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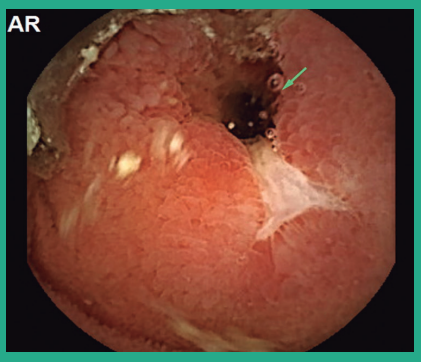


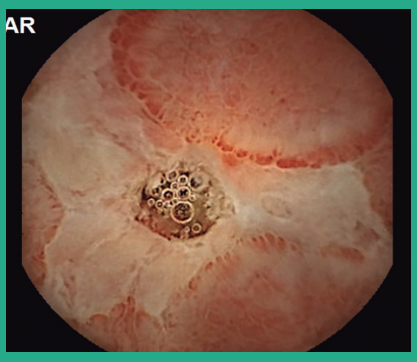


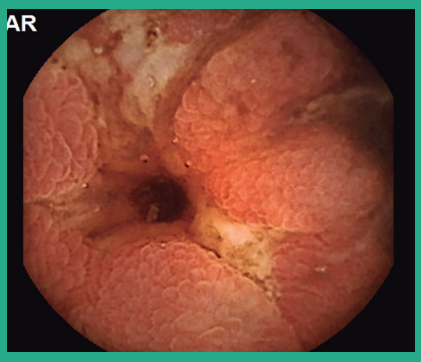




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# Revista Colombiana de Gastroenterología

## Original articles



## Review articles

## Case report



## Letter to the Editor



**Cover:** *Endoscopic videocapsule. Concentric ulcerated stenosis, surrounded by mucosal edema.*
*Courtesy by the authors: Santiago Castaño Quintero, Natalia Calvache, Mauricio Sepúlveda, Catalina Maldonado, Pedro Tomás Argüello, Juliana Escobar, Carlos Arturo Rojas.*
*Article: An endoscopic videocapsule finding of heterotopia of the gastric mucosa of the small intestine*

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# The role of endoscopic ultrasound in evaluating patients with dyspepsia in a Colombian population

Martín A. Gómez Zuleta,[1*] William Otero Regino,[2] Óscar Ruíz Morales.[3]

1 Specialist in gastroenterology and internal medicine at the National University Hospital of Colombia, Hospital Occidente de Kennedy and the Gastroenterology and Endoscopy Unit in Bogotá D.C., Colombia
2 Professor of medicine and coordinator of gastroenterology at the National University of Colombia, Gastroenterologist at the National University Hospital of Colombia and Clínica Fundadores in Bogotá, D.C., Colombia
3 Specialist in gastroenterology and internal medicine at Universidad San Martín, Kennedy West Hospital and the National University Hospital of Colombia in Bogotá D.C., Colombia

*Correspondence: martinalonsogomezz@gmail.com.

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## Abstract

Dyspepsia is defined as upper abdominal pain or discomfort that is considered to originate in the upper gastrointestinal tract. Many diseases and clinical conditions can cause dyspepsia. Among others, they include peptic ulcers, gastric and esophageal cancer, medications, biliary lithiasis, pancreatitis, and pancreatic cancer. Traditionally, dyspepsia is only evaluated with digestive endoscopy whose diagnostic yield is only 27%. On the other hand, endoscopic ultrasound combines an endoscopic image and an ultrasound image thereby potentially broadening diagnostic range to detect more of the causes of dyspepsia allowing treatment of patients in a timelier manner. **Objective**: To evaluate whether endoscopic ultrasound increases the diagnostic yield of endoscopy (27% in our environment) in the initial approach to previously unstudied dyspepsia. **Materials and methods:** This is a prospective study of analytical prevalence in adult patients with previously unstudied dyspepsia who were examined at a university institution in Colombia. The patients included were seen in the gastroenterology unit from January to October 2016 and underwent upper digestive endoscopy and endoscopic ultrasound. Under anesthesiologist-guided sedation, the stomach and duodenal esophagus were first evaluated endoscopically. Then retrograde endoscopic ultrasound was used to evaluate the pancreas in its entirety, the extra hepatic bile duct, the gallbladder, the celiac trunk, the left lobe of the liver and the mediastinal region. All abnormalities were noted on the patient's admission form. **Results:** In total we included 60 patients of whom 65% were female and whose average age of was 40.8 years (SD: 12.5). The findings in the endoscopic phase of the endoscopic ultrasound were mainly chronic Gastritis 43 patients (71.6%), the rest had a structural lesion (17 patients): esophagitis 5 (8.3%), gastric ulcer 2 (3.3%), duodenal ulcer 5 (8.3%), gastric cancer, 4 (6.6%), gastric subepithelial lesion (GIST) 1 (1.6%). In the endoscopy phase, we found 11 cases of cholelithiasis (18.3%), one case of choledocholithiasis (1.6%), and five cases of chronic pancreatitis (8.3%). Only 17 patients of these patients (28.3%) had a structural finding in the endoscopy phase, but 18 additional patients (30%) had some positive finding in the ultrasound phase. In other words, the diagnostic yield rose to 58.3% ($p < 0.001$). **Conclusion:** Although this study's sample size is small, it suggests that using endoscopic ultrasound in the initial evaluation of dyspepsia could be useful since it increased diagnostic yield in this group of patients from 28.3 to 58.3%. This is very significant because patients with dyspepsia and negative endoscopy are usually classified as functional and only treated with medications. However, in recognition of the methodological limitations of this study, it should be considered an initial exploration. Larger, controlled studies should be considered to confirm this work. Another factor that should be considered is the cost of endoscopic ultrasound which is much higher than the upper digestive endoscopy.

## Keywords

Endoscopic ultrasound, evaluation, dyspepsia, gastric cáncer.

 

## INTRODUCTION

Dyspepsia is a clinical syndrome characterized by pain or discomfort in the upper abdomen. It affects at least 20% of the world's population. (1, 2) It has multiple causes including benign and malignant pathologies, negatively affects the quality of life, (8) and is often incorrectly called chronic gastritis or acid peptic disease. (3, 4) In some countries the annual incidence of dyspepsia has been found to be approximately 1%, and has been estimated that one in two people will consult a physician for dyspeptic symptoms at some time in their lives. Dyspepsia accounts for 5% of the people seen by general practitioners and for approximately 20% to 30% of those seen by gastroenterologists. (5-7) When a patient has dyspepsia whose cause has not been determined, it is called uninvestigated dyspepsia (UD). (8) The approach to adult patients includes upper gastrointestinal endoscopy and occasionally includes upper abdominal ultrasound. (1, 3) Dyspepsia can be secondary or organic if there are obvious alterations, it is called functional dyspepsia (FD) if examinations and images show no alterations that explain symptoms. (2, 3)

Early use of endoscopy is cost-effective, (9, 10) but the timing of upper endoscopy varies from place to place. In developed countries, it is recommended after age 55, but in developing countries with high incidences of gastric cancer, it is recommended at age 35. (3) In Colombia, no studies of cost-effectiveness have been carried out for UD, but studies of the prevalence of endoscopic lesions in patients with UD have been performed. More than 10 years ago, a prospective study of patients with UD found that 73% had FD. (11). Another Colombian study of patients with UD found cholelithiasis in 21%. (12)

Overall, the diagnostic yield of upper endoscopy alone for identification of organic causes does not exceed 30% , (1, 11) so other methods that have greater sensitivity need to be used. As understanding of these patients deepens, unknown causes may be found. In this regard, dyspepsia secondary to helicobacter pylori, a new entity that was previously included in the FD category, has recently been described. (13) It has now been shown that approximately 5% of patients with H. pylori can be cured of dyspepsia if the infection is eradicated. (13, 14) This new finding demonstrates the need to continue investigating unknown etiologies that could explain dyspeptic symptoms. When upper endoscopy is negative in the traditional diagnostic approach, the diagnosis is FD. If no further studies are performed, the patient is treated with proton pump inhibitors (PPIs), prokinetic agents or antidepressants for several months. (8) This can mask unidentified pathologies that may lead to probable complications.

Endoscopic ultrasound (EUS) combines the image from conventional upper endoscopy with an ultrasound image. When radial equipment is used, the ultrasound image has a range of about 6 cm which can cover the entire esophagus, stomach or duodenum. (15) Since Pentax 360-Degree Radial-Array Ultrasound Gastroscopes are frontal, unlike Olympus Radial Ultrasound Endoscopes which are oblique, endoscopic views identical to those of conventional endoscopy can be obtained prior to the ultrasound phase. Visibility beyond the upper gastrointestinal lumen allows diagnoses of additional pathologies that may be associated with dyspepsia. Taking into account the high frequency of dyspepsia, as well as the lack of research other than the upper endoscopy in our environment, we decided to perform this study of EUS for diagnosis of patients with UD. The objective is to evaluate whether EUS increases the diagnostic yield from the 27% yield of conventional endoscopy here in Colombia.

## MATERIALS AND METHODS

This is a prospective study of the prevalence of UD found in adult patients at a university institution in Colombia. The patients included came to the gastroenterology unit from January to October 2016 where they underwent upper endoscopy. After patients had agreed and signed consent forms, the Pentax echoendoscope was used instead of a conventional endoscope. On the basis of the ROME IV criteria, we defined dyspepsia as the presence of upper GI tract symptoms of postprandial fullness, early satiety and epigastric pain or burning. If no structural lesion is found endoscopically, it is defined as functional dyspepsia (FD). (8) Endoscopy indications used were those of the dyspepsia guide of the Colombian Association of Gastroenterology which recommends performing upper endoscopy in all patients with UD who are over 35 years old regardless of whether or not they have alarm symptoms. (16) We excluded patients who had any contraindication for performance of endoscopy with sedation, patients who had previously undergone upper endoscopy, patients with histories of gastrointestinal surgery including cholecystectomies, and patients who had had endoscopic retrograde cholangiopancreatography (ERCP), and patients who had had abdominal ultrasound images, magnetic resonance imaging (MRI) or computed tomography (CT). EUS was performed in the usual way. (17)

Procedures were performed under sedation administered by an anesthesiologist. A Pentax echoendoscope, described above, was used. First, the endoscope was used to examine the esophagus, stomach and duodenum according to the protocol described by Yao. (18) This consists of the evaluation of 21 areas in the proximal, middle and distal third

of the stomach using both direct view and rearview. Two biopsies each were taken from the antrum and the corpus to check for H. pylori infections. Additional biopsies were taken when patients had apparent structural lesions. After the ultrasound phase, EUS was used to the major papilla. A retrograde evaluated the entire pancreas, the extrahepatic bile duct, the gallbladder, the celiac trunk, the left lobe of the liver and the mediastinal region. All abnormalities were noted on the patient's admission form. The protocol, investigation and informed consent form were approved by the ethics committee of the participating institution.

## RESULTS

In total, sixty patients with an average age of 40.8 years + 12.5 years were included. Sixty-five percent of them were women. In the first phase, forty-three of the patients (71.6%) were endoscopically diagnosed with chronic gastritis while 17 had structural lesions including five cases of esophagitis in 5 (8.3%), two cases of gastric ulcers (3.3%), five cases of duodenal ulcers (8.3%), four cases of histologically proven gastric cancer (6.6%), and one case of a gastrointestinal stromal tumor (GIST) (1.6%). H. pylori was found in 42 patients (70%), atrophic gastritis was found in 8 patients (13%), and intestinal metaplasia was found in six (10%).

In the second phase, EUS found cholelithiasis in 11 patients (18.3%), choledocolithiasis in one (1.6%), chronic pancreatitis defined according to by Rosemont's criteria in five (8.3%), a pancreas cyst suggestive of mucinous cystadenoma in one (1.6%), stage T2 pancreatic cancer in one (1.6%) and mediastinal adenopathies in one patient who also had gastric cancer (1.6%). (19) Overall, 17/60 patients (28.3%) had structural alterations found in the endoscopy phase and 18/60 (30%) had some positive finding that had not been found in the endoscopic phase. In other words, these cases would have been technically considered to have FD. Only 25 patients (41.6%) had no findings in both the endoscopy phase and the EUS phase. In all cases, the gallbladder, bile duct, head, body and tail of the pancreas were properly visualized. Overall findings are shown in Figure 1.

## DISCUSSION

This study found that 28.3% of the patients with UD had alterations found during the endoscopic phase which is similar to the 27% found in a previous investigation by the National University and which corroborates the poor performance of upper endoscopy in our environment. (11) In the ultrasound phase using EUS equipment with frontal vision, additional lesions that could explain dyspeptic symptoms were detected in 30% of the patients for a total of 58.3% (p <0.001). In other words, only 25 (41.6%) of the 60 patients had normal results.

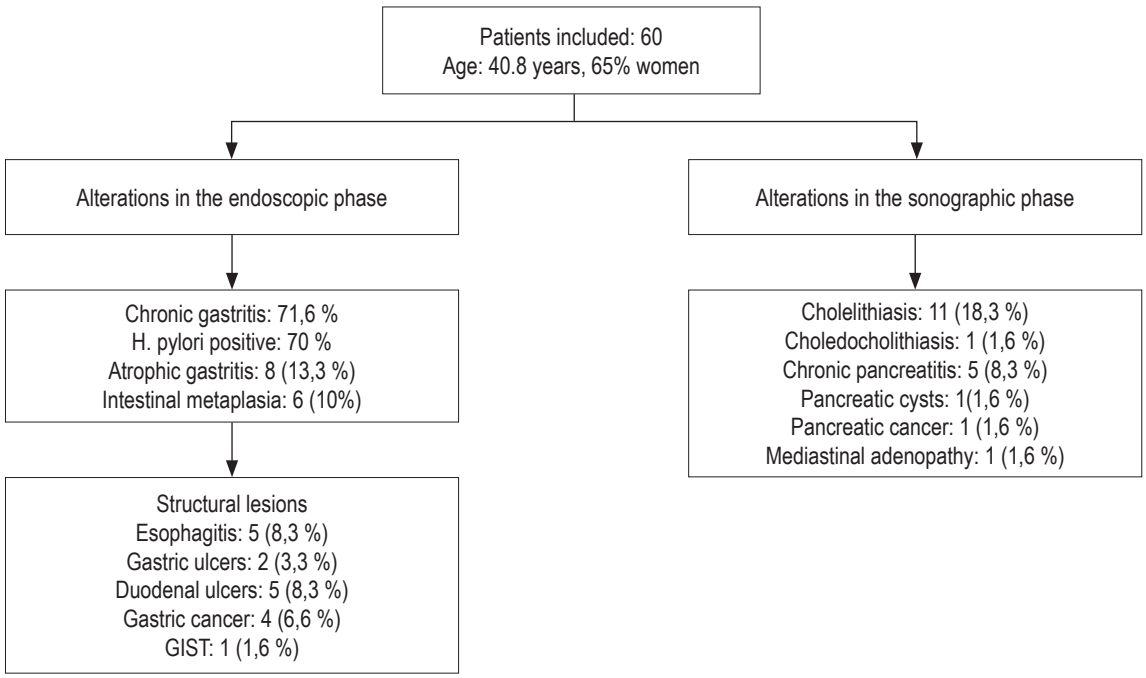


**Figure 1.** Overall results of the study.

The finding of cholelithiasis in 18% of patients coincides with the prevalence of this pathology in the west. (20, 21) However, it cannot be concluded that gallbladder stones cause dyspeptic symptoms since the symptom most frequently associated with them is colic. To determine the association of the two, a study with a greater number of patients, probably a case and control study, would be required. However, all gastroenterologists know that patients with cholelithiasis do not necessarily manifest the typical colic in the right hypochondrium but may manifest postprandial symptoms in the epigastrium which are very suggestive of dyspepsia. If the finding of cholelithiasis is eliminated, the diagnostic yield of EUS exceeds that of upper endoscopy by 12%. Given the types of pancreatic pathologies found, it can be inferred that when only upper endoscopy is taken into account for UD patients, negative findings can lead to the erroneous conclusion that the patient has FD which should be managed with prolonged administration of prokinetics, PPIs or antidepressants. (22) These medications would not achieve significant improvement but could generate anxiety in patients. For the safety of patients and doctors, in many cases research into the cause of dyspepsia should continue with additional tests such as abdominal ultrasound, CT scans and other studies. (8, 22)

A new approach for patients with FD and persistent symptoms is posed by the findings that more than 11% of UD patients have pancreatic pathologies while others suffer from choledocholithiasis. For these patients, the next step should be biliopancreatic EUS rather than another upper endoscopy. EUS is even preferable to conventional ultrasound, CT scans and abdominal MRI. A study conducted more than 15 years ago suggested that the EUS could also be more cost-effective. (23) A more recent study from the United States by Chang et al. showed that, in the presence of symptoms, using EUS as the first exam is more cost-effective than upper endoscopy followed by abdominal ultrasound. (24) Compared to abdominal CT scans and MRI, the advantages of EUS are even more evident. Taking into account our results and those of international studies, we consider that it is necessary and timely to determine the place of biliopancreatic EUS in patients with UD in our environment. We consider that it would be premature to recommend this test for all patients with UD given the high cost of EUS in our setting. Nevertheless, the prevalence of biliopancreatic pathologies demonstrates that it should become the test of choice for FD patients who do not improve with conventional treatments.

A very important issue is that complexity of EUS has been exaggerated here in Colombia. Performing gastroesophageal or pancreatic EUS is relatively simple, does not take more than 5 or 10 minutes, and training is not very complex. This recalls what happened with the introduction of ERCP in Colombia more than 50 years ago,. It was considered to be a very complex procedure that could only be performed by a very few gastroenterologists in very few medical centers. Currently, ERCPs are routine procedures performed by many gastroenterologists the world over, and ERCP is a much more complex and dangerous procedure than is EUS. (24) The real complexity of EUS lies in therapeutic and invasive procedures such as staging of pancreatic cancer, punctures and drainage. It is time to demystify non-therapeutic EUS and understand reality. It is not difficult to imagine that EUS could be used for initial evaluation of UD in the near future. This is a complex pathology that, curiously, many consider to be an insignificant or easy-to-solve problem when it is called gastritis or acid peptic disease. In fact, addressing it is complex due to its recurrent nature. In addition, it causes deterioration of patients' quality of life, has high costs for the world's health care systems, and can have serious unsuspected etiologies, such as those found in this study.

To our knowledge, this is the first study of this type on the initial evaluations of patients with dyspepsia using EUS with frontal equipment done in Latin America. A study with a similar design done more than 15 years ago used an Olympus echoendoscope which only provides oblique views. (25) That study did not detect as many endoluminal lesions as did endoscopy. Unlike the Fuji and Pentax equipment, Olympus echoendoscopes do not have frontal vision, which makes it impossible to use for conventional endoscopy. (15) Because it limits the endoscopic phase, many areas cannot be evaluated which can leave lesions such as ulcers and tumors undiscovered.

It is also important to keep in mind that defensive medicine is frequently exercised. (26) Many patients press their doctors to reach a rapid diagnosis because they are anxious about their conditions and do not accept that their pain is only explained by gastritis. When the doctor is influenced, multiple tests that may even be more expensive than an EUS can be the result.

