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Original Article

Cystic fibrosis, gastroduodenal inflammation, duodenal ulcer, and *H. pylori* infection: The "cystic fibrosis paradox" revisited

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Abstract

Background: In cystic fibrosis (CF) patients a duodenal impaired bicarbonate secretion and unbuffered gastric acid are always described and the development of duodenal ulceration is uncommon (CF paradox). *Helicobacter pylori* (HP) infection is the main cause for duodenal ulceration and its prevalence in CF patients is controversial.
Aim: The objective of this study is to evaluate HP prevalence, gastric histology, and duodenal ulceration in adult FC patients.
Methods: 32 adult CF patients were submitted to ^{13}C-urea breath test and serum immunoblotting test for HP diagnosis. Among them, 20 patients were submitted to endoscopy.
Results: 19/32 (68%) patients showed positive serology. Endoscopy showed erosive duodenitis (15%), and duodenal ulcer scar in 10%. On duodenal histology, 94.5%, showed active inflammation and 66.7% gastric metaplasia.
Conclusion: HP infection prevalence in adult CF patients was similar to that of general Brazilian population. CF patients have all the duodenal spectrum of alterations, including duodenal ulcer. CF paradox may not exist.

Keywords: Cystic fibrosis and duodenal ulcer; Cystic fibrosis and *Helicobacter pylori* infection; Cystic fibrosis and gastritis

1. Background

Cystic fibrosis (CF) is the most common recessive genetic disorder in the white population, with an incidence estimated at 1 in 2500–3000 live births [1].

All CF patients present with reduced pancreatic HCO_3^- secretion in response to secretin stimulation and pancreatic insufficiency is present in 85% of the patients [2]. The CFTR is also expressed in the duodenal mucosa. The basal and stimulated duodenum secretion of HCO_3^- is largely dependent on CFTR [3,4]. The CF patients, compared with normal subjects, present with lower postprandial duodenal pH by 1–2 pH units [3].

In CF patients both duodenal and pancreatic secretion of HCO_3^- are diminished and the duodenal pH is inferior than in healthy subjects [3]. Although HCO_3^- secretion, by neutralizing acid in the mucus layer in the duodenum, has been considered one of the most important defense mechanism for the development of duodenal ulcer [5], the studies on the prevalence of peptic ulcer in this population show normal or even reduced prevalence [6,7], giving rise to the 'CF paradox' [8]. Gastroduodenal physiological studies in anesthetized rats, have suggested that once HCO_3^- cannot be secreted to duodenal lumen, due to the defective CFTR, a trapped intracellular HCO_3^- would occur and protect the

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cytoplasm from irreversible acidification, preventing duodenal mucosal cells from injury and ulcer formation [8,9].

Helicobacter pylori infection is the major global etiologic factor for duodenal ulcer disease [10]. There are few studies in the literature about the prevalence of *H. pylori* infection in patients with CF and the results are controversial [11–14].

The aim of this study is to evaluate the prevalence of *H. pylori* infection in CF patients and to evaluate the endoscopic and histological findings in gastroduodenal mucosa of these patients.

2. Methods

2.1. Patient selection

The patients were recruited from the Adult Cystic Fibrosis Unit at Hospital das Clinicas, Federal University of Minas Gerais, Belo Horizonte, Brazil. All patients were adults (≥ 18 years old) and had the diagnostic of CF based on the presence of one or more characteristic clinical features and confirmed by an elevated sweat chloride concentration (> 60 mmol/L), according to the consensus of the Cystic Fibrosis Foundation [1]. All patients were submitted to the ^{13}C-urea breath test (UBT) and serologic test for detection of *H. pylori* infection. All the patients were also invited to perform an upper endoscopy. Exclusion criterion was the impossibility of suspending the use of oral antibiotics and proton pump inhibitor (PPI), for 30 days and 10 days respectively, before performing the UBT and upper endoscopy. The exclusion criterion for performing the upper endoscopy was severe pulmonary insufficiency defined by the use of supplemental oxygen, hypercarbia (pCO_2 > 45 mm Hg) and/or a force expiratory volume in 1 s (FEV1) below 30% of the predicted value.

