhoea, is provided in Table 3. The prevalence of *Arcobacter* species in human stools ranged from 0.1% to 1.25% in studies that derived the information from culturing, whereas the detection from faeces by PCR ranged from 0.4% to 13% [9,10,12–14,32–37]. In one study, performed in Belgium and France where the prevalence was determined by culture [13], *A. butzleri* occupied the fourth place (3.5%) among *Campylobacter*-like organisms, while *A. cryaerophilus* occupied the seventh place (0.5%). In another study performed in South Africa using multiplex PCR detection, *A. butzleri* showed a higher prevalence (6.2%) after *C. jejuni* (10.2%) [10]. In the same study, *A. cryaerophilus* and *A. skirrowii* showed lower incidences (2.8% and 1.9%, respectively). In two other studies that detected *Arcobacter* using the same multiplex PCR method a higher incidence was also observed [12,38]. One was a case–control study of faeces from diabetic patients in Italy [38]. In that study there was 78.9%

TABLE 3. Characteristics of the patients from different diarrhoea surveys in which *Arcobacter* spp. were detected by culture or PCR-based methods

Number of patients	Country	Age (range or mean)	M/F ratio	Prevalence of *Arcobacter* spp. (%) among diarrhoeic patients		Type of diarrhoea and symptoms (%)														Reference
				Culture	PCR	Acute	Chronic	Watery	Blood	Nausea/ Vomiting	Abdominal pain	Fever >38°C	Monomicrobial infection (%)	Underlying disease (%)	Antimicrobial treatment (%)	Relapse (%)	Asymptomatic (%)		
19 535	South Africa	Paediatric (NS)	NS	0.4	ND	100	0	NS	NS	NS	NS	NS	NS	NS	NS	NS	49.7		[34]
67 599	Belgium and France	30 days to 90 years	NS	0.11	ND	50.8	16.4	50.8	6.0	27.9	29.5	32.8	82.0	16.4	26.2	6.6	19.7		[13]
2855[1] 322	France South Africa	54 years 1 month to 88 years	1.44 0.77	1.0 ND	ND 13.0	59.0 47.8	3.4 NS	NS NS	21.1 3.1	10.5 NS	57.9 NS	26.3 NS	93.3 83.1	15.8 13.7	26.3 NS	5.3 NS	NS 20.8		[14] [10]
400[2]	India	≥18 years (NS)	1.4	1.25	ND	100	0	NS	NS	NS	NS	NS	50.0	50.0	NS	NS	0		[9]
345 201[3]	France USA/ Europe	41.4 years NS	0.56 NS	0 ND	1.2 8.0	100 100	NS NS	NS NS	NS NS	NS NS	NS NS	NS NS	NS 78.6	NS NS	NS NS	NS NS	0 0		[35] [12]
1380	New Zealand	49 y	1.0	0.9	ND	100	0	NS	NS	8.3	100	NS	75.0	NS	NS	NS	0		[32]
3287 140	Turkey Chile	26.6 years <5 years to >50 years	1.25 0.96	0.3 0.7	ND 1.4	100 100	0 0	33.3 NS	0 NS	22.2 NS	100 NS	11.1 NS	NS 50.0	NS NS	NS NS	NS NS	0 45.3		[33] [36]
493	The Netherlands	35 years	0.88	0	0.4	100	NS	NS	NS	NS	NS	NS	0.4	NS	NS	NS	NS		[37]

NS, not specified; ND, not done.
[1]Surveillance study including only patients with diarrhoea due to *Campylobacter*-like microorganisms.
[2]Case–control study that included 200 infected patients and 200 non-infected controls.
[3]US or European travellers that suffered acute diarrhoea after returning from Mexico, Guatemala or India.
Reference 6 is not included, because despite *A. cryaerophilus* was isolated from the blood, the infection was not proven. The patient had a motorcycle accident and died 24 hours after hospitalization.

on-diarrhoeic faeces of patients with type 2 diabetes, versus the 26.2% found for the controls (non-diabetic non-diarrhoea subjects). In the second study, an 8.0% incidence was reported among US/European travellers who suffered acute diarrhoea while visiting Mexico, Guatemala and India [12]. Other recent studies compared the ability to detect *Arcobacter* using in parallel molecular and culture methods [36,37]. Collado *et al.* [36] detected the species *A. butzleri* in 1.4% of stool samples of patients with diarrhoea, using a genus-specific PCR and a species-specific multiplex PCR method, whereas it was isolated from only 0.7% of samples by culture. In the other study, de Boer *et al.* [37] developed a multiplex real-time PCR able to detect *A. butzleri* and campylobacters from the faeces of patients with diarrhoea; testing this method in parallel with culture. Using this method, *A. butzleri* was detected in 0.4% of samples but was not recovered by culture. The higher prevalence obtained using molecular methods supports the statement that *Arcobacter* spp. could be underestimated as enteropathogens because of limitations in the current culturing methods, and demonstrates the importance of routinely screening stool samples for the species of this genus using molecular methods in parallel.

The isolation in our patient of *A. cryaerophilus* in the absence of other enteropathogens and the remission of the diarrhoea symptoms after treatment with amoxicillin/clavulanic acid, to which the bacteria was sensitive, seems to indicate that this bacterium could be considered the aetiological agent of the diarrhoea process. Despite not being able to find the contagious source of *Arcobacter* in the environment of our patient, we were able to speculate that, in this case, it could have been acquired through the consumption of poorly cooked poultry meat or fish. Interestingly, the patient showed recurrent episodes with abdominal pain, which seems to be a typical clinical presentation for this genus.

Acknowledgements

Conflict of Interest

None declared.

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