The limitations of this study include its sample size (not calculated) and the fact that it was performed at only one center. It would be convenient to conduct studies with larger samples to confirm the findings of this study.

## CONCLUSION

This study was found that the diagnostic yield of EUS exceeds that of upper endoscopy by 30% in patients with UD. EUS identified pathologies in 58.3% of the patients whereas upper endoscopy alone could only identify them in 28.3% of the patients ( $p < 0.001$). When upper endoscopy is negative for a patient with UD, current recommendations call for a diagnosis of FD and indefinite pres-

cription of medications whose efficacy is moderate. Our findings indicate the potential for using EUS as the initial evaluation examination as well as the potential for using it as a follow-up examination instead of a CT scan or MRI when symptoms persist. Studies of the cost-effectiveness of EUS for these purposes in our environment should be undertaken to determine whether this test should become the first choice instead of conventional endoscopy.

## Conflicts of Interest

None.

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# Effectiveness of vitamins C and E adjuvant to standard triple therapy for Helicobacter pylori in a cohort from the Peruvian Amazon

Wildor Samir Cubas,[1*] Rómulo Reyes Cahuila,[2] Heriberto Arévalo Ramírez,[3] Antonio M. Quispe.[4]

1 Faculty of Human Medicine at the Universidad Nacional de San Martín in San Martín, Peru
2 Gastroenterology Service of the Hospital Essalud II-Tarapoto in San Martín, Peru
3 Microbiology and Parasitology Area of the Universidad Nacional de San Martín in San Martín, Peru
4 Universidad Continental in Lima, Perú

***Correspondence:** wsamircubas@gmail.com

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## Abstract

**Introduction and Objectives:** Adjuvant therapy with vitamins C and E has been proposed to increase standard triple therapy's Helicobacter pylori eradication rate. This study tested this hypothesis in a cohort of patients from the Peruvian Amazon. **Material and Methods:** We retrospectively evaluated a cohort of 50 patients at Tarapoto Hospital who were treated for H. pylori infections from July to December 2016. Of these, 25 were randomly selected to receive standard triple therapy of 1 g amoxicillin, 500mg clarithromycin and 20mg omeprazole twice a day for 14 days plus adjuvant vitamins C and E. The other 25 only received standard triple therapy. The effectiveness of both treatments was estimated and compared using a general linear regression model using the Poisson family of distributions and log link with H. pylori eradication confirmed by histopathology as the outcome of interest. **Results:** A comparison of the two groups found no significant differences in their baseline symptoms, histopathological diagnoses, ages (38 ± 11 years vs. 36 ± 10 years) or genders (65% male vs. 63% male). A comparison of the effectiveness both treatments found a non-significant increase in eradication rates of 9.5% (91% vs. 82%, incidence rate ratio = 1.11; 95% confidence interval: 0.92 to 1.36). **Conclusions:** Adjuvant therapy with vitamins C and E may help increase the effectiveness of standard triple therapy for H. pylori in patients in the Peruvian Amazon, although this hypothesis needs to be confirmed in a clinical trial.

## Keywords

Ascorbic acid; Vitamin E; drug therapy; Helicobacter pylori; Peru (source: Decs BIREME).

## INTRODUCTION

Worldwide, H. pylori infections are some of the most common bacterial infections in adults. (1) In developing countries, prevalence is estimated to be above 70%, while in developed countries it is close to 35%. (2) This bacterium colonizes the stomach and usually produces symptoms in 32% of cases. The most frequent are abdominal pain, regurgitation, heartburn, nausea and hyporexia. (3) Currently, the World Health Organization (WHO) lists H. pylori as a type 1 carcinogen due to its close relationship with gastric cancer. (4) For this reason, and because it is a highly pathogenic microorganism, initiation of eradication therapy is recommended at the time of diagnosis. (5)

Currently, first-line H. pylori eradication treatment is standard triple therapy (STT) which consists of administration of two antibiotics, 2 g of amoxicillin twice daily and 500 mg of clarithromycin twice daily, and 20 mg of omeprazole, a proton pump inhibitor, twice daily for two weeks. (5) Until the last decade, the best H. pylori eradication rates achieved were in the range of 77% to 82%. (6, 7) Since then, various modifications have been proposed for increasing these rates. Among them are quadruple therapy, sequential therapy, hybrid therapy and adjuvant therapy with vitamins C and E. (8)

Adjuvant therapy with vitamins C and E has generated great expectations because it is relatively safe and accessible and because some reports have indicated that it can raise era-

 

dication rates to above 90%. (9) Vitamin C's adjuvant effect has been shown to be due to its ability to inhibit the formation of N-nitrous compounds and reactive oxygen metabolites in the gastric mucosa. (10) Both of these are considered vital for growth and carcinogenicity of H. pylori. (11) The adjuvant effect of vitamin E is due to its ability to inhibit lipid peroxidation and oxidative stress in the microenvironment created by H. pylori in the gastric mucosa. (12) These two factors are also considered to be essential factors for growth and pathogenesis of H. pylori. (13)

The first studies that evaluated the effects of adjuvant therapy with vitamins C and E yielded unfavorable results, (14) and the first metaanalysis published by Li in 2011 stated that there were insufficient significant findings evidence to recommend the therapy (relative risk = 0.93; 95% confidence interval (CI): 0.56 to 1.53) (15) However, newer studies show satisfactory and significant results with eradication rates for adjuvant therapy with vitamins C and E exceed those of standard triple therapy by 20%. (16) According to the latest published reports, the difference could be even larger for patients with low levels of antioxidant capacity and iron deficiency anemia. (17,18) This is very important for Peru where the prevalence of iron deficiency anemia exceeds 40%. (19) In the Peruvian jungle regions including the department of San Martín, prevalence of iron deficiency anemia is around 24%. (20) In most cases, this pathology is associated with malabsorption of iron related to low concentrations of vitamin C. (21) For this reason, our study attempts to determine the efficacy of the use of vitamins C and E, two antioxidants, as treatment adjuvant to STT for H. pylori in a cohort of patients from the Peruvian Amazon.

## MATERIALS AND METHODS

### Study Design

A retrospective cohort study was conducted in the district of Tarapoto in the province of San Martín (6 ° 29′00 ″ S, 76 ° 22′00 ″ W, population ~ 118,000) in the department of San Martín, in the northeastern region of Peru. The entire cohort consisted of patients with H. pylori infections diagnosed at the Social Security Hospital (EsSalud) of Tarapoto between July and December 2016. Patients who received STT plus adjuvant treatment with vitamins C and E were labeled the "exposed" cohort in this study. In order to estimate the effects attributable to adjuvant treatment with vitamins C and E, the exposed cohort was compared with a control cohort that was labelled "unexposed". For this, a random sample (1:1) was taken from hospital records by simple random sampling from the total number of patients who were diagnosed with H. pylori infections and treated with STT during the same period of time. The control cohort was not exposed to adjuvant therapy with vitamins C and E. To compare the effectiveness of the treatment, both cohorts (exposed and unexposed) were followed retrospectively to measure and compare the eradication rates of H. pylori. In order to avoid information bias, eradication of H. pylori was defined a priori as a confirmed histopathological and upper endoscopy diagnosis.

### Population and Sample

The exposed cohort and the unexposed cohort consisted of patients who were adults aged 18 to 60 years old, who had symptoms of abdominal pain, regurgitation, heartburn, nausea and/or hyporexia, and who had been diagnosed histopathologically with H. pylori. The exposed cohort consisted of those patients treated during the study period while the unexposed cohort was chosen randomly (sample 1: 1) from among all patients who had been diagnosed and treated previously and who met the criteria. Both cohorts received STT, but only the exposed cohort also received adjuvant treatment with vitamins C and E. Patients were excluded if they had had prior treatment for H. pylori, histories of gastric or duodenal ulcers, neoplasms of any kind, had been diagnosed as carriers of any metabolic disease, if they were pregnant or lactating women, if they had been treated with antibiotics in the six months prior to the study, if they were allergic to penicillins or other antibiotics, and if they had histories of previous gastric surgery. The sample size was estimated on the basis that a minimum of 50 patients (25 exposed and 25 unexposed) would be required to find differences in eradication rates over 25%, a 70% eradication rate was assumed in the unexposed, and an exploratory 90% CI and a study power of 80% were set. To maximize the power of study, from the beginning we planned to include all patients who met the selection criteria during the study period

### Standard Triple Therapy for H. pylori

STT was provided for free to all patients by the Social Security hospital (EsSalud) of Tarapoto. STT, considered the first line H. pylori treatment, (8) consists of twice daily oral administration of 1 g of amoxicillin, 500 mg of clarithromycin, and 20 mg of omeprazole for 14 days.

### Standard Triple Therapy Plus Adjuvant Treatment with Vitamins C and E

The use of STT plus adjuvant treatment with vitamins C and E is a potential new alternative therapy for H. pylori. It consists of twice daily administration of 500 mg of vitamin

C and 200 IU of vitamin E until 30 days after the completion of STT. (9)

### Data Collection

The medical records from the Social Security hospital (EsSalud) in Tarapoto of all of these patients were used as the primary source of information. In the case of the exposed cohort, all data of interest were identified by the principal investigator (Wildor Samir Cubas, WSC) and taken from patients' medical records. For the unexposed patients, a form was first elaborated with patients' medical record numbers in chronological order. Next, the sample was taken, and then the data was collected. In both cases, age, gender, work environment, origin, main symptoms, disease duration and endoscopic and histopathological findings before and after therapy were recorded. All the variables of interest were measured in the standard way and collected retrospectively from the medical records of each study subject. To facilitate data collection, a checklist with ranges of values and pre-established categories was developed to ensure reliable data collection. Once this process was finished, the data were typed in duplicate and any discrepancies were resolved by another review of the medical records.

### Data Analysis

Our descriptive analysis of baseline clinical-epidemiological characteristics of the study population included standard deviations (SD) of quantitative variables and absolute and relative frequencies of qualitative variables. Fisher's exact test and the $\chi^2$ test were used for comparison of proportions of the baseline characteristics of the exposed and unexposed. A multivariate Poisson regression analysis was performed to estimate the efficacy attributable to adjuvant therapy with vitamins C and E. The nested model method controlled by baseline characteristics was used to isolate the effect of adjuvant treatment. In this analysis, age, gender, adherence to treatment, disease time and number of symptoms were taken as potential confounding factors. In all cases, data analysis was performed using the STATA MP v13 statistical package considering a 95% CI.

### Ethical Considerations

The ethics committee of the Hospital Nacional Docente Madre Niño "San Bartolomé" in Lima, Peru reviewed and approved the protocol of this study. The confidentiality of information was respected although informed consent was not necessary because the data was obtained retrospectively.

## RESULTS

### Study Population Characteristics

Between July and December 2016, a total of 50 patients with H. pylori infections were evaluated and received eradication therapy. Of these, five patients (10%) were excluded from the analysis because they did not complete treatment. Of these five, two belonged to the exposed group and three belonged to the unexposed group. Among the 45 patients analyzed, no differences were found between exposed and unexposed patients (23 versus 22) in terms of male predominance (65% vs. 64%) and average age (38 ± 11 versus 36 ± 10 years ), which was 37 ± 11 years (range: 19-59 years). The majority of patients came from the city of Tarapoto (74% versus 64%), and the rest came from rural areas of the town's periphery (26% versus 36%). The majority worked in the public sector (52% vs. 63%), and the rest were private sector workers (39% vs. 31%) or unemployed (9% vs. 5%). The main reason these patients came to the Gastroenterology Department of the Social Security Hospital (EsSalud) in Tarapoto was abdominal pain (43% versus 40%) which was followed by regurgitation (22% versus 27%), heartburn (17% vs. 18%), hyporexia (13% vs. 5%) and nausea (4% vs. 9%). Clinical manifestations had presented more than seven days prior to coming to the hospital in most cases (74% versus 77%). According to endoscopic findings prior to eradication therapy, the most frequent gastric lesions were antral gastritis (43% vs. 55%), pangastritis (43% vs. 27%) and mild intestinal metaplasia (13% versus 18%)

### Efficacy of H. Pylori Eradication Therapies

The overall efficacy of H. pylori eradication therapies, the eradication rate, was estimated at 87% (95% CI: 76% to 97%). That for the exposed group was 91% (95% CI: 79-100%) while that for the unexposed group was 82% (95% CI: 64-99%). Based on these eradication rates, a ratio of incidence rates of 1.12 (95% CI 0.88 to 1.41) was calculated.

## DISCUSSION

Adjuvant therapy with vitamins C and E has been reported to be an effective alternative for increasing the eradication rate of H. pylori attributable to STT. Although this may be the case for H. pylori patients in the Peruvian Amazon, the results of our study do not allow us to make this conclusion even though our data indicate that adjuvant therapy increased the eradication rate by 9.5% (91% vs. 82%; incidence rate ratio = 1.11; 95% CI: 0.92 to 1.36). Nevertheless, this effect was statistically not significant (Figure 1). This could

be because the effect does not exist or because it exists, but its magnitude is too small to have been detected with a power of study as small as ours.

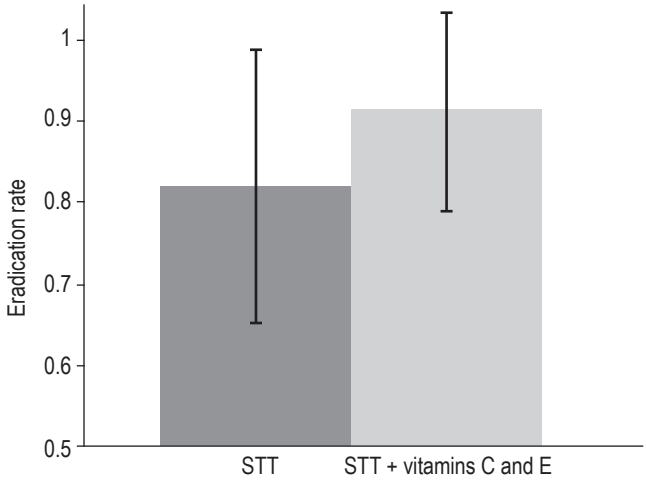


**Figure 1.** Effectiveness attributable to adjuvant use of vitamins C and E with standard triple therapy for patients infected with H. pylori in the Peruvian Amazon. Adjuvant treatment with vitamins C and E may increase eradication rates obtained with STT in patients infected with H. pylori (91% vs. 82%, incidence rate ratio = 1.11; 95% CI : 0.92 to 1.36).

According to several previous studies, the eradication rates attributable to STT plus adjuvant vitamins C and E can be as high as 94%. (9) This eradication rate is very similar to the 91% found in our study (Table 1). These rates may be explained by deficiencies of its antioxidant capacities of the populations studied. This was evidenced in an experimental study carried out in Asia where the patients in the sample infected with H. pylori also had low levels of antioxidant capacity. After administration of eradication therapy plus adjuvant vitamins C and E, eradication rates were higher than with standard triple therapy. (16) Subsequent studies have found that low levels of antioxidants are related to increased virulence and persistence of H. pylori, and that increasing antioxidant levels can affect survival of the bacteria. (22, 23) Another factor involved in H. pylori pathogenesis is its direct relationship with iron deficiency anemia in infected individuals resulting from poor absorption of iron when concentrations of antioxidants are low. This is the case with vitamin C in patients with H. pylori infections. (17, 21) This may add to the problem in South American countries like Peru where the latest reports of H. pylori prevalence and anemia exceed 60% and 40%, respectively. (19, 24). In the Peruvian Amazon, including the department of San Martín, anemia's prevalence is approximately 24%. (20)

**Table 1.** Eradication rate of H. Pylori according to exposure to therapy with vitamin C and E

| Variables | Exposed | | Not exposed | |
|---|---|---|---|---|
| | n | % | n | % |
| Eradication | | | | |
| Yes | 21 | 91 | 18 | 82 |
| No | 2 | 9 | 4 | 18 |
| Total | 23 | 100 | 22 | 100 |

Source: clinical records of patients infected with H. pylori from the Gastroenterology Service of the Social Security Hospital (EsSalud) of Tarapoto between July and December 2016.

The findings of our work indicate that STT plus adjuvant vitamins C and E has therapeutic results that are superior to those of STT alone (91% vs. 82%). Given the close relationship between H. pylori infections, anemia, and low levels of antioxidants, we can infer that supplementing eradication therapies with vitamins C and E may have indirectly improved antioxidant levels in this study's subjects which could have contributed to raising the H. pylori eradication rate above that of STT alone. Although some studies done in the past decade suggest that the evidence for recommending this adjuvant therapy is insufficient, (15) a number of other studies have demonstrated its therapeutic effectiveness. (25-27)

As in other studies, H. pylori infections were observed most frequently in male adult patients (24, 28, 29, 30, 31) However, contrary to expectations, the majority of patients infected with H. pylori (68%) came from urban areas of Tarapoto while a minority came from rural areas (Table 2). This may be due to a design effect, since H. pylori infections are commonly reported to be associated with poor socioeconomic conditions and poor basic services with limited access to drinking water. However, in Peru potable water does not seem to prevent new H. pylori infections. In fact, according to a recent study carried out in Lima, where the majority of the population has access to drinking water, it is common to find remains of H. pylori genetic material in drinking water. (32) What is even more worrisome is that strains of H. pylori that are resistant to standard levels of sodium hypochlorite (chlorine) are not uncommon, either. (33)

In conclusion, adjuvant treatment with vitamins C and E may increase the effectiveness of standard triple therapy for H. pylori in patients in the Peruvian Amazon. Nevertheless, to demonstrate this conclusively more experimental research is needed.

**Table 2.** Population characteristics

| Variables | Exposed | | Unexposed | |
|---|---|---|---|---|
| | n | % | n | % |
| Sex | | | | |
| Male | 15 | 65 % | 14 | 64 % |
| Female | 8 | 35 % | 8 | 36 % |
| Place of residence | | | | |
| Tarapoto | 17 | 74 % | 14 | 64 % |
| Periphery | 6 | 26 % | 8 | 36 % |
| Labor sphere | | | | |
| Public | 12 | 52 % | 14 | 63 % |
| Private | 9 | 39 % | 7 | 32 % |
| Unemployed | 2 | 9 % | 1 | 5 % |
| Reason for consultation | | | | |
| Abdominal pain | 10 | 43 % | 9 | 41 % |
| Regurgitation | 5 | 22 % | 6 | 27 % |
| Heartburn | 4 | 17 % | 4 | 18 % |
| Hyporexia | 3 | 13 % | 1 | 5 % |
| Nausea | 1 | 4 % | 2 | 9 % |
| Disease duration | | | | |
| > 7 days | 17 | 74 % | 17 | 77 % |
| < 7 days | 6 | 26 % | 5 | 23 % |
| Initial histopathology | | | | |
| Antral Gastritis | 10 | 43 % | 12 | 55 % |
| Pangastritis | 10 | 43 % | 6 | 27 % |
| Intestinal metaplasia | 3 | 14 % | 4 | 18 % |

Source: clinical records of patients infected with H. pylori from the Gastroenterology Service of the Social Security Hospital (EsSalud) of Tarapoto between July and December 2016.