The study was approved by the Ethical Committee of the Hospital das Clinicas, Federal University of Minas Gerais and all participants gave their written informed consent.

2.2. Study design

A transversal, descriptive study of the prevalence of *H. pylori* infection and gastroduodenal abnormalities in a group of adult CF patients was performed.

2.3. Clinical assessment of CF patients

A clinical record was fulfilled for each patient with demographic and clinical information that were extracted by interviewing the patients and from data on medical records. The following data were recorded for the patients: age; age at diagnostic; pulmonary, pancreatic and hepatic status; chronic use of inhaled antibiotics; chronic use of azithromycin; number of times of oral or venous antibiotic use in the last 12 months; gastrointestinal (GI) symptoms; chronic use of PPI; history of being already submitted to an upper endoscopy; and previous treatment for *H. pylori* infection.

2.4. Detection of H. pylori infection

2.4.1. UBT

The UBT is a non invasive indirect test to determine the presence of *H. pylori*. It has the best sensitivity among the non invasive tests (95%, in the range of the invasive tests) and also an excellent specificity [15]. The UBT has been previously validated in the Brazilian population [16]. The UBT is performed using a citric meal, composed of 75 mg of ^{13}C-labeled urea. If the patient is infected with *H. pylori*, the urease produced by the bacteria breaks down the labeled urea and it can be detected in the air expired. After 8 h of fasting, UBT was performed using 75 mg of ^{13}C-labeled urea dissolved in 200 mL of orange juice. Breath samples were collected in aluminized plastic bag to determine the baseline value before ingestion and at 30 min after ingestion of the substrate. Breath samples were analyzed by infrared spectroscopy (IRIS DOC, Wagner Analysen — Technik, Bremen, Germany). The results were expressed in delta over baseline-value (DOB) by one thousand (‰). A DOB above 4.0‰ was considered positive for *H. pylori* infection.

2.4.2. Serology — immunoblot

For the serologic test we used an immunoblot kit, the Helicoblot 2.1 (Genelabs Diagnostics, Singapore). It is a qualitative assay used for the detection of IgG antibodies specific for different antigens of *H. pylori* in the human serum. The immunoblotting technique is considered the gold standard of serologic tests [17].

The Helicoblot 2.1 immunoblot kit (Genelabs Diagnostics, Singapore) was performed according to the manufacturer's recommendations. Venous blood sample (15 mL) was drawn from the patients just before performing UBT. The results were assessed by a laboratory assistant unaware of the identity of the samples.

To determine the prevalence of *H. pylori* infection and evidence of past infection we considered the positivity of the serologic test. Active *H. pylori* infection was determined by the positivity of the UBT or if the bacteria were detected in the histological examination, as described below.

2.5. Upper endoscopy and gastric pH measurement

The exam was performed using the videoendoscope Fujinon 530 (Fujinon, Japan). The endoscopic findings were expressed according to the Sydney System classification [18].

Biopsies were taken from the corpus and antrum (one of the lesser and one of the greater curvature of each site), from the bulb and second portion of the duodenum (2 biopsies of each site).

In all patients a measurement of the gastric pH was performed. A conventional pHmetry equipment was used (Sigma Instrumentos LTDA — Belo Horizonte, Brazil). After calibration in a buffer solution of pH 7.01 and 1.01, the catheter was introduced through the working channel of the endoscope and placed in contact with the layer of gastric secretion in the greater curvature of the corpus. Three measures, in a 30 second

interval, were recorded and the final value was obtained by the mean value of the three measures.

2.6. Histological assessment

Biopsies of the corpus and antrum were stained with H&E for histological examination and with Giemsa for *H. pylori* identification. The histological findings were expressed according to the updated Sydney System classification [19].

Biopsies of the bulb and the second part of the duodenum were stained with H&E for histological examination. Biopsies of the bulb were also stained with Alcian Blue associated to periodic acid Schiff (PAS) to better identify gastric metaplasia. The histological findings were expressed according to the criteria proposed by Genta [20], as it follows in Table 1.

Gastric foveolar metaplasia was graded as mild, moderate or marked. Mild gastric metaplasia was diagnosed by the presence of a minimum of three cilindric cells PAS positive juxtaposed. Moderate gastric metaplasia implied frequent focal areas and marked implied extensive areas of gastric metaplasia.

When activity of inflammation differed between antrum and corpus, and bulb and second part of duodenum the activity grade in the most severely affected part was considered. When activity changed among different biopsies of the same part, the predominant grade was considered.

All the stains were performed following classic, standardized techniques and the biopsies were analyzed by a gastroduodenal pathologist unaware of the identity, clinical and endoscopic information of the samples.

2.7. Statistical analysis

Statistical analysis was performed using techniques of descriptive statistic (tables and percentages), Fisher's exact test and Student's *t*-test. Fisher's exact test was performed to verify an association between qualitative variables and Student's *t*-test was performed to compare the gastric pH in relation to the presence or absence of peptic duodenitis. The analyses were conducted by means of Minitab 16. The level of significance was set at $p < 0.05$.

Table 1
Classification proposed by Genta for histological duodenal findings [18].

Term	Definition
"Duodenitis"	Detection of polymorphonuclear neutrophils in the native duodenal epithelium (active inflammation)
"Peptic duodenopathy"	Presence of gastric foveolar metaplasia, easily confirmed by PAS/Alcian Blue stain, with no active inflammation
"Peptic duodenitis"	Presence of gastric foveolar metaplasia and active inflammation

3. Results

3.1. Baseline characteristic of the patients

The patients were enrolled in the study from September 2009 to July 2010. Forty-eight patients were regularly followed in the Adult Cystic Fibrosis Unit at Hospital das Clínicas, UFMG, but seven patients didn't have the confirmed diagnosis of CF according to the consensus of the Cystic Fibrosis Foundation, six patients didn't give the consent to participate in the study, and one patient died before performing the exams. Two patients weren't able to stay 30 days without the use of oral or venous antibiotics to perform the exams. Thus, a total of thirty-two patients participated in the study. The baseline characteristics of the patients are summarized in Table 2.

Twenty three patients (71.9%) complained of gastrointestinal symptoms. Most of the patients (16/23, 69.6%) complained of more than one symptom and the predominant symptom was heartburn (15/23, 65.2%). The frequency of the symptoms is described in Table 3.

Table 2
Baseline demographic and clinical characteristics of the 32 cystic fibrosis patients included in the study.

Characteristics	n (%)
Male	15 (46.9)
Female	17 (53.1)
Mean age, years (range)	29.3 (18–77)
Age at diagnostic of CF	
<18 years	20 (62.5)
>18 years	12 (37.5)
Pulmonary involvement†	
Absent	4 (12.5)
Mild	13 (40.6)
Moderate	7 (21.9)
Marked	7 (21.9)
Pancreatic insufficiency	22 (68.7)
Hepatic involvement∞	6 (18.7)
Chronic use of inhaled antibiotics	16 (50.0)
Chronic use of azithromycin	16 (50.0)
Number of times of oral or venous antibiotic use in the last 12 months	
Mean	2.2
None	9 (28.3)
1–2 times	12 (37.5)
3–4 times	5 (15.6)
5 times or more	6 (18.8)
Chronic use of PPI[£]	6 (18.7)
Previous upper endoscopy	15 (46.7)
Previous *H. pylori* treatment	
Yes	3 (9.4)
No	22 (68.7)
Unknown	7 (21.9)
Complaint of any GI[€] symptoms	23 (71.9)

Note: †Pulmonary involvement mild: forced expiratory volume in 1 s (FEV 1) >60% of predicted value, moderate: FEV1 59–40% and marked: FEV1<39%. ∞Presence of cirrhosis or in use of oral bile acid therapy, [£]PPI: proton pump inhibitor, [€]GI: gastrointestinal.