## Authorship Contributions

WSC, RRC, HAR and AMQ participated in the design of the study, the interpretation of the results and the writing of the manuscript. In addition, WSC, RRC and HAR participated in data collection; and AMQ participated in data analysis.

## Conflicts of Interest

The authors declare that they have no conflicts of interest related to this article.

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# Prevalence of gastroesophageal reflux disease found by pH measurements in preterm infants with suggestive symptoms

Carlos Alberto Velasco Benítez,[1*] Ernesto León Vallejo Mondragón,[2] Mauricio Alberto Arévalo Sanabria.[3]

1 Pediatrician, Gastroenterologist, Nutritionist, and Senior Professor at Universidad del Valle in Cali, Colombia
2 Pediatrician, Cardiologist and Professor at Universidad Libre, Seccional Cali in Cali Colombia
3 Pediatrician, Neonatologist, and Assistant Professor at Universidad del Valle in Cali, Colombia

***Correspondence:** carlos.velasco@correounivalle.edu.co.

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## Abstract

**Introduction:** Gastroesophageal reflux is a common physiological phenomenon in preterm infants and is frequently diagnosed in neonates for whom it is an important clinical phenomenon. **Objective:** To determine the prevalence and symptoms of gastroesophageal reflux disease (GERD) by 24-hour ambulatory esophageal pH monitoring of preterm neonates. **Methodology:** This is a study of the prevalence of GERD among patients in the Neonatal Intensive Care Unit of Cali, Colombia. Esophageal pH of infants was monitored when GERD was suspected. In addition, sociodemographic and clinical variables were recorded and taken into account. Univariate analysis by means of measures of central tendency and bivariate analysis were preformed using the chi-squared test and Student's T test with $p < 0.05$ established as significant. **Results:** Twenty preterm newborns whose ages from birth ranged from 27.6 days to 36.5 days and whose gestational ages ranged from 3.8 weeks to 31.6 weeks were included. Twelve were male, and eleven (55.0%) had abnormal pH. Gastric waste and heart disease were associated with abnormal pH. **Conclusion:** The prevalence of GERD found through pH monitoring was relatively high in this group of infants compared findings in the world literature although no clear associations were found between the symptoms analyzed and other factors except for heart disease and gastric waste.

## Keywords

Newborn, prevalence, gastroesophageal reflux, esophageal monitoring.

## INTRODUCTION

Gastroesophageal reflux (GER) is defined as the return of the gastric contents to the esophagus, with or without regurgitation or vomiting. It must be distinguished from gastroesophageal reflux disease (GERD) which includes a series of GER symptoms. These can affect a child's quality of life and cause pathological complications such as failure to grow, problems with eating and/or sleeping, chronic respiratory problems, esophagitis, hematemesis, apnea and life-threatening events. (1, 2) GER is a common physiological phenomenon in preterm infants which is frequently diagnosed in neonatal intensive care units (NICU). It can lead to prolonged hospital stays and high in-hospital costs which makes it an important clinical phenomenon in NICUs. (3, 4)

GER in preterm infants is often diagnosed and managed based on clinical manifestations rather than specific paraclinical tests. In addition, there is little evidence of the damage caused by GER in preterm infants, so questionable anti-GER drugs are routinely used in this age group. (4)

Nonspecific signs and symptoms attributable to GER include food intolerance or aversion, poor weight gain, frequent regurgitation, apnea, oxygen desaturation, bradycardia, arching and irritability. (1, 3, 4)

Classically, pH monitoring (pHm) in the lower esophagus has been used to diagnose GER in children and adults. Two methods are in use: 24-hour outpatient esophageal pH

monitoring and multichannel intraluminal impedance testing (MII). MII measures esophageal movements of liquids, solids and air by electrical impedance, and it shows whether movements are antegrade or retrograde while it simultaneously measures pH. (5) The normal reference values for pH monitoring in preterm infants are those of Ng et al. (6)

The objective of this study is to determine the prevalence and symptoms of GERD by pHm in preterm infants at the Hospital Universitario del Valle (HUV) Evaristo García in Cali, Colombia.

## MATERIAL AND METHODS

This observational, descriptive, non-experimental, cross-sectional and comparative study was conducted in preterm infants who were hospitalized in the Newborn Intensive Care Unit of the Hospital Universitario del Valle (HUV) Evaristo García in Cali, Colombia between January and June 2013. Infants diagnosed as premature who had pathologies typical of GER such as respiratory distress syndrome, sepsis and metabolic disorders were included.

Premature newborns with symptoms suggestive of GERD such as desaturation during feeding, bloating, vomiting, unexplained apnea, residue, coughing, crying, irritability, life-threatening events and lack of weight gain not attributable to another pathology were included. Preterm infants who had already received anti-reflux medications were excluded. Before starting the study, members of the families of the preterm infants were told the nature and purpose of the investigation and had opportunities to request more information and discuss any questions they may have had. All infants were being fed enterally at the time of the study. Some of those with nasogastric feeding in situ were also in their normal sleeping position, whether supine or prone.

Each preterm infant underwent outpatient esophageal pH monitoring for a minimum of 20 continuous hours. Monitoring was preceded by a 4-hour fast. A disposable 1-channel pediatric catheter with antimony tip was attached to a Mark III pH monitor from Synetics Medical that had been calibrated before the study with buffer solutions at pHs of 4.0 and 7.0. The length of catheter to be introduced through one of the infant's nostrils was calculated on the basis of the formula of Strobel et al. (size x 0.252 + 5 x 0.86). (7) It was corroborated by a portable chest x-ray which helped locate the tip of the catheter between the sixth and eighth thoracic vertebrae. Once in place, the catheter and monitor were secured with surgical tape to prevent displacement for duration of pHm. Symptoms and signs present during the procedure were registered.

Synetics Medical software was used to analyze pH plots which were then interpreted according to the standard normal values developed by Ng et al. The reflux index, the number of acid episodes, the number of acid episodes longer than 5 minutes and the duration of the longest acid episode were all included in the analysis. (6)

The statistical analysis performed with the Stata 15 software included measures of central tendency such as percentages, averages and standard deviations and univariate analysis using the chi-square test ($\chi 2$) and Student's t test with $p < 0.05$ considered to be significant.

The risk of this study was classified as minimal according to Resolution 8430 of 1993 of the Ministry of Health of Colombia which established ethical standards of research with human beings. The rights and welfare of each participant were guaranteed in accordance with the Helsinki Declaration. Before a patient was included in the study, parents or guardians signed an informed consent document allowing data to be used in research and ensuring confidentiality and professional handling of the study's data and results.

## RESULTS

### General Characteristics

An observational, descriptive, non-experimental, cross-sectional, comparative study of 20 preterm infants was performed. Average post-birth age was 36.5 + 27.6 days, average gestational age was 31.6 + 3.8 weeks, average weight was 1493.3 + 579.8 grams, and the average Ballard Maturational Assessment Score was 31.6 + 3.7 weeks. Twelve of the infants were male, 18 were mixed race, and 17 were from Cali, Colombia. The mothers' average age was 25.0 + 7.4 years old. Ten had had no prenatal monitoring, ten infants were born as part of multiple births two of which were vaginal and eight of which were caesarian. Infants were hospitalized because they were premature and had pathologies such as respiratory distress syndrome, sepsis and metabolic disorders.

### Outpatient Esophageal pH Monitoring

Eleven of the 20 preterm infants (55.0%) had abnormal esophageal pH measurements (Table 1).

**Table 1.** Measurements of esophageal pH for eleven outpatient preterm infants at the Hospital Universitario del Valle (HUV) Evaristo García in Cali, Colombia

| Variable | Average (n = 11) | Normal values according to Ng et al. (6) |
|---|---|---|
| Study duration (hours) | 21.4 | |
| Reflux Index (%) | 18.1 | 0.7 + 1.1 |
| Number of acid episodes | 157 | 7.6 + 11.2 |
| Number of acid episodes> 5 minutes | 13.7 | 0.5 + 1.1 |
| Longest episode (minutes) | 70 | 4.6 + 6.1 |

## Signs and Symptoms Found in Outpatient Esophageal pH Monitoring

Residues and heart disease in these infants was associated with abnormal pH-measurements (Table 2).

**Table 2.** Signs and symptoms and outpatient esophageal pH measurements in 20 preterm infants at the Hospital Universitario del Valle (HUV) Evaristo García in Cali, Colombia

| | pH measurement | | | | pH measurement | | |
|---|---|---|---|---|---|---|---|
| | Normal | Abnormal | *p* | | Normal | Abnormal | *p* |
| Cyanosis | | | | Cough | | | |
| Yes | 5 | 4 | 0.203 | Yes | 6 | 5 | 0.085 |
| No | 15 | 7 | | No | 14 | 6 | |
| Apnea | | | | Respiratory distress syndrome | | | |
| Yes | 11 | 8 | 0.086 | Yes | 11 | 6 | 0.996 |
| No | 9 | 3 | | No | 9 | 5 | |
| Vomiting | | | | Regurgitation | | | |
| Yes | 13 | 6 | 0.303 | Yes | 8 | 4 | 0.731 |
| No | 7 | 5 | | No | 12 | 7 | |
| Gastric residuals | | | | Abdominal distension | | | |
| Yes | 10 | 3 | 0.024 | Yes | 3 | 1 | 0.85 |
| No | 10 | 8 | | No | 17 | 10 | |
| Drooling | | | | Necrotizing enterocolitis | | | |
| Yes | 1 | 0 | 0.281 | Yes | 1 | 1 | 0.38 |
| No | 19 | 11 | | No | 19 | 10 | |
| Failure to gain weight | | | | Irritability | | | |
| Yes | 1 | 1 | 1 | Yes | 1 | 1 | 0.38 |
| No | 19 | 10 | | No | 19 | 10 | |
| Cardiopathy | | | | Sepsis | | | |
| Yes | 3 | 3 | 0.001 | Yes | 10 | 5 | 0.673 |
| No | 17 | 8 | | No | 10 | 6 | |
| Use of aminophylline | | | | Use of antibiotics | | | |
| Yes | 8 | 5 | 0.605 | Yes | 18 | 9 | 0.196 |
| No | 12 | 6 | | No | 2 | 2 | |

## DISCUSSION

The use of pH-measurement including multichannel intraluminal impedance is relatively common for investigation of gastroesophageal reflux disease (GERD) in preterm infants (preterm infants). It is performed on between 24.0% (8) and 32.0% of the patients in neonatal care units. (9) Some authors believe that the validity of GERD diagnostic tests, including pH monitoring, cannot be estimated on the basis of current knowledge. They argue for clinical trials to determine the usefulness of these and other tests. (10-12).

According to the current Practical Clinical Guidelines for Pediatric Gastroesophageal Reflux of the North American Society of Pediatric Gastroenterology, Hepatology and Nutrition (NASPGHAN) and the European Society for Pediatric Gastroenterology Hepatology and Nutrition (ESPGHAN), when pHm cannot be done with MII, other pHm methods should be used to correlate persistent symptoms with acid gastroesophageal reflux events. (2) This study uses pHm, which detects more episodes of reflux than does MII according to Rossor et al. (13)

## Prevalence of GERD in Preterm Infants

More than half of the preterm infants studied in the Newborn Intensive Care Unit of the HUV of Cali, Colombia had abnormal pH. These data are very similar to those described by Di Fiore et al. (14) who reported that 59.0% of their study participants had GERD diagnosed by pHm. The percentage diagnosed with GERD in our study was greater than the percentages identified Sivalingam et al., Rossor et al. and of Funderburk et al. who found of 30.0%, 21.0%, and 10.0% respectively using MII. (13, 15 16)

Prevalence variability could be the result of different techniques and different interpretations of results used to diagnose GERD. Other factors that could account for these variations include sociodemographic characteristics and differences in postnatal and/or gestational ages from one study to another. This implies a need for greater standardization in subsequent analyses. Similarly, results may be influenced by the total number of preterm infants studied. A small sample is likely to have a higher prevalence since the population analyzed is suspected of having GERD.

## Signs and Symptoms Associated with GERD in Preterm Infants

Few studies mention associations between symptoms and GERD which is why indices have been used to interpret MII/pHm for diagnosis of GERD in neonates. Nevertheless, a study by Barriga Rivera et al. of neonates with cardio-respiratory symptoms has failed to demonstrate that the symptom index (IS), the symptom sensitivity index (ISS) and the probability of association of symptoms (PAS) are useful for this purpose. (17) The relationship between GERD and cardiorespiratory events in neonates is controversial. (18) In our results, children with heart disease without respiratory symptoms had abnormal pH more often than did children without heart disease ($p < 0.05$). These data are similar to those found by Qureshi et al. (19). They found that 6.1% of cardiorespiratory symptoms during sleep were associated with events diagnosed as GERD using MII/pHm and concurrent polysomnography.

In this study, there were no preterm infants with apparently life-threatening events, but Macchini et al. reported them in 80.0% of the children diagnosed with GERD by

pHm. (20) Although GERD and apnea occur frequently in preterm infants as shown by Rossor et al., (21) we found no association between GERD and apnea. Gastric residue was found in a statistically significant percentage of the infants with abnormal pH in our study, but more observation of the feeding of these infants is required to identify other possible confounders. Although we did not take into account whether preterm infants were stimulated by non-nutritive sucking, a cross-sectional study of preterm infants by Corvaglia et al. has suggested that it is reasonable to use pacifiers with these neonates since their use had no effects on acid and non-acid GER evaluated by MII. (22)

Causality between reflux events and abnormal signs in preterm infants is limited. Given clinical suspicion of GERD in preterm infants, diagnostic procedures such as MII/pHm should be performed. (23) Nevertheless, Salvatore et al. have found poor correlation between parental reports of GERD symptoms, pHm results, and endoscopic evidence of GERD. (24) According to a study by De Rose et al., (25) MII/pHm not only plays a diagnostic role for preterm infants, it also offers prognostic value in terms of duration of drug treatment. In this therapeutic sense, Loots et al. (26) managed to demonstrate that administration of proton pump inhibitors, either omeprazole at 1 mg/kg/day or esomeprazole at 0.5 mg/kg/day for 2 weeks, improves the integrity of the esophageal mucosa in infants between 0 and 6 months of age who have been diagnosed with GERD by MII/pHm.

Weaknesses of this study include those associated with the type of feeding and with gastric residue of preterm infants fed by nasogastric tube in terms of quantification, volume, children with or without nasogastric tube, whether gastric residues were present or absent, and whether the infants were prone or supine. The use of a nasogastric tube can be a confusing factor as well as a risk factor for increased episodes of GERD while episodes of GERD in prone position are minor.

In conclusion, the prevalence of GERD diagnosed by pH monitoring in preterm infants in this study was relatively high compared to results found in the world's literature. No clear associations with the symptoms analyzed, except for heart disease and gastric waste, were found. Finally, we were unable to analyze these associations due to lack of knowledge in terms of quantification, volume, and presence or absence of nasogastric tubes and positions. This emphasizes the need for further studies to determine possible associations and appropriate management of GERD.

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# Characterization of patients with chronic hepatitis C treated in a high complexity hospital in Medellín

Mónica Ledezma-Morales,[1*] Juan Carlos Restrepo G.,[2] Pedro Amariles,[1] María Camila Trillos A.,[3] Rubén Darío Vargas R.[3]

1 Pharmaceutical Promotion and Prevention Group and the University of Antioquia in Medellín, Colombia
2 Hepatology and Liver Transplant Unit at the Hospital Pablo Tobón Uribe and the Gastrohepatology Group at the University of Antioquia in Medellín, Colombia
3 Faculty of Medicine of the University of Antioquia in Medellín, Colombia

***Correspondence:** monica.ledezma.morales@gmail.com

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## Abstract

**Introduction:** Throughout the world hepatitis C (HepC) is a public health problem. Estimates for its prevalence in Colombia range from 0.5% to 1% but 2.1 % for patients over 50 years of age. The Hepatology Unit at the Hospital Pablo Tobón Uribe (HPTU) has been a benchmark for management of HepC in Medellín and Colombia for years. **Objective:** To describe sociodemographic and clinical characteristics together with health outcomes of patients with chronic HepC who were treated at the HPTU between 2013 and 2018. **Materials and methods:** This is an observational, descriptive and retrospective study of patients with chronic HepC, treated between January 1, 2013 and March 31, 2018. **Results:** One hundred and eight patients were analyzed. The average age was 55.8 years (SD 13.7), 51.9% were men, and 78.7% belonged to the contributory health care scheme. Most frequently, the disease was transmitted by blood, and genotype 1 predominated in the group of patients analyzed. The effectiveness of interferon schemes was 46.9% while that of Direct-Acting Antivirals (DAA) was 94.6%. Adverse drug reactions were found in 68.2% of patients treated with interferon/ribavirin schemes but in only 25.9% of the patients treated with DAA. **Conclusions:** In this group of patients treated at HPTU, DAA were safer and more effective than interferon/ribavirin schemes.

## Keywords

Hepatitis C, Colombia, antivirals, interferons, direct action antivirals.

## INTRODUCTION

Hepatitis C (HepC) is a global public health problem whose prevalence is between 2% and 3%. It progresses to chronic diseases, and 70% to 90% of patients develop chronic liver diseases including cirrhosis and hepatocellular carcinoma (HCC). (1 , 2) Especially vulnerable populations including injectable drug users and people with inadequate healthcare. In Colombia, it is estimated that the prevalence of HepC in the overall population is between 0.5% but that it is 2.1% in people over 50 years of age. (3)

The goal of treatment is to reduce adverse health consequences such as terminal liver disease and HCC and reduce mortality from any cause by achieving sustained virological response (SVR). (4) This is defined as an unmeasurably small viral load at 12 weeks after the end of interferon-free therapies or at or 24 weeks interferon-based therapies. (5)

Treatment of HepC has evolved considerably. Treatment with pegylated interferon (peg-IFN) and ribavirin (RBV) are not tolerated well by many patients and which only achieve SVR in 6% to 56% of patients. (2, 6) Consequently, they are being replaced by direct action antivirals (DAAs) which achieve SVR in more than 90% of patients, have shorter treatment times and reduce the number of adverse events. (5, 7, 8) In the United States, second generation DAAs were approved in 2013. In Colombian they were considered to be vital drugs that were not available until simeprevir (SMV), daclatasvir (DCV) and asunaprevir

 

went on the market in 2015. These were followed by the treatment regimen of paritaprevir/ombitasvir/ritonavir/dasabuvir (PrOD) in 2016 and by sofosbuvir (SOF) and ledipasvir (LDV) in 2017. (9)

Hospital Pablo Tobón Uribe (HPTU) is a referral center for hepatology patients which is responsible for providing care for chronic HepC patients from various parts of Colombia. Nevertheless, systematic information on the characteristics of the diseases and patient population had not been published before now. Therefore, the objective of this work was to describe the sociodemographic, clinical characteristics and health outcomes of patients with HepC treated at the HPTU between 2013 and 2018.

## MATERIAL AND METHODS

### Type of Study

This is an observational, descriptive and retrospective study.