Table 3
Predominant gastrointestinal symptoms and related frequencies in 23 symptomatic cystic fibrosis patients.

Symptom	n	(%)
Heartburn	15	65.2
Epigastric pain	9	39.1
Bloating	8	34.8
Flatulence	8	34.8
Abdominal distension	8	34.8
Nausea	5	21.7
Abdominal pain	3	13.0
Diarrhea	2	8.7
Constipation	1	4.3
Postprandial fullness	1	4.3

3.2. Detection of *H. pylori* infection

3.2.1. UBT

All the patients included in the study performed the UBT and it was positive in seven patients (21.9%).

Half of the patients (16/32) were in chronic use of inhaled antibiotics. Regarding *H. pylori* status, there was no statistically significant difference between the group of patients in use of inhaled antibiotics and the group without the use ($p=0.39$).

3.2.2. Serology — immunoblot

All the patients included in the study performed the serologic test, however the results were inconclusive in four samples due to the impossibility of reading the bands. In the 28 samples analyzed 19 (67.8%) were positive for the *H. pylori* infection.

Fig. 1 shows the positive results of the serologic test in 19 patients and Fig. 2 shows the negative results in 9 patients.

3.3. Upper endoscopy and gastric pH measurement

Upper endoscopy was performed in 20 patients. Nine patients refused to perform the exam and three patients were excluded due to severe pulmonary insufficiency. Biopsies were taken from 18 patients because two patients had coagulation disorder.

The endoscopic findings are summarized in Table 4.

The measurement of gastric pH was performed in 19 patients. In one patient it was not measured due to the equipment dysfunction at the time of the procedure. The mean gastric pH was 1.89 (SD: 0.51, min–max: 1.19–2.87).

3.4. Histological assessment

In the H&E histological gastric mucosa evaluation, 66.7% (12/18) were normal gastric mucosa, 11.1% (2/18) presented non active chronic gastritis and 22.2% (4/18) presented chronic active gastritis. No atrophic gastritis or intestinal metaplasia were observed. In the Giemsa histological evaluation 22.2% (4/18) presented *H. pylori* infection, all of them with a mild density of infection. The four patients with histological *H. pylori* infection presented UBT and serologic test also positives.

The histological assessment of the duodenal mucosa showed that 94.5% (17/18) had active inflammation. In 66.7% (12/18) peptic duodenitis was identified and in 27.8% (5/18) duodenitis. The evaluation of gastric metaplasia in peptic duodenitis showed

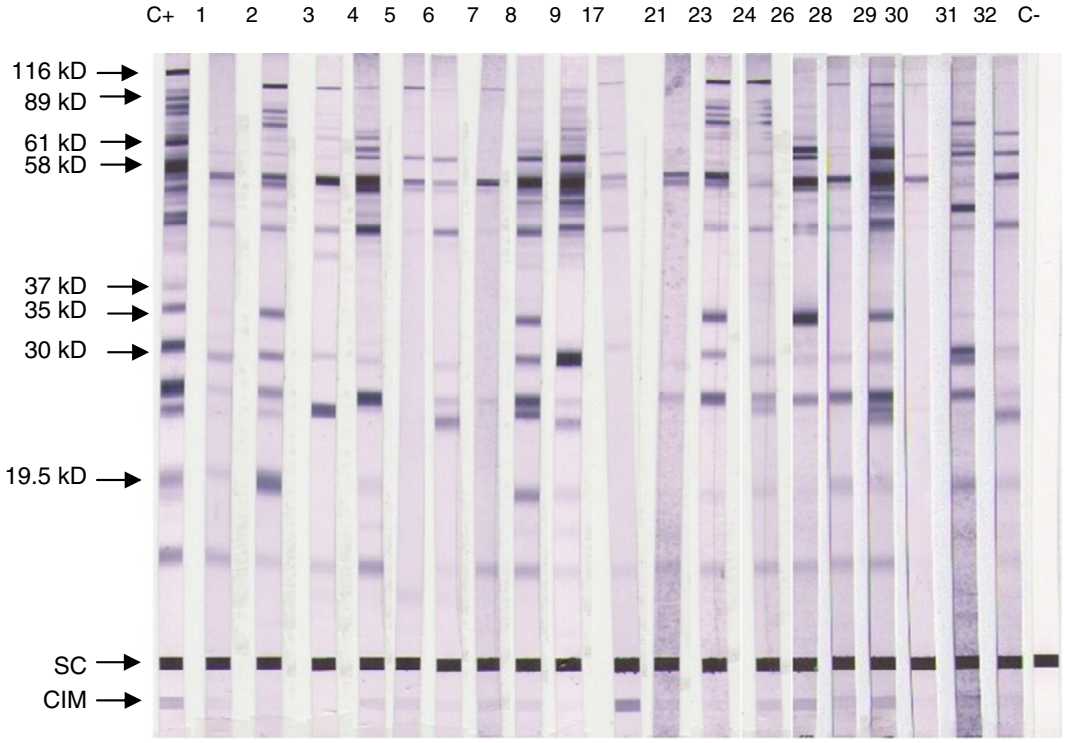

Fig. 1. Positive serologic test results in 19 cystic fibrosis patients.

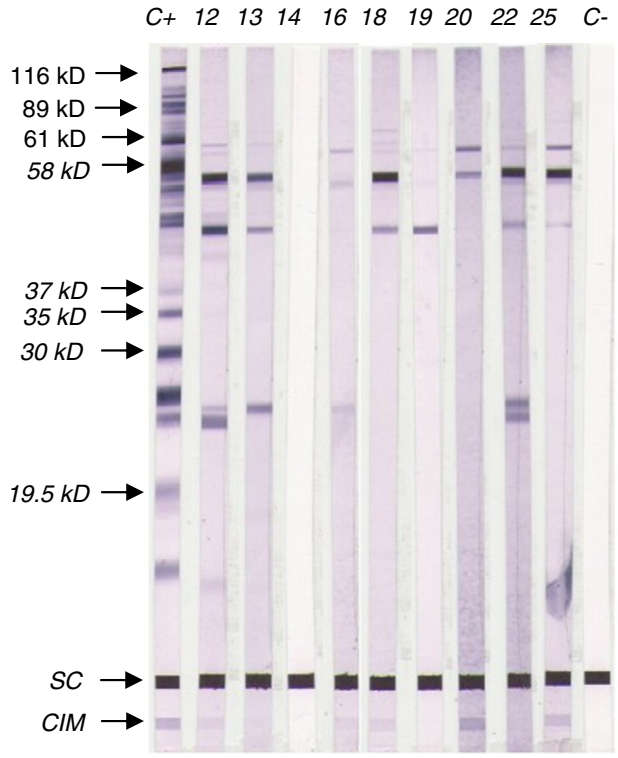

Fig. 2. Negative serologic test results in 9 cystic fibrosis patients.

that it was mild in eight out of 12 (66.7%), moderate in two out of 12 (16.7%) and marked in two out of 12 (16.7%) patients.

When comparing the gastric pH values of the patients with peptic duodenitis with the others there was a statistically significant difference between them, being the gastric pH lower in the patients with peptic duodenitis ($p = 0.028$).