### Study Population

Patients with chronic HepC whose diagnoses were confirmed by detection of hepatitis C virus RNA and who were treated in the HPTU between January 1, 2013 and March 31, 2018 were included in this study. Patients who were not treated pharmacologically, patients who were treated before 2013, and patients whose treatment information was incomplete were excluded.

### Variables

Sociodemographic information collected included patient sex, age, schooling, insurance, affiliation regime, and residence department.

Clinical information collected included HCV transmission mechanism, HCV genotype/subtype, fibrosis/cirrhosis status, co-infection with human immunodeficiency virus (HIV) and/or hepatitis B virus (HBV), previous treatment schemes, treatment with DAA, variants associated with resistance (VAR), adverse drug reactions (ADR), number of non-anti-HCV medications used by the patient, hospitalization in the HPTU related to HepC, and SVR.

### Information Gathering Process

Consolidation of the medical records of patients with ICD-10 codes B182 and B171 was obtained from the investigating hepatologist. Sociodemographic and clinical variables were extracted from the electronic medical record and recorded on a form in Microsoft Access® 2010.

### Statistical Analysis

Absolute frequencies and relative frequencies were used for qualitative variables, and variables, means and standard deviations were used for quantitative variables. Statistical analysis of the data was performed with SPSS 23®.

### Ethical Considerations

The Committee on Research and Research Ethics of the HPTU approved this study (Protocol 2018.033).

## RESULTS

One hundred eight patients were included in the analysis (Figure 1). Of these, 51.9% were men, and the average age was 55.8 years (standard deviation [SD] 13.7) (Table 1). The most frequent transmission mechanism was a blood transfusion (25%), genotype 1 had the highest prevalence (77.8%), 39.8% of patients had advanced fibrosis/cirrhosis (F3-F4), 77.5% of patients in F4 had compensated cirrhosis, 4.6% had HCC, 90.7% had no coinfections, and 31.5% were hospitalized in the HPTU for causes related to HepC. Other clinical features can be seen in Table 2.

### Treatment of HCV Infections

Thirty-sever percent of the patients were treated solely with peg-INF, 24.1% were treated with peg-INF followed by rescue therapy with DAA, and 38.9% were treated only with DAA (Table 3).

Of those treated with peg-INF (61.1%), 59.1% received boceprevir or telaprevir. Of these, 46.9% reached SVR (Figure 2). There were no SVR reports for five patients, three patients were waiting for interferon-free therapies, and one patient died due to a septic shock of urinary origin and severe hepatic encephalopathy. DAAs were prescribed for twenty-six patients who did not reach SVR.

Of the patients treated with peg-IFN, 68.2% had reports of ADRs in the EMH. ADRs occurred most frequently with boceprevir schemes. A total of 216 ADRs were recorded with asthenia and neutropenia each accounting for 8.8%, anemia for 7.9%, and leukopenia and adynamia for 6.9% each.

### Use of Direct-Acting Antivirals

The most frequently prescribed DAAs were SOF/LDV and SOF/DCV/RBV (Table 3). Of the patients for whom DAAs were prescribed, 79.4% reportedly began treatment, and 88.9% of these completed treatment

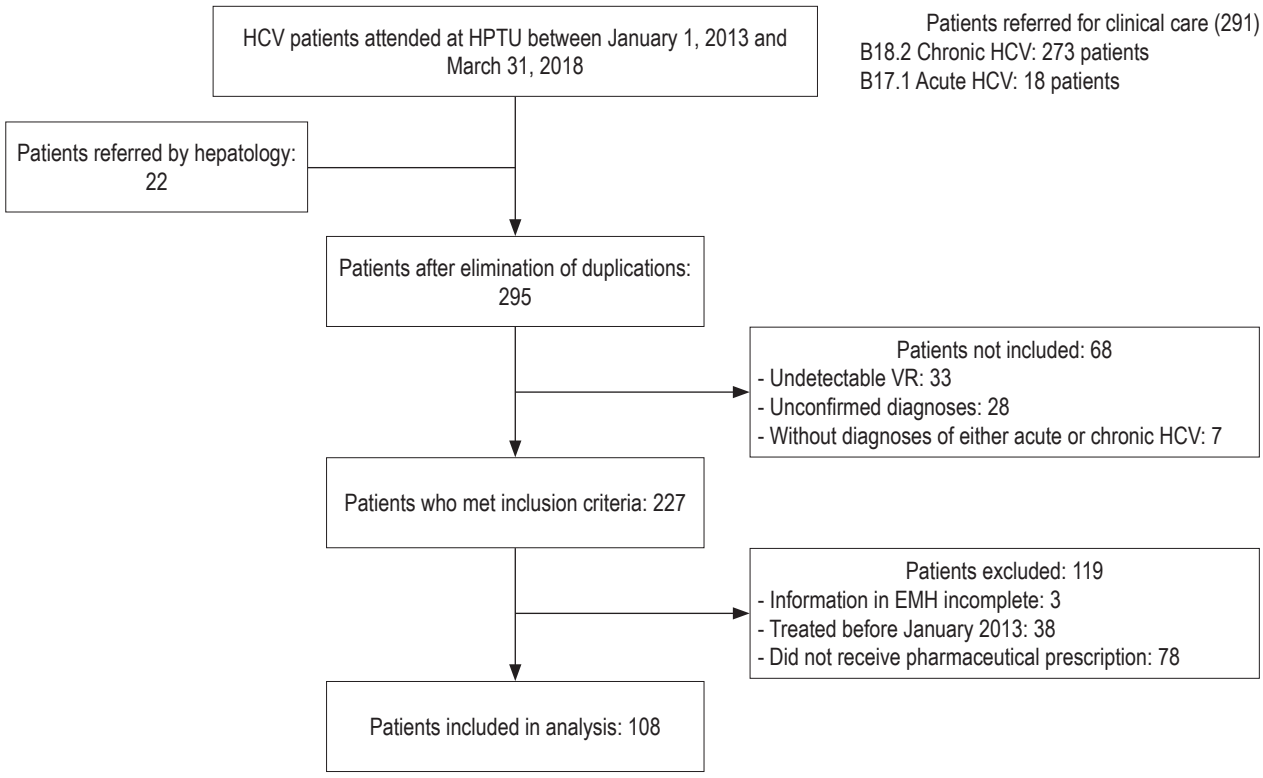


**Figure 1.** General diagram of the investigation. VR: viral load; EMH: electronic medical history; HPTU: Hospital Pablo Tobón Uribe.

**Table 1.** Sociodemographic characteristics of patients with chronic hepatitis C

| Characteristics | Frequency | % (n = 108) |
|---|---|---|
| Sex | | |
| Men | 56 | 51.9 |
| Women | 52 | 48.1 |
| Age | | |
| ≤30 | 5 | 4.6 |
| 31-40 | 12 | 11.1 |
| 41-50 | 15 | 13.9 |
| 51-60 | 32 | 29.6 |
| 61-70 | 30 | 27.8 |
| 71-80 | 12 | 11.1 |
| >81 | 2 | 1.9 |
| Education | | |
| Basic primary | 12 | 11.1 |
| Basic secondary | 23 | 21.3 |
| Technical | 5 | 4.6 |
| Professional | 2 | 1.9 |
| Graduate school | 24 | 22.2 |
| No report | 3 | 2.8 |
| Basic primary | 39 | 36.1 |

| Characteristics | Frequency | % (n = 108) |
|---|---|---|
| Health care system regimen | | |
| Subsidized | 11 | 10.2 |
| Contributive | 85 | 78.7 |
| Exception | 6 | 5.6 |
| Individual | 2 | 1.9 |
| No report | 4 | 3.7 |
| Health care benefit plans | | |
| SURA EPS | 24 | 22.2 |
| Nueva EPS | 19 | 17.6 |
| Coomeva EPS | 14 | 13.0 |
| Others | 50 | 46.3 |
| No report | 1 | 0.9 |
| Residence Department | | |
| Antioquia | 86 | 79.6 |
| Atlántico | 5 | 4.6 |
| Risaralda | 5 | 4.6 |
| Quindío | 3 | 2.8 |
| Cundinamarca | 2 | 1.9 |
| Others | 7 | 6.5 |

(Figure 3). Of the patients who finished treatment, 77.1% (37/48) had a viral load report at 12 weeks after the end of treatment. Of these, 94.6% achieved SVR (Figure 4). The remaining 5.4% did not achieve SVR due to a VAR, mainly related to NS5A inhibitors. The first patient took DCV/asunaprevir for 24 weeks without achieving SVR. In this case, no other scheme was initiated, given the costs and risks of side effects. The second patient received SOF/SMV/RBV for 12 weeks, but did not reach SVR. The specialist reported that the treatment was not available. It should be noted that a third patient presented VAR but achieved SVR (Table 5).

DAA safety was analyzed for all patients who reportedly began treatment; there were records of ADRs associated with DAA for 25.9% (14/54) of these patients. Thirty-seven ADRs attributed to seven DAA schemes were identified. SOF/DCV/RBV had the highest frequency, followed by SOF/LDV/RBV. The most frequent ADRs were anemia (16.2%), asthenia (10.8%), headaches and flu symptoms (8.1% each) (Table 6).

**Table 2.** Clinical characteristics of patients with chronic hepatitis C

| | Frequency | % (n = 108) |
|---|---|---|
| Possible transmission mechanism | | |
| Blood transfusion | 27 | 25.0 |
| Sexual transmission | 8 | 7.4 |
| Use of contaminated injection equipment (person who injects psychoactive drugs) | 7 | 6.5 |
| Adverse event related to health procedures | 4 | 3.7 |
| Occupational Exposure | 1 | 0.9 |
| Blood transfusion and other forms of blood transmission (tattoos, piercings, scarification) | 1 | 0.9 |
| Other forms of blood transmission (tattoos, piercings, scarification) | 1 | 0.9 |
| Maternal transmission to child | 1 | 0.9 |
| Unknown | 58 | 53.7 |
| Genotype | | |
| 1 | 7 | 6.5 |
| 1a | 33 | 30.6 |
| 1a-1b | 1 | 0.9 |
| 1b | 43 | 39.8 |
| 2 | 7 | 6.5 |
| 2a | 1 | 0.9 |
| 2b | 2 | 1.9 |
| 3 | 2 | 1.9 |
| 4 | 3 | 2.8 |
| Not genotyped | 9 | 8.3 |
| Coinfection | | |
| HIV | 7 | 6.5 |
| HBV | 3 | 2.8 |
| None | 98 | 90.7 |
| Liver transplant status | | |
| No transplant | 91 | 84.3 |
| Liver transplant status | | |
| Transplanted | 16 | 14.8 |
| Prior transplant or on transplant list | 1 | 0.9 |
| Fibrosis status | | |
| Not specified | 20 | 18.5 |
| F0 | 8 | 7.4 |
| F1 | 15 | 13.9 |
| F1-2 | 3 | 2.8 |
| F2 | 12 | 11.1 |
| F2-3 | 3 | 2.8 |
| F3 | 4 | 3.7 |
| F3-4 | 3 | 2.8 |
| F4 (Cirrhosis) | 40 | 37.0 |
| Cirrhosis (Child-Pugh-Turcotte) | | |
| Compensated (A) | 31 | 77.5 |
| Uncompensated (B) | 6 | 15.0 |
| Uncompensated (C) | 2 | 5.0 |
| Not classified | 1 | 2.5 |
| Hepatocellular carcinoma | | |
| Yes | 5 | 4.6 |
| No | 101 | 93.5 |
| Suspected | 1 | 0.9 |
| No report | 1 | 0.9 |
| Extrahepatic manifestations | | |
| Dermatological | 9 | 8.3 |
| Hematological | 5 | 4.6 |
| Autoimmune disorders | 3 | 2.8 |
| Renal | 2 | 1.9 |
| None | 89 | 82.4 |
| Hospitalization in HPTU related to HCV | | |
| Yes | 34 | 31.5 |
| No | 74 | 68.5 |

**Table 3.** Prescribed hepatitis C treatment schemes

| Direct action antiviral schemes | Interferon based schemes | | | | | Total |
|---|---|---|---|---|---|---|
| | BOC/peg-INF/RBV | peg-INF/RBV | TPV/peg-INF/RBV | peg-INF | None | |
| None | 24 | 10 | 5 | 1 | | **40** |
| SOF/LDV | | | | | 12 | **12** |
| SOF/DCV/RBV | 3 | 4 | 1 | | 4 | **12** |
| SOF/DCV | | 1 | 1 | | 7 | **9** |
| PTV/OBV/R/Dasabuvir /RBV | | | | 1 | 8 | **9** |
| PTV/OBV/R/Dasabuvir | | 3 | | 1 | 5 | **9** |
| DCV/Asunaprevir | 1 | 2 | 1 | | 4 | **8** |
| SOF/LDV/RBV | 1 | 3 | 1 | | 2 | **7** |
| SOF/SMV/RBV | | 1 | | | | **1** |
| SOF/RBV | 1 | | | | | **1** |
| Total | **30** | **24** | **9** | **3** | **42** | **108** |

BOC: boceprevir; DCV: daclatasvir; LDV: ledipasvir; OBV: ombitasvir; peg-IFN: pegylated interferon; PTV: paritaprevir; R: ritonavir; RBV: ribavirin; SMV: simeprevir; SOF: sofosbuvir; POS: Telaprevir.

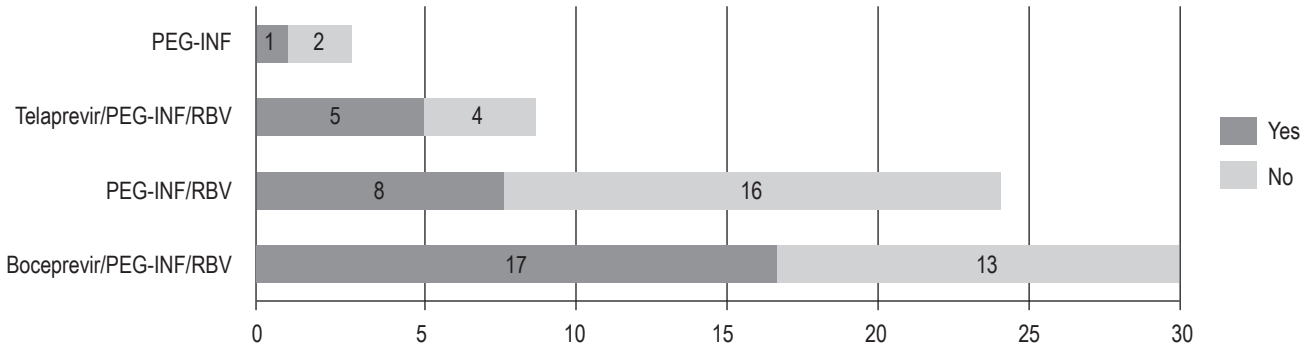


**Figure 2.** Sustained virological response range with interferon (n = 66). peg-INF: Pegylated interferon; RBV: ribavirin.

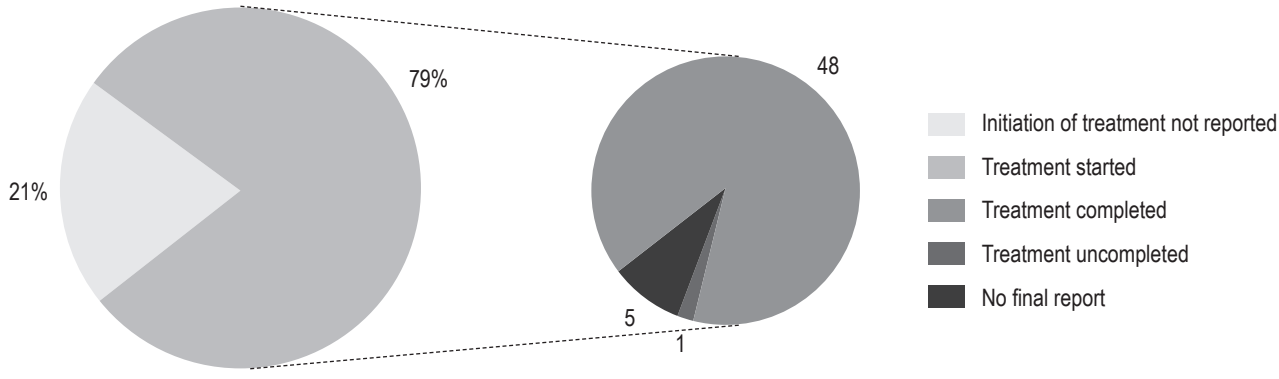


**Figure 3.** Status of treatment with direct-acting antivirals (n = 68).

**Table 4.** Adverse reactions to schemes with interferon, ribavirin and protease inhibitors (boceprevir or telaprevir)

| ADR | Medication | | | n | % |
|---|---|---|---|---|---|
| | BOC/peg-INF/RBV | peg-INF/RBV | TPV/peg-INF/RBV | | |
| **Systemic** | **37** | **42** | **7** | **86** | **39.8** |
| Asthenia | 8 | 9 | 2 | 19 | 8.8 |
| Adynamia | 7 | 7 | 1 | 15 | 6.9 |
| Fever | 5 | 5 | 1 | 11 | 5.1 |
| Muscle pains | 2 | 6 | | 8 | 3.7 |
| Headaches | 4 | 2 | | 6 | 2.8 |
| General malaise | 2 | 4 | | 6 | 2.8 |
| Hyporexia | 3 | 2 | | 5 | 2.3 |
| Chills | 2 | 1 | 1 | 4 | 1.9 |
| Coughing | 1 | 2 | | 3 | 1.4 |
| Flu symptoms | 1 | 1 | | 2 | 0.9 |
| Odynophagia | | 1 | | 1 | 0.5 |
| Polymyositis with elevated CK | | 1 | | 1 | 0.5 |
| Rhinorrhea | | 1 | | 1 | 0.5 |
| Dyspnea | | | 1 | 1 | 0.5 |
| Respiratory symptoms | 1 | | | 1 | 0.5 |
| Sinusitis | | | 1 | 1 | 0.5 |
| Weakness | 1 | | | 1 | 0.5 |
| **Hematological** | **36** | **9** | **12** | **57** | **26.4** |
| Neutropenia | 12 | 4 | 3 | 19 | 8.8 |
| Anemia | 13 | 1 | 3 | 17 | 7.9 |
| Leukopenia | 8 | 3 | 4 | 15 | 6.9 |
| Thrombocytopenia | 2 | | 1 | 3 | 1.4 |
| Pancytopenia | 1 | | 1 | 2 | 0.9 |
| Hematological alterations | | 1 | | 1 | 0.5 |
| **Gastrointestinal** | **10** | **9** | **2** | **21** | **9.7** |
| Nausea | 3 | 2 | | 5 | 2.3 |
| Epigastralgia | 3 | | | 3 | 1.4 |
| Gastroesophageal reflux | 1 | 2 | | 3 | 1.4 |
| Vomiting | 2 | 1 | | 3 | 1.4 |
| Diarrhea | 1 | | 1 | 2 | 0.9 |
| Loss of appetite | | 2 | | 2 | 0.9 |
| Dyspepsia | | 1 | | 1 | 0.5 |
| Belching | | 1 | | 1 | 0.5 |
| Other gastrointestinal symptoms | | | 1 | 1 | 0.5 |
| **Neuropsychiatric** | **11** | **8** | | **19** | **8.8** |
| Depression | 6 | 4 | | 10 | 4.6 |
| Insomnia | 1 | 1 | | 2 | 0.9 |
| Dysgeusia | 1 | | | 1 | 0.5 |
| Hypersomnia | | 1 | | 1 | 0.5 |
| Hypomania | | 1 | | 1 | 0.5 |
| Suicidal ideation | 1 | | | 1 | 0.5 |
| Anxiety | | 1 | | 1 | 0.5 |
| Irritability | 1 | | | 1 | 0.5 |
| Vertigo | 1 | | | 1 | 0.5 |

**Table 4.** Adverse reactions to schemes with interferon, ribavirin and protease inhibitors (boceprevir or telaprevir) (*continued*)

| ADR | Medication | | | n | % |
|---|---|---|---|---|---|
| | BOC/peg-INF/RBV | peg-INF/RBV | TPV/peg-INF/RBV | | |
| **Dermatological** | **9** | **2** | **6** | **17** | **7.9** |
| Itching | 4 | | 2 | 6 | 2.8 |
| Rash | 2 | 1 | 3 | 6 | 2.8 |
| Alopecia | 3 | | | 3 | 1.4 |
| Skin lesions | | 1 | 1 | 2 | 0.9 |
| **Misceláneos** | **4** | **4** | **4** | **12** | **5.6** |
| Anal pain | | | 3 | 3 | 1.4 |
| Canker sores | | | 1 | 1 | 0.5 |
| Weight gain | 1 | | | 1 | 0.5 |
| Dysphonia | | 1 | | 1 | 0.5 |
| Weight loss | | 1 | | 1 | 0.5 |
| Pleural pain | | 1 | | 1 | 0.5 |
| Phosphenes | 1 | | | 1 | 0.5 |
| Hemoptysis | | 1 | | 1 | 0.5 |
| Hyperbilirubinemia | 1 | | | 1 | 0.5 |
| Bleeding hemorrhoid | 1 | | | 1 | 0.5 |
| Endocrines | **1** | **2** | **1** | **4** | **1.9** |
| Thyroid disorders | | 2 | 1 | 3 | 1.4 |
| Increase in blood glucose | 1 | | | 1 | 0.5 |
| **Total** | **108** | **76** | **32** | **216** | **100.0** |

BOC: boceprevir; peg-INF: pegylated interferon; ADR: adverse drug reaction; RBV: ribavirin; POS: Telaprevir.