4. Discussion

In our study the prevalence of *H. pylori* infection in CF patients was of 67.8%, similar to that (66.5%) recently observed in a serological survey in blood donors in Brazil [21]. There are few studies on the prevalence of *H. pylori* infection in CF patients and the results are controversial. Przyklenk et al. [11], in 1989, in Germany, using enzyme immunoassay, assessed the presence of serum anti-*H. pylori* antibodies in CF patients and controls and found that the prevalence of infection was low and similar in both groups (11% X 16%). Yahav et al. [14], in 2006, in Israel, analyzing the presence of *H. pylori* stool antigens in 30 CF patients, showed a lower prevalence of *H. pylori* infection (16.6%) compared to controls (30%). Studies by Johansen et al. [13] and Israel et al. [12] have questioned the value of enzyme immunoassay in the detection of *H. pylori* infection in CF patients, due to the cross-reactivity with anti-*Pseudomonas* antibodies. Our study is the first one using the immunoblotting technique for the detection of *H. pylori* infection in CF patients. Because *H. pylori* antibodies detected by immunoblotting, especially those anti-CagA, can remain in the plasma longer than the antibodies identified by enzyme immunoassays, and even for years after successful eradication therapy, immunoblotting seems to be the most sensitive method to detect a past *H. pylori* infection [22] and the immunoblotting technique is the gold standard of serologic tests [17].

Although in our population the serologic evidence of *H. pylori* infection was of 67.8%, the evidence of active infection was of 21.9%, and only three patients (9.4%) reported previous specific *H. pylori* treatment. Most of the patients (66.7%) had histological normal gastric mucosa and the infected patients showed on histology a mild density of infection. In adults *H. pylori* infection is chronic and the bacteria are rarely eliminated spontaneously or by the use of antibiotics for other purposes [10]. In the lack of nutrients or in adverse situations, such as the chronic use of antibiotics or proton pump inhibitors, *H. pylori* can evolute to a coccoidal form [15]. Recent studies have suggested that the coccoidal form, previously considered non viable form of the microorganism, is an adaptative survival form with a role in transmission, and is considered as partially responsible for the recrudescence of infection after antimicrobial treatments [15,23]. She et al. [23] showed that the *H. pylori* colonization and virulence factors, including urease, are reduced in coccoidal form, what could prevent the induction of inflammatory response in the host. Our findings of low prevalence of active infection, gastric mucosa histological exams without evidence of inflammation in most of the patients, and low density of infection in the infected patients allow us to speculate that, because of the frequent lifetime use of antibiotics, maybe a portion of the patients are still infected by *H. pylori* in its coccoidal form or it has been eliminated by the use of antibiotics for the treatment of pulmonary infections, frequently known in this group of patients. Since our study is a descriptive study of prevalence of *H. pylori* infection and gastroduodenal findings we can only speculate about the coccoidal forms. The identification and the precise value of the presence of *H. pylori* coccoidal forms are still restricted to experimental and investigative studies, which use methods not easily available for its identification. The identification of the coccoidal form is still not recognized as necessary in the determination of the prevalence of *H. pylori* infection and further studies would be imperative to do on this field in CF patients to confirm this hypothesis.

Table 4
Endoscopic findings in the esophagus, stomach and duodenum of twenty cystic fibrosis patients.

	n	(%)
Esophagus		
Normal	13	(65)
Esophagus varices	2	(10)
Hiatal hérnia	4	(20)
Erosive esophagitis	4	(20)
Barrett's esophagus	1	(5)
Stomach		
Normal	9	(45)
Antral gastritis	9	(45)
Portal hypertension gastropathy	2	(10)
Duodenum		
Normal	15	(75)
Erosive duodenitis	3	(15)
Ulcer scar	2	(10)

In contrast with the absence or low prevalence of gastric mucosa abnormalities, we observed more expressive duodenal alterations. Endoscopically, 25% of the patients showed duodenal alterations, being erosive duodenitis in 15% and duodenal ulcer scar in 10%. Regarding symptoms we were unable to make a correlation with duodenal findings due to the high prevalence of gastrointestinal symptoms in CF patients, directly or not related to the defective CFTR (Table 3).

Histologically, the vast majority of patients (94.5%) showed active duodenal inflammation, being peptic duodenitis observed in 66.7% of the patients. Among the patients with active inflammation 64.7% showed *H. pylori* positive serologic test. The mean value of gastric pH was 1.89 and the patients that presented peptic duodenitis showed statistically significant lower pH values ($p = 0.028$). Unquestioned correlation between gastric metaplasia and gastric hyperacidity has been demonstrated in experimental studies, with the evidence of its greater frequency and extension in Zollinger–Elisson patients and, lower frequency and extension in hypocloridric patients with gastric cancer [24,25]. Although small intestinal inflammation appears to be a common finding in CF patients and many factors could be implicated in its cause [26], we believe that, the duodenum of CF patients, more exposed and vulnerable to the physiologic gastric acidity, due to the reduction of duodenal and pancreatic HCO_3^- secretion, probably developed gastric metaplasia as a defense mechanism. The group of alterations observed in the duodenal mucosa, such as active inflammation, gastric metaplasia, erosive duodenitis and even ulceration scar also composes the classical spectrum of duodenal alterations observed and induced by *H. pylori* infection.

Therefore we question a clinical relevant role, if present, of the protective mechanisms involved in the 'CF paradox'. As proposed by Kaunitz et al. [8], in CF patients the prevalence of duodenal ulceration is not increased in relation to the overall population due to greater duodenal cellular protection, with maintenance of HCO_3^- intracellular, secondary to the CFTR deficiency. Our findings did not confirm that hypothesis. In our view, the frequent and prolonged lifetime use of different antibiotics in CF patients reduces the prevalence of active *H. pylori* infection by eliminating the microorganism or induces it to adopt the coccoidal form, with reduced potential of inflammatory response induction. Therewith, the gastric mucosa does not show relevant inflammatory activity on histology, and in the duodenum the expressive alterations already described, including duodenal ulceration scar, are a consequence of *H. pylori* infection aggravated by insufficient duodenal neutralization of gastric acid.

The small size of our population and the fact that we didn't perform microbiological studies regarding antimicrobial sensitivity didn't allow us to perform inter-group comparative studies on the use of antibiotics within our sample. However, to try to better elucidate the potential role of the prolonged and frequent use of antibiotics in the natural history of duodenal ulcer in CF patients we analyzed the studies on CF in the early days of the antibiotic era. Hellerstein [27], in 1946, first described CF in patients over 20 years of age. Andersen [28], in 1958, in autopsy study in CF children, reported peptic ulcer as being 'a fairly common finding' in children over 3 or 4 years of age, particularly in the posterior or left wall of the duodenum a short distance below the pylorus. Postulated, already at that time, that lack of pancreatic juice to neutralize the gastric juice was the presumed factor. Koch [29], in 1959, reported a high prevalence (41.5%) of peptic ulcer in a radiologic study in CF patients. Oppenheimer et al. [30], in 1975, in an autopsy series of 146 CF patients, reported a prevalence of 8% of peptic ulcer. Bernard et al. [31], in 1962, evaluated 115 patients with chronic obstructive pulmonary disease and observed that the patients who presented the sweat chloride test positive showed a much higher prevalence of peptic ulcer (22%), especially duodenal ulcer, when comparing with the patients with a negative test (1.3%). Boucher et al. [32], in 1961, studied the sweat chloride test in patients with bronchopulmonary pathologies and observed several cases of an association of emphysema, peptic ulcer and sweat abnormalities.

In conclusion, the prevalence of *H. pylori* infection in our CF adult patients was similar to that of the general Brazilian population. Infected patients showed low prevalence of active infection, low density of gastric infection, minimal inflammatory response in the gastric mucosa and frequent and active inflammation in the duodenal mucosa, including a 10% prevalence of duodenal ulceration. These findings may allow us to hypothesize that the *H. pylori* infection, prolonged use of antibiotics and insufficient duodenal neutralization of gastric acidity are the main responsible for the gastroduodenal findings in CF. The historical analysis seems to confirm that but more studies are awaited. The possible mechanisms of duodenal protection, due to the defective CFTR, do not seem to be sufficient to prevent the duodenal inflammation and the occurrence of duodenal ulcer in CF patients.

Conflict of interest statement

All authors that have participated in the study have no conflicts of interest.

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