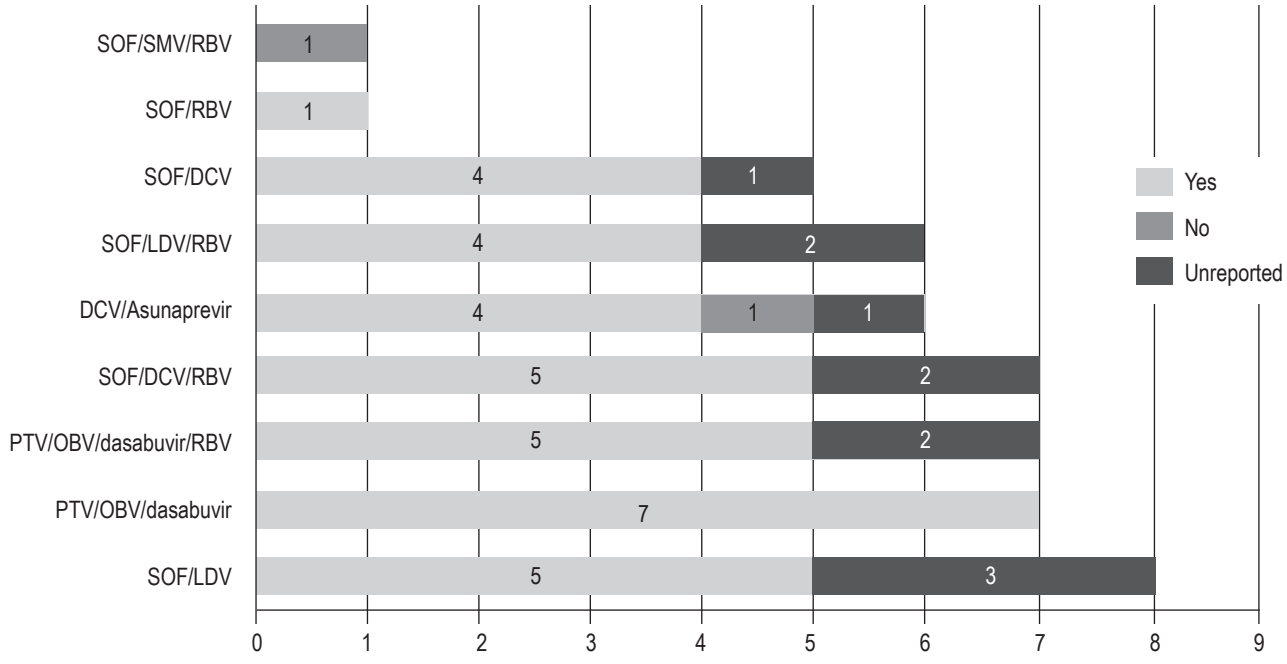


**Figure 4.** Scope of sustained viral response with Direct Action Antiviral schemes (n = 48). DCV: daclatasvir; LDV: ledipasvir; OBV: ombitasvir; PTV: paritaprevir; r: ritonavir; RBV: ribavirin; SMV: simeprevir; SOF: sofosbuvir.

**Table 5.** Patients with variants associated with resistance

| | VAR | Sex | Age | GT | Scheme | Weeks | SVR |
|---|---|---|---|---|---|---|---|
| 1 | L31V and Y93H: resistance to DCV, EBV, LDV, OBV, VEL | Female | 78 | 1b | DCV/asunaprevir | 24 | No |
| 2 | Y93N: resistance to DCV, ELB, LDV, OBV | Male | 78 | 1a | SOF/SMV/RBV | 12 | No |
| 3 | L31V: resistance to: DCV, EBV, LDV, OBV, reduced susceptibility to VEL Q80K: SMV resistance. | Female | 35 | 1a | SOF/LDV/RBV | 24 | Yes |

DCV: daclatasvir; EBV: elbasvir; GT: genotype; LDV: ledipasvir; OBV: ombitasvir; RBV: ribavirin; SVR: sustained virological response; SMV: simeprevir; SOF: sofosbuvir; VAR: variant associated with resistance; VEL: velpatasvir.

**Table 6.** Recorded adverse reactions to direct-acting antiviral treatment schemes

| ADRs \ Medication | SOF/DCV/ RBV | SOF/LDV/ RBV | DCV/ asunaprevir | PTV/OBV/r/ dasabuvir/ RBV | SOF/ DCV | SOF/ LDV | PTV/ OBV/r/ dasabuvir | n | % |
|---|---|---|---|---|---|---|---|---|---|
| **Systemic** | 7 | 3 | 4 | 1 | | | 1 | 16 | 43.2 |
| Asthenia | 2 | | 1 | | | | 1 | 4 | 10.8 |
| Flu symptoms | 1 | | 1 | 1 | | | | 3 | 8.1 |
| Headaches | 2 | 1 | | | | | | 3 | 8.1 |
| Lower limb pain | 1 | 1 | | | | | | 2 | 5.4 |
| Constitutional nonspecific symptoms | | 1 | | | | | | 1 | 2.7 |
| Arthralgia | | | 1 | | | | | 1 | 2.7 |
| Adynamia | | | 1 | | | | | 1 | 2.7 |
| Dizziness | 1 | | | | | | | 1 | 2.7 |
| **Hematological** | 4 | 2 | | | | | | 6 | 16.2 |
| Anemia | 4 | 2 | | | | | | 6 | 16.2 |
| **Neuropsychiatric** | 2 | 1 | 1 | | 1 | 1 | | 6 | 16.2 |
| Insomnia | 1 | | | | 1 | | | 2 | 5.4 |
| Depression | 1 | 1 | | | | | | 2 | 5.4 |
| Irritability | | | 1 | | | | | 1 | 2.7 |
| Alteration of immediate memory | | | | | | 1 | | 1 | 2.7 |
| **Gastrointestinal** | 1 | 2 | | 2 | | | | 5 | 13.5 |
| Diarrhea | 1 | | | 1 | | | | 2 | 5.4 |
| Nausea | | 1 | | | | | | 1 | 2.7 |
| Gastrointestinal symptoms | | | | 1 | | | | 1 | 2.7 |
| Dyspepsia | | 1 | | | | | | 1 | 2.7 |
| **Miscellaneous** | 1 | | | 1 | 1 | | | 3 | 8.1 |
| Hypotension | 1 | | | | | | | 1 | 2.7 |
| Weight loss | | | | | 1 | | | 1 | 2.7 |
| Mild indirect hyperbilirubinemia | | | | 1 | | | | 1 | 2.7 |
| **Dermatological** | | | 1 | | | | | 1 | 2.7 |
| Itching | | | 1 | | | | | 1 | 2.7 |
| **Total** | 15 | 8 | 6 | 4 | 2 | 1 | 1 | 37 | 100.0 |

DCV: daclatasvir; LDV: ledipasvir; OBV: ombitasvir; PTV: paritaprevir; r: ritonavir; ADR: adverse drug reaction; RBV: ribavirin; SMV: simeprevir; SOF: sofosbuvir.

None of the reported ADRs caused treatment discontinuation.

### Polypharmacy in Patients with Hepatitis C

Four or more medications in addition to anti-HCV schemes were used by 46.3% of the patients used (Table 7). No records of outpatient medications were found for 17.6% of the patients.

**Table 7.** Polypharmacy in patients with chronic hepatitis C (n = 108)

| Number of non-HCV medications | Frequency | % |
|---|---|---|
| <4 | 39 | 36.1 |
| 4-7 | 35 | 32.4 |
| 8-11 | 13 | 12.0 |
| >12 | 2 | 1.9 |
| No report | 19 | 17.6 |

## DISCUSSION

This is the first study of patients with HepC at the HPTU to look at the effectiveness and safety of DAAs. The distribution of HepC by sex and age was similar to that reported by Santos et al. Based on 1538 samples collected by referral laboratories in Colombia, they found an average patient age of 53 years (SD 14) with approximately 70% of patients between 40 and 70 years. (10) Genotype 1 and subtype 1b were found in 77.8% and 39.8% of the patients analyzed, respectively. According to Santos et al., they are the predominant genotype and subtype in Colombia. (10)

Advanced fibrosis/cirrhosis (F3-F4) was found in 39.8% of the patients with compensated cirrhosis in 77.5% of the cases in stage F4. An analytical cross-sectional study conducted in Cartagena for three months found that 50% of 41 patients had advanced cirrhosis/fibrosis, and 68% had compensated cirrhosis. (11) These differences may be due to the number of patients analyzed and to the short time within which information was collected in that study. The proportion of patients with cirrhosis was higher than that described by Hajarizadeh et al. (4-24%). (1) This can be explained by the level of complexity of the HPTU where patients with more advanced stages of disease are generally treated.

As in reports by other authors in Colombia and Latin America, blood transfusions constituted the main risk factor for contracting HCV. (12, 13) This result was expected since screening of blood donations for HCV in Colombia only began in 1993 and only reached 99% coverage in 1995. (14) Considering that the onset of cirrhosis begins 20 years after HCV exposure, the number of HepC diagnoses could increase over the next few years as the result of transfusions from before 1993. (1)

### Effectiveness of Antiviral Therapy

SVR was achieved by 46.9% of patients given peg-IFN which is within the range of 6% to 56% reported in the literature. (8) For genotype 1, the most common genotype in this group, the response rate can reach 50%. (15)

An SVR of 94.6% was found in the group of patients who finished treatment with DAA. The cause of therapeutic failure in the other 5.4% was found to be VAR to NS5A inhibitors. This is consistent with Buti et al. who found that 1% to 7% of patients treated with DAAs do not reach SVR. (16) Causes could be attributable to the patient, the treatment regimen and/or the virus. (17)

VARs are changes in the nucleotide sequence responsible for synthesis of the proteins that are molecular targets of DAAs. This ability to generate resistance, typical of viruses, is greater in HCV than in other viruses such as HBV and HIV. (17) The VARs found in this study were L31V and Y93H which target NS5A inhibitors. VARs related to the nucleotide analog NS5B sofosbuvir were not reported. This can be explained by its high genetic resistance barrier. (18)

Similar to reports by other authors, the SVR rates of patients with VAR to NS5A and without VAR to NS5A were similar in this study. (19) Some researchers disagree about the relationship of VAR and SVR, so they recommend determining these variants at baseline especially in cases that involve a null response prior to therapy. (17, 18) Current Colombian guidelines for managing HepC recommend analyses of resistance to NS3 and/or NS5A only for patients who have not achieved SVR. (20)

The most frequent VARs in genotype 1b are reported to be L31V/M and Y93H/N. Y93H results in high levels of resistance to drugs that act on NS5A. It is important to note that VARs to NS5A continue to be present as long as two years after the end of treatment, so it is essential to consider them before administering rescue therapy. (17)

### Safety of Antiviral Therapy

The availability of DAA has led to an improvement in the tolerability of treatment as in this study in which 25.9% of patients who received DAAs presented some type of ADR compared to 68.2% of those who received peg- INF. Although the analysis of the severity of ADRs was not the subject of this study, it was observed that patients with peg-INF/RBV had more severe ADRs especially hospitalizations due to anemia in which patients required blood products and infections associated with leukopenia or neutropenia.

We found that 39.8% of the patients who received peg-INF/RBV had systemic ADRs, especially asthenia, adynamia, fevers, myalgia and headaches. This is similar to reports the literature which show that these symptoms develop in 11% to 50% of cases, appear within a few hours following administration of medication, and have spontaneous remission from 24 hours to several days later. (21-25) Hematological ADRs are the most common of those due to peg-INF/RBV and are the main cause of low adherence rates, dose reductions and treatment discontinuation. (21, 22, 26) In this study, they occurred in 26.4% of the patients. They developed neutropenia and anemia which could be associated with bone marrow suppression by peg-IFN and RBV-induced extravascular hemolysis. (23, 27)

Systemic ADRs accounted for the largest portion (43.2%) of those that occurred in patients who received DAAs. They were followed by neuropsychiatric ADRs (16.2%), hematological ADRs (16.2%) and gastrointestinal ADRs (13.5%). Barrajón et. Al. reported very similar results in a retrospective analysis of 355 patients treated with DAAs. They found that 43.7% of their study population developed ADRs, mostly systemic (37.1%), gastrointestinal (18%) and neurological (15.8 %). (28) It can be inferred that the appearance of hematological and neuropsychiatric ADR swas related to the use of RBV combined with SOF/DCV or SOF/LDV. Development of anemia and depression occurred more frequently in these patiens than in those who did not receive RBV. Calleja et al. have also reported a high incidence of anemia (91%) in patients who received SOF/LDV/RBV. (7)

These results show that there are still cases in which the addition of RBV or peg-INF is necessary even though the use of DAA increases tolerability to antiviral treatment. This is especially true for patients previously exposed to interferon who present with cirrhosis which increases the risk of ADRs. (4, 20 , 28)

### Polypharmacy in Patients with HepC

Polypharmacy can be defined as the use of five or more daily medications. (29) Our study found that 46.3% of the patients were polymedicated. This can be explained by age (> 50 years) and HepC patients with coexisting diseases which required additional medications.

Polypharmacy can increase susceptibility to medication-related problems such as ADR, falls, hospital readmissions, and drug interactions. (29) This makes establishment of comprehensive health care programs that include pharmacotherapeutic follow-up imperative to prevent and resolve these medication-related problems.

## CONCLUSIONS

Characterization of patients with HepC treated at the HPTU during the study period found a similar distribution among men and women with higher prevalences between 40 and 70 years of age and with transfusions as the most frequent transmission mechanism. DAAs were safer and more effective than schemes with peg-IFN/RBV, but RBV is still necessary in cirrhotic patients with previous exposure to treatment, and this increases the risk of ADR.

There is a need to implement comprehensive patient-centered care with access to health services and medications throughout the course of treatment and appropriate pharmacotherapeutic follow-up. Similarly, prospective studies evaluating the safety and effectiveness of DAAs in patients with chronic HepC are needed.

## LIMITATIONS

This study has several limitations. Given its retrospective nature, it is directly dependent on the quality of information recorded in the electronic medical records. During data collection, incomplete records were detected which could diminish the quality of the study. Similarly, medical notes lacked uniformity indicating that the hospital's electronic medical records need to be standardized from the start to the end dates of treatment. Reports of viral loads, concomitant treatment and possible mechanisms of transmission all need to be recorded for adequate patient follow-up as well as for the national epidemiological report.

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### Conflicts of Interests

The authors declare that they have no conflicts of interest.

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# Clinical effectiveness of two esomeprazole presentations in a pilot trial

Carlos Arturo Rojas,[1*] Mario Sepúlveda Copete,[1] Jairo Alberto García Abadía,[1] Héctor Raúl Echavarría Abad,[2] Fernando Rosso Suárez,[3] Andrés Fernando Jiménez,[4] Andrés Mauricio Castro Llanos.[5]

1 Internist and Gastroenterologist in the Endoscopy Unit of Fundación Valle del Lili in Cali, Colombia
2 Surgeon and Gastroenterologist in the Endoscopy Unit of Fundación Valle del Lili in Cali, Colombia
3 Internist, infectologist, epidemiologist. Clinical Studies Coordinator at the Clinical Research Center of the Fundación Valle del Lili in Cali, Colombia
4 Director of Clinical Research, internist, epidemiologist and infectious disease specialist at the Clinical Research Center of the Fundación Valle del Lili in Cali, Colombia
5 Statistician at the Clinical Research Center of the Fundación Valle del Lili in Cali, Colombia

***Correspondence:** crojo16@yahoo.com.

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## Abstract

**Introduction:** This pilot studied the clinical effectiveness of two presentations of esomeprazole in patients with dyspepsia with undiagnosed causes. **Methods:** We conducted a pilot clinical trial of two 40 mg Esomeprazole presentations. Patients with dyspepsia of unknown cause at a gastroenterology clinic in a referral hospital were included. They received one or the other presentation daily for 28 days. Patients were initially evaluated with endoscopy and biopsy and received follow-up examinations at two and four weeks. Adverse events were recorded, and clinical symptom scales and quality of life questionnaires validated in Spanish (SODA and QoL-PEI) were used. In addition, gastric pH levels were measured continuously for 24 hours on day 14 of treatment. Serum levels of the medication administered were also measured on day 14 of treatment. A two-way repeated measures ANOVA was used to compare mean differences between the two groups. When significant differences in times were found, a Bonferroni correction was made. **Results:** A total of 33 patients were randomized into two groups: 16 patients in one group and 17 in the other. There were no differences in the percentages of gastric pH inhibition at day 14 of treatment ($p = 0.9795$). There were no differences in serum level concentrations on day 14 ($p = 0.2199$). No significant differences were found in severity and quality of life scales in the first two weeks of treatment. However, in the last two weeks of treatment the test product showed a larger decrease in pain ($p = 0.0048$) and superiority in compliance ($p = 0.01$) on the SODA subscale. There were no serious adverse events, and there were no statistical differences between the presentations of non-serious adverse events. **Conclusions**: The Test product and the Reference product showed similar effects on clinically relevant variables.

## Keywords

Esomeprazole, SODA; QoL-PEI, proton pump inhibitors, dispepsia.

## INTRODUCTION

Dyspepsia is defined as chronic and recurring pain or discomfort in the central part of the upper abdomen. (1) According to the criteria of the ROMA IV consensus, there are two types. The first has a defined organic cause while the second has no specific cause and is called functional dyspepsia (FD). FD is considered to be due to physiological alterations, immunological alterations, hypersensitivity and/or brain-intestine interactions. In addition, it is associated with daily eating and life style habits and may be related to Helicobacter pylori infections which are of great importance in our environment due their prevalence of approximately 60%. (2-4)

Fifteen to forty percent of the world's population are thought to have dyspeptic symptoms, and of these, 70% are idiopathic. The annual incidence of dyspepsia is approximately 1%, and it is estimated that 50% of people will consult a physician because of these symptoms at some point in their lives. (1-3)

The negative impact of dyspepsia on the quality of life has encouraged the development of assessment scales for measuring severity, disability and alterations of daily life. There are two instruments that have been validated in

 

Spanish: the SODA (Severity of Dyspepsia Assessment) scale which assesses the intensity of pain, associated symptoms and level of compliance, and the Dyspepsia Related Health Scale (DRHS) which determines the impact that this disease has on daily life. (4-11)

Part of standard dyspepsia management focuses on control of gastric acid. Proton pump inhibitors (PPIs), one of the main classes of drugs used for this purpose, have been widely used to treat both FD and organic dyspepsia. (1, 5-8) Esomeprazole, a PPI, is indicated for relief of gastrointestinal symptoms, healing of gastric lesions, and maintenance of healing. (5) Esomeprazole improves dyspeptic symptoms through several mechanisms. First, patients with dyspepsia are hypersensitive to duodenal acid. Second, patients with dyspepsia have low-grade inflammation that is worsened by acid secretion. Inhibition of gastric acid secretion by esomeprazole modifies these effects.

Controlled release forms of esomeprazole have been developed to improve absorption and bioavailability thus avoiding early chemical degradation which limits effectiveness. NEXIUM-MUPS®, developed by AstraZeneca, includes a system that uses a Multiple-Unit Pellet System (MUPS) that releases micropellets of the PPI as the tablet disintegrates. In Colombia, an esomeprazole formulation has been developed that uses a polymer coating that resists acid as the tablets pass through the gastric acid medium. They disintegrate when they reach the less acidic pH (pH> 4.5) of the proximal portion of the duodenum.

The objective of this study was to compare clinical responses to these two formulations of esomeprazole by evaluating serum concentrations in the first hour after intake and measuring efficacy due to the increase in gastric pH at 24-hour follow-ups. The SODA and DRHS scales were used to assess patients' clinical evolution and clinical safety related to adverse events of special-release esomeprazole therapy and reference esomeprazole therapy. Doses of 40 mg/day of all medications were used in dyspeptic patients in whom organic causes of dyspepsia had not been proven.

## MATERIALS AND METHODS

A blinded two-arm, randomized, controlled trial was conducted to compare 40 mg/day doses of two different presentations of esomeprazole for 28 days. The study population consisted of the patients with abdominal and digestive symptoms suggestive of dyspepsia who came to the gastroenterology clinic at Fundación Valle del Lili between July 2016 and March 2017, and who had not undergone previous diagnostic studies. Patients who were older than 18 years with a final diagnosis of previously unstudied dyspepsia were included. Exclusion criteria included unexplained weight loss; dysphagia; anemia; bleeding; jaundice; history of gastric surgery; neoplasms; erosive esophagitis; pregnancy; lactation; known allergy to esomeprazole; use of nonsteroidal anti-inflammatory drugs (NSAIDs), PPIs or drugs with potential interactions within the two weeks prior to coming to the clinic, and prior endoscopic diagnosis of alkaline pH, digestive ulcers or malignancy.

This study was carried out at the Fundación Valle del Lili in accordance with the 2013 Helsinki Declaration, the International Conference on Harmonization (ICH) Good Clinical Practice (GCP) Guideline, Colombian Resolution 8430 of 1993 and Resolution 2378 of 2008, and the Guidelines for good clinical practice. The study was approved by the biomedical research ethics committee, and each participant consented to the study. The subjects were not compensated for their participation. This study has been included in the International Clinical Trials registry.

We sought to include at least 30 volunteers in each group in this pilot clinical trial to test normal distribution. However, due to recruitment problems, only 16 patients were included in one group and 17 patients in the other group.

The study began with screening upper endoscopies of volunteers which included routine biopsies and measurement of gastric pH an Inolab 7110® pH meter and staining with Congo red and Litmus paper to exclude patients with pH> 4 which is suggestive of hypochlorhydria. After screening, patients were randomly assigned to the two groups. One group received modified-release esomeprazole from Technochemicals (test esomeprazole), and the other group received NEXIUM-MUPS® from AstraZeneca (reference esomeprazole). Both products are registered and marketed in Colombia for the indication used in this study. The randomization sequence was performed with Randomization® software which created blocks of six participants. (12) Security envelopes relating the participant's code and the group to which s/he was assigned were then created.

The attending physician and the research team were blind to the randomized drug throughout the study. Since the presentations of the medications were different, it was not possible to ensure the blinding of the study subjects. The treatment provided on the day of recruitment consisted of twenty-eight 40 mg tablets of esomeprazole to be taken daily at least 30 minutes before breakfast for 28 day. Patients were required to keep a daily log. Follow-up visits were scheduled at 2 and 4 weeks to evaluate study outcomes (Figure 1).

The two week follow-up also evaluated the impact on gastric pH of treatment with esomeprazole by means of 24 hour ambulatory pH monitoring with Versaflex® Z dual pH sensor catheters with 8 impedance rings. Data was was stored on a digitraper pH Z Given® Imagin device and subsequently downloaded and analyzed with the Accuview® pH-Z 5.2 program.

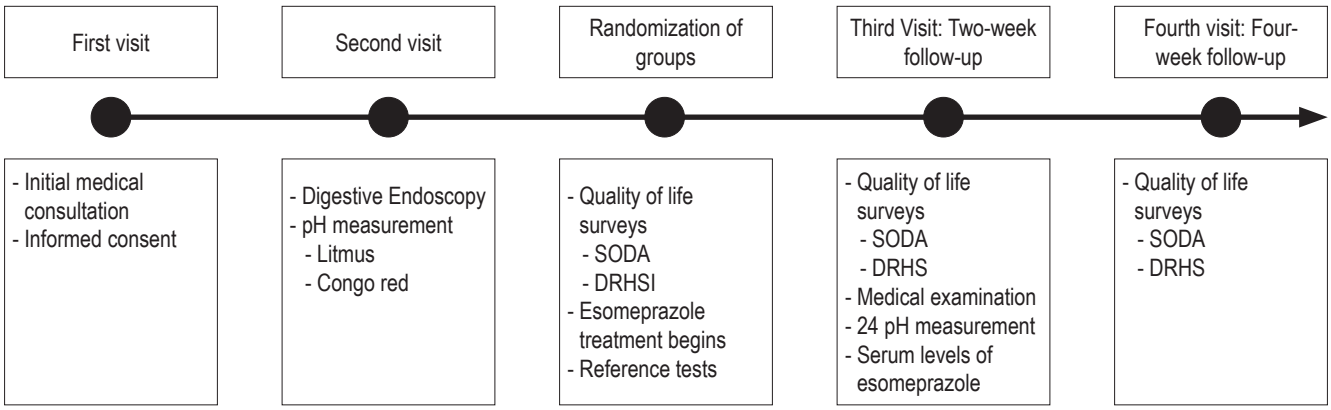


**Figure 1.** Distribution of clinical trial activities

We decided to take drug serum levels on day 14 of treatment as a measure that could be correlated to pH measurement and clinical outcomes. Two weeks after each patient started treatment, a five ml sample of venous blood was taken within the first hour after the patient took her/his daily dose of esomeprazole. This was sufficient time to guarantee esomeprazole concentrations in the blood at equilibrium. Plasma was frozen at -20° C. Subsequently, the sample was analyzed with a UHPLC Lachrom Ultra-VWR liquid chromatograph whose diode array detector was used to determine serum esomeprazole levels.

The SOSA and DRHS surveys and assessment scales were used for clinical evaluations on the day of recruitment and at subsequent follow-up visits at two and four weeks after the start of treatment. The version of SODA validated by the Benites et al. was used together with the score adjustment for balancing subscales suggested and applied by Rabeneck et al. (10, 11) For analysis, it was divided into subscales of pain intensity, associated non-painful symptoms such as belching, heartburn, and swelling, and level of compliance. The first two subscales express greater severity at higher scores while the third expresses a higher level of perceived well-being at higher scores. DRHS was used with the same methodology and at the same times as the SODA scale, but a single global score in which greater severity of symptoms is expressed at higher scores was used. Unlike SODA, one of the components of DRHS scores reflects disability associated with pain. (9)

Clinical safety was monitored at each visit through analysis of patient's daily logs in which they recorded any associated symptoms and adverse events during treatment.

### Statistical Analysis

All participant information was uploaded into a database on the BD Clinic® platform. The descriptive analysis expressed continuous variables as means and standard deviations (SD) or medians and interquartile ranges (IQR). They were compared with a Student's T test or the or Mann-Whitney test depending on whether the assumption of normality was fulfilled. Categorical variables were presented in proportions and correlated with the chi square ($\chi 2$) test or Fisher's exact test depending on the observations.

Subsequently, analysis of variance (ANOVA) of two factors (drug-time) with 99 repeated measurements was performed with the clinical scales to establish differences. Upon finding significant differences in the times for the main effect of ANOVA, pairwise comparison was performed using Bonferroni correction for multiple comparisons. Analyses were performed with STATA statistical package 12.1.

## RESULTS

A total of 205 patients were screened, 55 were recruited, and the final overall sample included 33 patients. The main cause of exclusion was gastric pH suggestive of hypochlorhydria (Figure 2). (13) During follow-up, two participants who could not perform pH-metrics were excluded from the analysis.

The comparison of baseline sociodemographic and clinical characteristics, summarized in Table 1 found no significant differences between the groups. The average serum concentration of the test esomeprazole was 0.67 μmol/L (0.18-1.61) and that of the reference esomeprazole was 0.28 μmol/L (0.16-0.53) but the difference was not statistically significant ($p = 0.219$). Similarly, the comparison of inhibition of acid secretion to a constant gastric pH> 4 showed an average time for the test esomeprazole of 19.98 h (SD ± 3.87 [83.3%]) and 19.95 h (SD ± 3.55 [83.2%]) for reference esomeprazole, $p = 0.986$.

Statistically significant differences were found for both survey scales at four weeks of treatment, and the pain inten-

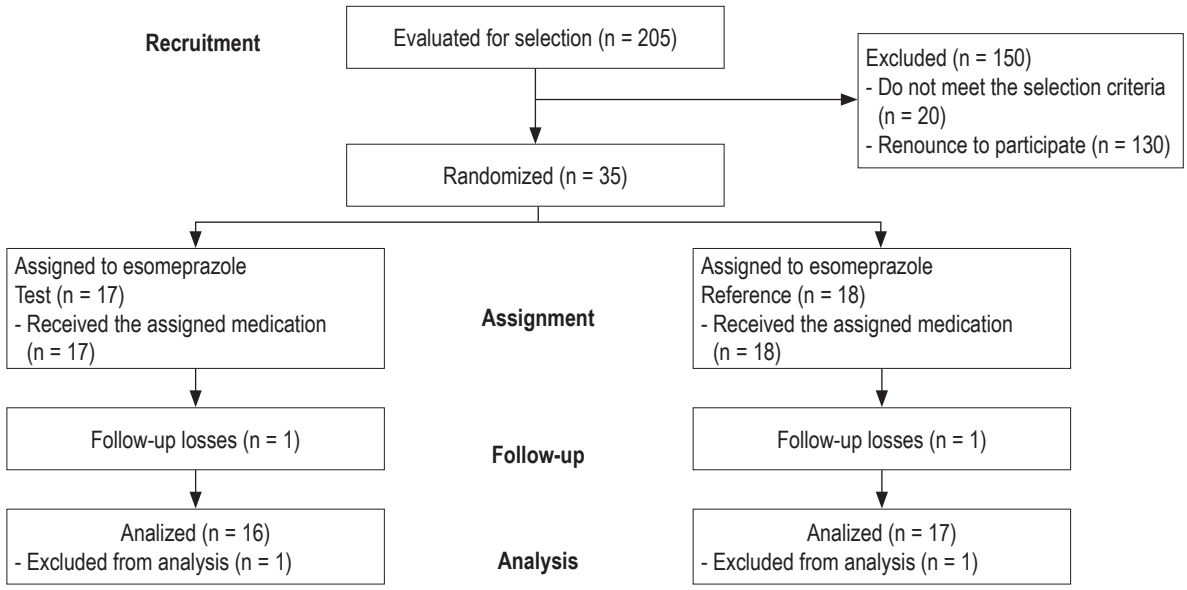


**Figure 2.** Flowchart of participants from recruitment between July 2016 and April 2017 through to the end of the clinical trial.

sity subscale scores decreased more for the test esomeprazole than they did for the reference esomeprazole. Similarly, improvement in compliance was more noticeable in the test product than in the reference product (Table 2). These trends were repeated the two factor ANOVA which found differences in the time variable, but only for interaction in the pain subscale. Differences in the compliance subscale were found between treatments ($p = 0.012$) (Table 3). The Bonferroni adjustment found that there are significant differences ($p < 0.05$) between the start and end time of the treatment at 4 weeks in the SODA subscales and the DRHS scale independently for each type of esomeprazole. However, the SODA pain subscale found no significant differences in this time ($p = 0.018$).

The proportion of patients who experienced adverse events during the study was similar for both groups. At four weeks, it was 6.3% for the group who received the test drug (Tecnoquímicas esomeprazole) and 5.9% for the group who took the reference drug (AstraZeneca esomeprazole) ($p = 0.999$). There were no serious adverse effects and all adverse effects had resolved before the end of the study. All of these adverse effects are among those referred to in the technical sheets as being associated with the use of esomeprazole and include nausea, dry mouth, belching and flatulence.

## DISCUSSION

Serum concentrations measured in our patients varied considerably, similar to measurements of serum concentrations reported in the literature. These variations may be due to the designs of special release presentations, time of administration, physiological conditions at the time of drug use, and to varying abilities of individuals to metabolize PPI according to polymorphisms in their enzymes, especially CYP2C19. (6, 14-20)

Both drugs effectively increased gastric pH by inhibiting 83% of acid production which is at the upper limits of figures reported in similar studies which range from 50% to 85%. The minimum inhibition value in our study was 50% which is within the established range for clinical impact. (7, 8, 14, 15). There were no differences in esomeprazole serum levels at day 14 which may partly explain this finding. However, serum levels do not necessarily correlate with intracellular levels.

Significant decreases were observed in the SODA scores of both drugs. The pain subscale for Tecnoquímicas esomeprazole fell 20.8 points while that of the AstraZeneca esomeprazole fell 12.8 points. These decreases were slightly higher than those reported by Benites et al., who described decreases of 7 points. However, measurement of symptoms not associated with pain decreased only around 2.5 points, similar to the findings of Benites et al. Similar behavior to our findings and those of Benites et al., another similar study by Rabeneck et al. found that the greatest impact was on the pain subscale. They concluded that this result was possible because of effective control of gastric acid, which is the main cause of the sensation of pain, and that questions about compliance are associated with pain control. In rela-

**Table 1.** Comparison of baseline sociodemographic and clinical characteristics between groups: test esomeprazole (n = 16) and reference esomeprazole (n = 17)

| Variable | Overall | Test Esomeprazole | Reference Esomeprazole | *p* |
|---|---|---|---|---|
| Sex | **n = 33** | **n = 16** | **n = 17** | |
| Male, n (%) | 8 (24.2) | 4 (25) | 4 (23.5) | 1 |
| Female, n (%) | 25 (75.8) | 12 (75) | 13 (76.5) | |
| Age* | 38.2 ± 12.7 | 37.6 ± 11.4 | 38.8 ± 14.2 | 0.7919 |
| pH meter** | 1.81 (1.61-1.94) | 1.7 (1.5-2.04) | 1.85 (1.65-1.9) | 0.6266 |
| Litmus pH measurement* | 1.9 ± 0.68 | 1.8 ± 0.72 | 1.9 ± 0.66 | 0.7844 |
| Congo red pH measurement pH <4 | 33 (100) | 16 (100) | 17 (100) | - |
| Presence of H. pylori | **n = 33** | **n = 16** | **n = 17** | |
| Yes, n (%) | 22 (66.7) | 8 (50) | 14 (82.4) | 0.071 |
| No, n (%) | 11 (33.3) | 8 (50) | 3 (17.6) | |
| Antral distribution of H. pylori (n = 22) | **n = 22** | **n = 8** | **n = 14** | |
| Abundant, n (%) | 13 (39.4) | 4 (25) | 9 (52.9) | |
| Moderate, n (%) | 2 (6.1) | 1 (6.25) | 1 (5.9) | 0.831 |
| Low, n (%) | 7 (21.2) | 3 (18.75) | 4 (23.5) | |
| Distribution of H. pylori in the corpus (n = 22) | **n = 22** | **n = 8** | **n = 14** | |
| Abundant, n (%) | 9 (27.3) | 3 (18.75) | 6 (35.3) | |
| Moderate, n (%) | 4 (12.1) | 1 (6.25) | 3 (17.6) | 0.858 |
| Low, n (%) | 6 (18.2) | 3 (18.75) | 3 (17.6) | |
| Absent, n | 3 (9.1) | 1 (6.25) | 2 (11.8) | |
| Diagnosis from antral biopsy | **n = 33** | **n = 16** | **n = 17** | |
| Chronic non-atrophic chronic gastritis | 28 (84.8) | 13 (81.25) | 15 (88.2) | |
| Severe chronic gastritis without atrophy | 2 (6.1) | 1 (6.25) | 1 (5.9) | 0.794 |
| Chronic gastritis with atrophy | 3 (9.1) | 2 (12.5) | 1 (5.9) | |
| Diagnosis from biopsy of corpus | **n = 33** | **n = 16** | **n = 17** | |
| Chronic non-atrophic chronic gastritis | 31 (93.9) | 15 (93.75) | 16 (94.1) | |
| Severe chronic gastritis without atrophy | 1 (3) | 0 (0) | 1 (5.9) | 1 |
| Chronic gastritis with atrophy | 1 (3) | 1 (6.25) | 0 (0) | |
| Percentage of time pH> 4 (n = 33) | 88.2 (71.2-95.6) | 88.3 (71.3-97.05) | 87.3 (75.7-91.7) | 0.4594 |
| Adverse events | | | | |
| T1, two weeks | 5 (15.2) | 1 (6.3) | 4 (23.5) | 0.335 |
| T2, four weeks | 2 (6.1) | 1 (6.3) | 1 (5.9) | 1 |

* Mean ± SD. ** Median (IQR)

tion to compliance, we observed that the test esomeprazole had a higher final score for clinical improvement than did the reference esomeprazole. On average, scores improved nine points at the first follow-up and an 5.2 points at the second follow-up ($p = 0.0035$). These increases were also higher than those reported by Benites et al., which were 2.5 points in their study population. (10, 11)

The general frequencies of adverse events at four weeks in this study was 6.3% for the test esomeprazole and 5.9% for the reference esomeprazole. These frequencies are much lower than those found by Shin et al., who reported 40% in a sample of 36 patients, but the two studies are in agreement in that neither found any serious adverse events. This has also been described in various publications which have found that, when use is not prolonged, these drugs' have good pharmacological safety profiles. (14-21).

One limitation of this present study was that diagnostic means other than clinical and endoscopic examinations were not used even though ultrasound and laboratory tests could have ruled out other causes of dyspepsia. Although

**Table 2.** Comparison of drugs between independent times: time 0 = time of recruitment, time 1= 2 week follow-up, time 2 = 4 week follow-up.

| SODA Scale** and DRHS Scale*** Overall | General n = 33 | Esomeprazole TEST DRUG n = 16 | Esomeprazole AZ n = 17 | *p* |
|---|---|---|---|---|
| **SODA Pain intensity * (Range 2-47)** | | | | |
| Time 0 (without treatment) | 25.8 ± 5.5 | 24.4 ± 6.4 | 27.2 ± 4.4 | 0.1603 |
| Time 1 (2 weeks of treatment) | 19.5 ± 6.2 | 19.75 ± 7.15 | 19.3 ± 5.4 | 0.8376 |
| Time 2 (4 weeks of treatment) | 16.6 ± 9.8 | 12.18 ± 9.3 | 20.8 ± 8.5 | **0.0087** |
| **SODA Intensity associated symptoms* (Range 7-35)** | | | | |
| Time 0 (without treatment) | 17.8 ± 2.7 | 17.6 ± 1.8 | 18 ± 3.3 | 0.6911 |
| Time 1 (2 weeks of treatment) | 14.1 ± 2.9 | 13.9 ± 2.9 | 14.3 ± 2.9 | 0.7273 |
| Time 2 (4 weeks of treatment) | 13.9 ± 4.04 | 12.7 ± 3.9 | 15 ± 3.9 | 0.1118 |
| **SODA Compliance Level * (Range 2-23)** | | | | |
| Time 0 (without treatment) | 7.4 ± 3.2 | 8.2 ± 3.1 | 6.7 ± 3.3 | 0.2113 |
| Time 1 (2 weeks of treatment) | 12.1 ± 5.1 | 12.7 ± 5.6 | 11.5 ± 4.7 | 0.5046 |
| Time 2 (4 weeks of treatment) | 14.5 ± 5.5 | 17.2 ± 5.2 | 11.9 ± 4.4 | **0.0035** |
| **DRHS* (range 12-120)** | | | | |
| Time 0 (without treatment) | 65.5 ± 17.3 | 64 ± 17.3 | 66.8 ± 17.69 | 0.6401 |
| Time 1 (2 weeks of treatment) | 38.6 ± 13.4 | 37.5 ± 13.54 | 39.58 ± 13.58 | 0.6616 |
| Time 2 (4 weeks of treatment) | 39.7 ± 18.5 | 32.68 ± 14.2 | 46.29 ± 19.32 | **0.029** |

* Average ± SD Two-sample t test. ** Severity of dyspepsia assessment. *** Quality of life associated with intestinal problems questionnaire.

**Table 3.** Comparison between drugs by means of two factor ANOVA of repeated measures: time 0 = time of recruitment, time 1= 2 week follow-up, time 2 = 4 week follow-up.

| SODA** and DRHS*** two factor ANOVA of repeated measures | | | | | | | |
|---|---|---|---|---|---|---|---|
| **Scale** | **Drug** | **Time 0** | **Time 1** | **Time 2** | **trt** | **time** | **trt#time** |
| SODA pain | Test Drug* | 24.4 ± 6.4 | 19.75 ± 7.15 | 12.18 ± 9.3 | 0.0623 | **0** | **0.0048** |
| | Reference Drug* | 27.2 ± 4.4 | 19.3 ± 5.4 | 20.8 ± 8.5 | | | |
| SODA associated symptoms | Test Drug* | 17.6 ± 1.8 | 13.9 ± 2.9 | 12.7 ± 3.9 | 0.2215 | **0** | 0.2973 |
| | Reference Drug* | 18 ± 3.3 | 14.3 ± 2.9 | 15 ± 3.9 | | | |
| SODA compliance | Test Drug* | 8.2 ± 3.1 | 12.7 ± 5.6 | 17.2 ± 5.2 | **0.012** | **0** | 0.0968 |
| | Reference Drug* | 6.7 ± 3.3 | 11.5 ± 4.7 | 11.9 ± 4.4 | | | |
| DRHS | Test Drug* | 64 ± 17.3 | 37.5 ± 13.54 | 32.68 ± 14.2 | 0.1572 | **0** | 0.1357 |
| | Reference Drug* | 66.8 ± 17.69 | 39.58 ± 13.58 | 46.29 ± 19.32 | | | |

* Average ± SD. ** Severity of dyspepsia assessment. *** Quality of life questionnaire associated with intestinal problems.

dyspepsia is very prevalent, diagnosis and screening to exclude patients with organic dyspepsia is complex.

On the other hand, the statistical power of this pilot study at the time of closure was low. A representative sample for this pathology with a prevalence of 10% to 30% of the general population would have required at least 1500 patients to attain a statistical power of 80%. (22, 23) Also, the follow-up time and effectiveness in the study was four weeks, so our data cannot be extrapolated to clinical situations involving longer use of these medications. In addition, patients could not be blinded to the medication they were taking which may have introduced selection bias into our study.

We conclude that the two presentations of esomeprazole had very similar outcomes of interest in terms of increasing pH and answers to symptom questionnaires. No significant differences were observed in the evolution of the clinical assessment scales for the two treatments, but the effect of the test esomeprazole was better sustained over time than was that of the reference esomeprazole. This difference was statistically significance. It could be that this difference was

secondary to the greater number of positive cases for H. pylori in the reference esomeprazole group, although this difference was not statistically significant difference (p = 0.071). Both presentations of esomeprazole demonstrated that risks of use are very low for a four week course of administration in the population studied.


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## Conflicts of Interest

The authors declare that they have no conflicts of interest.


## Funding Sources

Tecnoquímicas.


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# The role of antispasmodics in managing irritable bowel syndrome

Valeria Atenea Costa Barney,[1*] Alan Felipe Ovalle Hernández.[1]

[1] Internal Medicine and Gastroenterology specialist in San Ignacio University Hospital, Pontificia Universidad Javeriana, Bogotá, Colombia.

***Correspondence:** atenea.costa@gmail.com

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**Abstract**
Although antispasmodics are the cornerstone of treating irritable bowel syndrome, there are a number of antispasmodic medications currently available in Colombia. Since they are frequently used to treat this disease, we consider an evaluation of them to be important.

**Keywords**
Antispasmodic, irritable bowel syndrome, pinaverium bromide, otilonium bromide, Mebeverin, trimebutine.

## INTRODUCTION

Irritable bowel syndrome (IBS) is one of the most frequent chronic gastrointestinal functional disorders. It is characterized by recurrent abdominal pain associated with changes in the rhythm of bowel movements with either or both constipation and diarrhea. Swelling and bloating are frequent occurrences. (1)

IBS is divided into two subtypes: predominance of constipation (20-30% of patients) and predominance of diarrhea (20-30% of patients). When both constipation and diarrhea are combined, it is called mixed IBS (up to 45% of patients) and IBS of undetermined type when the pattern of bowel movements is intermediate and cannot be classified as diarrhea or constipation. It is noteworthy that abdominal pain occurring more than once a week plus the temporal relationship of pain with defecation are what theoretically differentiates IBS from functional constipation. (2, 3)

According to the Rome IV criteria, IBS is diagnosed by abdominal pain that recurs at least one day a week plus two or more of the following: pain is associated with defecation; pain is related to a change in the frequency of bowel movements; and/or pain is related to a change of stool consistency. The criteria must be met for three consecutive months prior to diagnosis and symptoms must have started a minimum of six months before diagnosis. (3, 4)

There are no known structural or anatomical explanations of the pathophysiology of IBS and its exact cause remains unknown. Nevertheless, several mechanisms have been proposed. Altered gastrointestinal motility may contribute to changes in bowel habits reported by some patients, and a combination of smooth muscle spasms, visceral hypersensitivity and abnormalities of central pain processing may explain abdominal pain, which is an essential part of the complex of symptoms. (5)

It is estimated that IBS affects 11% of the world's population. In Europe, Asia and the United States its prevalence varies from 10% to 20%. The lowest prevalence in South Asia (7%) while the highest is in South America (21%). In Western countries it is twice as frequent in women. (6) IBS has a significant impact on health-related quality of life, results in lower labor productivity, higher absenteeism and increased use of health care with its attendant costs. In 2005, direct medical costs attributed to IBS in the United States were estimated at USD 1.5 to 10 billion per year. (1) IBS can also affect the doctor-patient relationship since

 

ineffective control of symptoms can decrease the credibility of doctors and encourage the patient to seek additional opinions. (7)

A heterogeneous group of medications called antispasmodic or spasmolytic drugs has been used in IBS therapy for decades. They act as direct smooth muscle relaxants (papaverine, mebeverin, peppermint oil), anticholinergic agents (butylscopolamine, hioscin, cimetropium bromide, pyrenzepine) or calcium channels blockers (alverine citrate, ethyl bromide, pinaverium bromide). Their goal is to reduce symptoms caused by defecation through increasing colonic transit time, improving stool consistency and/or reducing stool frequency. (2) The pharmacological action of these agents is not always clear, and their mechanisms are often mixed. However, metaanalyses of studies comparing antispasmodics with placebos or other treatments have consistently confirmed the positive effects of these drugs, and their side effect profiles have been excellent. (8)

## PATHOPHYSIOLOGY

The pathogenesis of IBS is considered to be multifactorial. A history of gastrointestinal infections, colonic or bacterial flora of an altered small intestine, increased intestinal permeability and immune activation may all play roles in the development of the disease. (9) Signals from the gastrointestinal tract are processed in the brain and can influence motility, secretion and immune function. The brain-gut axis is essential for regulation of the gastrointestinal system, so structural or functional alteration can lead to the development of disorders such as IBS. (10) Consequently, psychological factors and chronic stress may also be involved in triggering symptoms. (11)

Abnormal intestinal motility and visceral hypersensitivity remain the main factors in the pathogenesis of the disease. (12) Intraluminal factors such as serine proteases may increase colonic permeability of IBS patients by activating the protease-activated receptor-2. This results in visceral hypersensitivity. (13) Similarly, luminal cysteine proteases have been shown to increase colonic permeability through degradation of binding proteins resulting in visceral hypersensitivity possibly secondary to local microinflammation. (14) Immune activation of the colonic mucosa has been found to be significantly greater in IBS patients than in healthy controls. (15) In addition, mast cells have been implicated in the development of IBS. One study found that the number of mast cells in the colonic mucosa and the amounts of trypsin and histamine they released were markedly higher in IBS patients than in controls. (16) Mast cells in the vicinity of nerve endings has been significantly correlated with the severity and frequency of abdominal pain and discomfort in IBS patients. Enterochromaffin cells also play an important role in the development of visceral hypersensitivity because they produce and release serotonin which activates 5-HT3 receptors located in afferent sensory neurons. (17)

Abnormalities in colonic motility patterns are characterized by hyperreactivity due to prolonged increase of colonic motor activity after meals, increased motor activity in response to stressors or cholecystokinin (CCK), and increased motor response to abdominal distention. (18)

Visceral hypersensitivity alone is not painful, but it can cause abdominal pain in IBS patients due to the effect of any intense stimulus such as an exaggerated contraction of the colon. (19) Nevertheless, it has not been possible to establish a clear relationship between visceral hypersensitivity and motility disorders, and these two factors have generally been considered to be independent, and both require effective treatment. (20)

### Voltage Dependent Calcium Channels

Voltage-dependent calcium channels play a fundamental role in the intestine and in pharmacological management of IBS. These ionic channels mediate calcium influx in response to membrane depolarization, and they regulate intracellular processes such as contraction, secretion and neurotransmission in a variety of cells. (21) Calcium channels are classified by their properties and pharmacology. They include L-type calcium channels (long duration). They are high conductance channels that produce long-lasting depolarization and which are inhibited by dihydropyridine derivatives (DHP). (22, 23) Currents associated with this type of channel are important for muscle and endocrine cells in which contraction and secretion of substances are mediated. (21)

Type N (neuronal) currents are also durable, but require strongly negative potentials for complete elimination of inactivation and strong depolarization for activation. (23) Three other channels have been identified in Purkinje cells. Type P currents are blocked by low concentrations of ω-agatoxin, while type Q only responds to high concentrations. Residual currents, which were resistant to all known calcium blockers at the time of their discovery, were called type R (resistant). Type T (transient) voltage-dependent calcium channels are characterized by small and transient conductance activated by weak depolarization. (23) These currents are responsible for modulating the action potential and the performance of pacemakers.

In the 1980s DHP antagonists became the first calcium antagonists to be used medically. They block L channels and are used to treat hypertension by exploiting their properties as vasodilators. (22) Calcium antagonists have no effect on skeletal muscle, but they can have some influence

on heart muscle through reduction of activity and conduction of pacemakers. Because IBS includes abnormal gastrointestinal motility, calcium antagonists used for cardiovascular disease appear to have potential for relieving symptoms by relaxing the smooth muscles of the colon. Nicardipine, which has spasmolytic properties, was proposed as a possible IBS treatment in the late 1980s. (24) However, cardiovascular side effects have seriously limited the application these calcium antagonists. This led researchers to search for other substances that act selectively within the gastrointestinal tract.

## ANTI-SPASMODIC DRUGS

These medications act by inhibiting the action of acetylcholine on muscarinic receptors or by blocking calcium channels in the gastrointestinal smooth muscle. As a class, antispasmodics have been used in the treatment of IBS for many years. They treat the subgroup of IBS patients who have abnormal contractility of the gastrointestinal smooth muscle and altered gastrointestinal transit which contribute to pain and altered bowel habits. (25)

### Otilonium Bromide

Otilonium bromide's structure consists mainly of quaternary ammonium, so it is weakly absorbable from the gastrointestinal tract. Experimental studies show that it accumulates in the walls of the gastrointestinal tract after oral administration and is almost completely excreted in feces. (25) Otilonium bromide not only blocks L-type and T-type calcium channels, but also the M1, M2, M4 and M5 muscarinic receptors. The antagonistic effects of otilonium bromide on the M3 coupled calcium signaling pathway in human colonic crypt cells suggests antisecretory action in patients who have the diarrhea type of IBS. Antagonism of neuroquinine-2 receptors (NK-2) also causes spasmolysis while reducing peripheral sensory afferent transmission to the central nervous system, possibly contributing to greater efficacy. (26, 27) These effects suggest that otilonium bromide may be effective at reducing spasms and abdominal pain, the two main symptoms of IBS. (2)

Otilonium bromide has been evaluated for management of abdominal pain in IBS patients in a clinical trial. Patients diagnosed according to the Rome II criteria were randomly assigned to case and control groups. They received either 40 mg of ethyl bromide or a placebo three times a day for 15 weeks. Patients who took otilonium bromide had less frequent pain, bloating and bowel movements than did the control patients who took placebos. The outstanding result of this study was that otilonium bromide significantly reduced the frequency of abdominal pain from more than half of the days to less than one day per week while the patients who took placebos continued to have one to three episodes per week. During the 10-week follow-up period after the end of treatment, the likelihood of recurrence of symptoms was significantly higher in the placebo group than in the otilonium bromide group. (28, 29) This finding may be explained by the prolonged persistence of ethyl bromide in the colon wall due to its lipophilic properties. (25)

Among the most commonly reported side effects associated with the use of ethyl bromide are dry mouth, nausea, and dizziness. These may be caused by peripheral and central muscarinic antagonism and may be explained by the known ability of otilonium to bind muscarinic receptors. (27)

Otilonium bromide has been evaluated in 5 randomized controlled studies which included a total of 791 patients. (29-33) A metaanalysis found evidence of a beneficial effect [risk ratio (RR) = 0.70, 95% confidence interval (CI): 0.54-0.90; number needed to treat (NNT): 5, 44% CI, p = 0.13], but there was borderline heterogeneity among study results ($I^2$ = 44%, p = 0.13). The Colombian Association of Gastroenterology (Asociación Colombiana de Gastroenterología - ACG) clinical practice guidelines strongly recommends the use of ethyl bromide for increasing the frequency of overall improvement of symptoms in IBS patients but the quality of evidence is still low.

### Pinaverium Bromide

Pinaverium bromide, a derivative of quaternary ammonium, is poorly absorbed and has pronounced pharmacological effects in the gastrointestinal tract rather than in cardiovascular system. (34) Its gastrointestinal absorption rate is low and is characterized by hepatobiliary excretion. (35) Its effects are very similar to those of established L-type calcium channel blockers (nitrendipine, diltiazem) since it reduces the plateau phase of slow waves which inhibits calcium influx and prevents subsequent contractions. (36)

It has also been shown to inhibit the acetylcholine (ACh)-induced contractile response of smooth muscle in dog and rat colons. Acetylcholine is a neurotransmitter of the intrinsic cholinergic nerves. (36) Similarly, in smooth muscle cells of the colon isolated from normal or inflamed human colons, it inhibits contraction induced by other agonists (CCK). (37) The involvement of sensory afferent neurons in IBS has been demonstrated, and this could also explain the efficacy of pinaverium bromide for treating motility disorders and intestinal hypersensitivity, two key IBS symptoms.

A pilot study of 12 IBS patients has used surface electromyography to study how treatment with pinaverium bromide affects colonic motility. Surface electromyography was used during a two hour fasting period and a postprandial

period of two hours after a standard meal prior to and after 10 days of treatment with 50 mg of pinaverium bromide taken three times a day. Principal IBS symptoms including abdominal pain, bloating and impaired bowel habits began to improve on day 4 of treatment. Abnormal patterns of colonic motility including greater frequency, greater extent of contractions and impaired rhythm in motor activity decreased after 10 days of treatment. A continuation of that study included 22 IBS patients and 7 healthy controls. (38) Healthy controls received no treatment, but served as controls for electromyographic measurements. The study protocol was as described above, except the duration of pinaverium bromide therapy was extended to 14 days. The results showed that fasting and postprandial colonic motility parameters in IBS patients improved in relation to controls. These symptoms were effectively reduced in 14 days of pinaverium bromide therapy. Abdominal pain and bloating also improved significantly with treatment.

Adverse effects that have been described include hypersensitivity, angioedema, constipation, drowsiness, dysphagia, epigastric pain, erythema, headache, nausea, pruritus, vertigo, vomiting and xerostomia. The use of pinaverium bromide has generally been considered safe although its use is contraindicated in pregnant women. Although there are insufficient animal reproduction studies and no information on human pregnancies is available, there is a theoretical risk of sedation and hypotonia in newborns if pinaverium bromide is used at the end of pregnancy. However, no cases have been reported.

Evaluation of pinaverium bromide by four studies with a total of 615 patients found a statistically significant improvement of IBS symptoms (RR = 0.56; 95% CI 0, 38-0.82) with a NNT of 4 (95% CI 3-6) although the studies heterogeneity was statistically significant (I2 = 61%, p = 0.05). (39-42) The ACG's clinical practice guidelines strongly recommends pinaverium bromide for reducing abdominal pain in IBS patients although the quality of evidence is still low.

## Trimebutine

Trimebutine [3,4,5-trimethoxybenzoic acid 2 (dimethylamino)-2-phenylbutyl ester] has multifaceted modes of action. Its spasmolytic activity is unique, and it has significant non-selective agonist activity for the μ, κ and δ intestinal opioid receptors. Trimebutine has been reported to prematurely induce phase III of the migratory motor complex of the intestine, and it has also been shown to modulate visceral sensitivity. It probably acts on smooth muscles, enteric nerves, and the interstitial cells of Cajal which are key for initiation and regulation of gastrointestinal motility. Some studies have reported that trimebutine acts as a regulator of the Ca2 + and K + channel in the intestine. (43)

A multicenter, randomized, double-blind, non-inferiority clinical study of 197 patients has compared fenoverine with trimebutine. Subjects were randomized to receive 100 mg of fenoverine three times a day or 150 mg of trimebutine three times a day for 8 weeks. The primary evaluation criterion was the proportion of patients who experienced a 30% reduction of baseline abdominal pain by week eight as measured by the scale of intestinal symptoms. (44)

Assessment criteria were changes in abdominal distension, diarrhea, constipation, and general satisfaction scores. Fenoverine was found to be not inferior to trimebutine at week eight (treatment difference, 1.76%; 90% CI: 10.30 to 13.82; p = 0.81). Fifty-four of seventy-eight patients (69.23%) who took fenoverine and 56 of 83 patients (67.47%) who took trimebutine had 30% reductions in abdominal pain or discomfort compared to the baseline. (44)

There have been two systematic reviews that compared trimebutine to placebos for IBS patients. Both systematic reviews showed greater improvement of abdominal pain with trimebutine treatment than with placebos, but the difference was statistically significant in only one of the reviews. That systematic review was based on three randomized controlled trials. It found an RR of 1.32 with a 95% CI of 1.07 to 1.64. The difference in the other systematic review was not statistically significant. Its odds ratio (OR) was 1.28 with a 95% CI of 0.53 to 3.14. (45)

A systematic review based on two randomized controlled trials found that trimebutine's overall evaluation was not significantly better statistically than was the overall evaluation of placebos (RR: 0.97; 95% CI: 0.68 to 1.38; OR: 1.27; 95% CI: 0.58 to 2.79). Another systematic review based on a randomized controlled trial reported that there was no statistically significant difference in adverse events between trimebutine and placebos (OR: 0.62; 95% CI: 0.20 to 1.88). (45)

Another randomized controlled trial reported that clinical recovery was observed in 94.9% of patients treated with trimebutine. Spontaneous recovery was observed in 20.5% of untreated patients. These findings were based on responses of parents who were asked if their child had adequate relief of pain and discomfort related to IBS in the previous seven days. (45)

Another randomized controlled trial that compared trimebutine with mebeverine found that there was a statistically significant improvement of abdominal pain, consistency and frequency of feces and flatulence compared to the reference values for each drug after six weeks of treatment (p varies between <0.01 and <0.05). However, there were no statistically significant differences in the improvement of symptoms between the two drugs (p values range between <0.23 and <0.71). Compared to baseline, statistically significant symptom improvement was reported for both drugs

after one week of treatment. Quality of life was evaluated with the IBS-QoL questionnaire. It improved statistically significantly after treatment with trimebutine or mebeverine ($p < 0.05$). In addition, patients' improvement was statistically greater with trimebutine than with mebeverine ($p < 0.05$). The authors stated that there were no differences in adverse events between the two drugs, however, no quantitative data were presented. (45)

The ACG's clinical practice guidelines give a weak recommendation for trimebutine for improving abdominal pain in IBS patients although the quality of evidence is still low.

## Mebeverine

Mebeverine, a beta-phenylethylamine derived from reserpine, has relatively specific effects on smooth muscle cells without having atropine-like effects in humans. It directly blocks sodium channels and inhibits the accumulation of intracellular calcium, and in experiments with porcine models it was three times more potent than papaverine at inhibiting the ileal peristaltic reflex. Nevertheless, other animal studies of its pharmacology have failed to demonstrate this effect. (2)

An early study by Connell found that intravenous mebeverine decreased all sigmoid colonic motility, especially in hyperactive subjects but had less or no effect on hypoactive subjects. Mebeverin was superior to placebos in a 12-week study of treatment in IBS patients in terms of symptom improvement and overall well-being. Mebeverin prolonged ambulatory manometry in 12 IBS patients and 6 healthy controls, compared to placebos, and mebeverine had no significant effects on the motor complex of the small intestine. In contrast, a higher phase 2 motility index was observed in both diarrhea-type IBS and in constipation-type IBS. The phase 3 motility index was also affected. These alterations in the motor activity of the small intestine by mebeverine suggest possible spasmolytic and prokinetic effects in IBS patients. (2)

Positive results have also been obtained in studies of control of symptoms in IBS that did not compare the drug to placebos. Significant improvement with a minimum number of adverse events was observed after 6 weeks of treatment with simple and sustained forms of mebeverine. A comparison of pinaverium bromide to mebeverine in 91 patients with diarrhea-type IBS found that improvements in overall well-being were similar in both groups: frequency of defecation decreased markedly, consistency of bowel movements improved in both groups, and no significant side effects were observed. A clinical trial that compared the effects on diarrhea type IBS of ramosetron, a 5-HT3 antagonist receptor, with those of mebeverine found that both treatments were equally effective in reducing pain, discomfort and urgency, with improvement of Bristol stool scale scores and frequency of bowel movements compared to the baseline. (2)

Nevertheless, results have been controversial in comparisons of the effects of mebeverine with placebos and another medication and results have been measured by self-control. A recent systematic review which included eight randomized trials found that clinical improvement and abdominal pain relief with mebeverine were not statistically better than the results from placebos. No differences were found between the effectiveness of 200 mg and 135 mg doses of mebeverine. Tolerability was excellent, and there were no significant adverse effects. Similarly, mebeverine was not found to have better results than placebos in a study in 135 IBS patients recruited from general practice who met the Rome III criteria. Mebeverine, methylcellulose and placebos were compared with or without combination with cognitive behavioral therapy. (2) However, a study conducted in London found that cognitive behavioral therapy sessions plus mebeverine were beneficial and that symptom relief and reduction of social and labor disability persisted for up to 6 months after therapy. Depression and anxiety predict poor outcomes for IBS patients treated with mebeverine, but in cases of patients with behavioral disturbances such as avoidance the combination of mebeverine with cognitive behavioral therapy may be useful. (2)

The clinical practice guidelines published by the ACG give a weak recommendation in favor of the use of mebeverine for treating IBS due to low quality of evidence.

In conclusion, the individual effect of antispasmodics has been difficult to interpret since there are only a small number of studies evaluating each medication. Nevertheless, these studies have found that antispasmodics are more effective treatments of IBS than are placebos. Of the medications studied, otilonium and pinaverium are quaternary derivatives of ammonium which are poorly absorbed in the gastrointestinal tract. They act primarily at the local level by reducing adverse effects of this group of medications and reduce the risk of persistent symptoms significantly more than do placebos.

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# Pathophysiology of Hepatitis C and Diabetes Mellitus: Towards the cure of two epidemics in the 21st century

Harold Muñoz Díaz,[1] Adán Lúquez Mindiola,[2*] Andrés Gómez Aldana.[3]

1 Internist at the National University of Colombia and the National University Hospital of Colombia in Bogotá, Colombia
2 Internist and Gastroenterologist at the National University of Colombia and GutMédica Center of Digestive Diseases in Bogotá, Colombia
3 Internist from Javeriana University and Gastroenterologist from the National University of Colombia, currently at Fundación Santa Fe de Bogotá and GutMédica Center of Digestive Diseases in Bogotá, Colombia

***Correspondence:** ajluquezm@unal.edu.co.

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**Abstract**

Chronic hepatitis C virus (HCV) and diabetes mellitus (DM) are two public health problems that impact health care systems with overall high costs. HCV infections cause liver manifestations such as hepatitis, cirrhosis and hepatocellular carcinoma. They have also been involved in the pathogenesis of extrahepatic manifestations among which are metabolic disorders such as DM. Longitudinal and cross-sectional studies have reported a higher incidence and prevalence of DM in patients with chronic HCV infections. DM accelerates histological and clinical progression of chronic HCV infections and leads to cardiovascular complications. Recently, progress has been made in treatment with the introduction of new medications such as direct-acting antiviral drugs that improve glycemic control in these patients.

**Keywords**

Hepatitis C, chronic hepatitis C, diabetes mellitus.

## INTRODUCTION

Worldwide, hepatitis C virus (HCV) infections and diabetes mellitus (DM) are two of the main public health problems facing health care systems. They place a heavy overall burden on health care finance, especially in developing countries. (1, 2)

Currently, DM is defined as a group of metabolic diseases whose common characteristic is hyperglycemia caused by a deficit in the secretion and/or action of insulin. (3) Chronic hyperglycemia in DM has been associated with long term damage to, and dysfunction and failure of eyes, kidneys, nerves, heart and blood vessels. This affects the quality of life and increases mortality rates. (3, 4)

DM is classified as either type 1 or type 2 (TYPE 2). Type 1 accounts for 5% to 10% of DM cases and is characterized by the destruction β cells in the pancreas due to an autoimmune mechanism associated with the HLA-DR/DQ haplotype. It leads to absolute insulin deficits. Islet cell cytoplasmic autoantibodies (ICA) are predictive and diagnostic markers for T1D. Other autoantibodies found include anti-glutamic acid decarboxylase (anti-GAD), anti-insulin antibodies (anti-IA) and anti-protein tyrosine phosphatase (PTP) antibodies (IA-2, IA-2 beta). (5, 6) Type 2 diabetes accounts for 90% to 95% of the patients with DM. It is characterized by insulin resistance and varying degrees of insulin deficit. It can also lead to increased glucose production in the liver. There are probably several causes of this type of DM, but its specific etiology is not known exactly. (7)

The prevalence of chronic HCV infections ranges between 1.2% and 3.8% depending on geographic region. (8) Approximately 130 to 175 million people are currently infected: 3 to 4 million more are infected each year, and 350,000 people die from the disease every year. (9) It is the main cause of liver transplantation in developed countries

 

and is the main cause of morbidity and mortality related to the liver. (10, 11)

HCV is a common cause of chronic liver diseases including hepatitis, cirrhosis and hepatocellular carcinoma. It also involved in the pathogenesis of several autoimmune and rheumatologic diseases including arthritis, vasculitis, sicca syndrome, late cutaneous porphyria, lichen planus, kidney disease, thyroid diseases and pulmonary fibrosis. It is also involved in the development of lymphoproliferative disorders of β cells and has been associated with extrahepatic manifestations including metabolic alterations including DM. (14)

The objective of this work is to review the evidence of association of chronic HCV infections and DM related to epidemiology, pathogenesis, clinical symptoms, treatment and prevention.

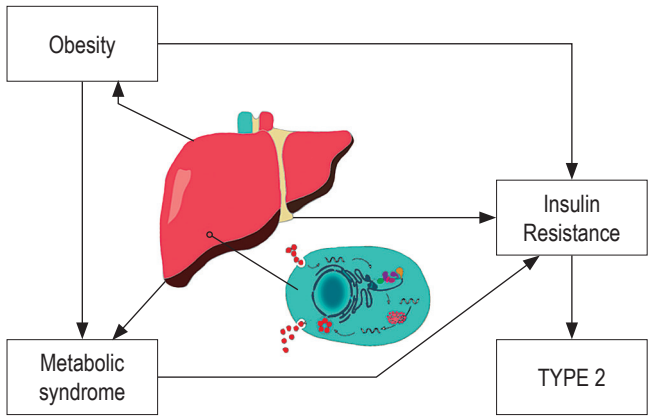


**Figure 1.** Relationship between HCV and metabolic abnormalities.

## METHODOLOGY

We conducted a search of the web using the following MeSH terms and keywords: hepatitis C, chronic hepatitis C, diabetes mellitus, epidemiology, physiopathology, diagnosis, therapeutics, and antiviral agents.

The search was limited to studies conducted in humans that were published in English or Spanish from the initial description of the association in 1994 to November 2018. The Cochrane, Central Controlled Trials, Medline, Embase and Science Citation Index electronic databases were used and then supplemented with manual searches. Publications considered to be most relevant by the authors were chosen.

## OVERVIEW

The liver plays an important role in carbohydrate metabolism. Chronic liver diseases frequently involve alterations in glucose homeostasis, carbohydrate intolerance and insulin resistance which may eventually lead to DM (Figure 1). (15-17) Moderate asymptomatic elevation of aminotransferases is also common in DM patients, especially those with TYPE 2, and has been associated with fat infiltration of the liver. (18)

Progression of liver fibrosis is responsible for the development of insulin resistance and type 2 diabetes, but DM can occur in early stages of liver disease. (19, 20) Initially, long-term hepatocyte damage was considered to be a cause of alterations in glucose homeostasis, but various studies have shown that patients with other chronic liver diseases such as hepatitis B virus (HBV) infections have lower prevalences of DM than do patients with chronic hepatitis C. (21-24)

The prevalence of HCV antibodies in the population with type 2 diabetes varies between 1.78% and 12.1%. (25, 26) Cross-sectional studies with a control groups of non-diabetic individuals have established that patients with type 2 diabetes have a higher prevalence of HCV antibodies than does the general population. (27-30) In contrast, the prevalence of HCV antibodies in patients with type 1 diabetes does not exceed the prevalence in the general population. (31) The NHANES III study found that people over 40 years of age with HCV infections have three times the probability of having type 2 as do those who are not infected. Non association with TYPE 1 was detected. (32) Another large community-based study has established that people between 39 and 49 years of age who have type 2 are very likely to test positive for the HCV antibody. (33)

Evaluations of patients with HCV and cirrhosis show that the prevalence of type 2 varies from 19.6% to 50%, a higher range than that reported for patients with chronic hepatitis. (34) A prospective study that compared 50 patients with cirrhosis due to HCV and 50 patients with cirrhosis without HCV found a higher prevalence of DM and higher baseline blood insulin levels in patients with HCV. It would appear that the presence of advanced liver disease is a strong diabetogenic factor, like HCV itself. (34).

The clinical consequence of the high prevalence of HCV infections in type 2 patients is that mild elevations of serum aminotransferases should not automatically be attributed to nonalcoholic fatty liver disease, and tests for HCV should be mandatory for diabetic patients with altered liver profiles. (35)

There is insufficient information about the duration of HCV in patients with DM to allow evaluation of their temporal relationship. One study has reported that all patients with HCV and type 2 had histories of blood transfusions 10 to 20 years prior to the onset of DM. (31) Another study found that type 2 was diagnosed 18 years after HCV infections. (36) A study of the temporal sequence in diabetic HCV positive patients found that HCV diagnoses preceded those of DM in 73% of cases. (37)

There are risk factors for HCV before the onset of DM in 52% of people who have both HCV and type 2, while none had risk factors for HCV after the onset of DM. (15) The absence of any epidemiological factor for HCV infections among diabetic patients and the evidence suggesting that the infection precedes DM supports the idea that the virus can cause or predispose HCV patients to develop DM. Nevertheless, definitive conclusions should be made on the basis of prospective studies. Age, obesity, family histories of DM, African-American origins, and coinfections of HCV and human immunodeficiency virus (HIV) are all risk factors associated with the development of DM. (38, 39) In contrast, the hypothesis that some specific HCV genotype predisposes those infected to the development of DM, or somehow protects the development of DM, remains controversial. (40)

Post-transplant diabetes mellitus (PTDM) is a medical condition that can arise following kidney and liver transplantation. Its incidence has increased in recent decades. (41) Independent risk factors for PTDM include administration of immunosuppressive agents to prevent and treat rejection, donor origin, and factors related to the recipient. (42) Chronic HCV infection is one current indication for orthotopic liver transplantation. The prevalence of PTDM in liver transplant recipients infected with HCV is between 40% and 64% which is significantly higher than the prevalence reported in patients transplanted for other causes of liver failure. In addition, it has been established that HCV is an independent risk factor for development of PTDM. (42) The incidence of HCV can reach 50% in patients with end-stage renal disease and has been identified as an independent risk factor for development of PTDM after kidney transplantation. (43) All these data reinforce the hypothesis that HCV is more likely to be a cause than a consequence of DM. In addition, the relationship between HCV and DM can contribute substantially to the harmful effects of the virus on patient and graft survival after liver or kidney transplantation. (43)

The link between HCV infections and DM has been explored both by assessing the prevalence DM and by studying impaired fasting glucose (IFG). A cohort of patients with chronic HCV hepatitis was observed to have almost three times more glucose abnormalities than did HCV negative patients including those with other liver diseases (32% versus 12%). Among the patients with HCV infections, a higher prevalence of DM and IFG was found (17% versus 7%, and 15% versus 5%, respectively). No differences were observed in cirrhotic patients with or without HCV infections. These findings suggest that the genuine connection between HCV infections and DM begins in the early stages of liver disease. (40)

The high prevalence of impaired glucose metabolism found in patients with HCV infections suggests that they should be considered a high-risk group who should be screened for DM and IFG. Lecube et al. performed oral glucose tolerance tests (OGTT) on 50 patients with chronic hepatitis C and 50 HCV negative patients in whom DM had not been diagnosed. Both groups were matched by age, body mass indexes (BMI) and sex. OGTT diagnosed new cases of DM in 18% of the HCV patients and diagnosed new cases of IFG in 30 % of these patients while only 4% and 18% of the HCV negative patients were found to have DM and IFG, respectively. (44)

Table 1 defines criteria for diagnosis of DM according to the American Diabetes Association (ADA). (45)

**Table 1.** Criteria for diagnosis of DM

| Criteria | Quantity |
|---|---|
| Random blood glucose* | ≥ 200 mg/dL |
| Fasting blood glucose* | ≥ 126 mg/dL |
| OGTT* | ≥ 200 mg/dL |
| $HBA_{1C}$ | ≥ 6.5 % |

* Diagnosis requires two abnormal results from the same sample or from two separate samples. $HBA_{1C}$: glycosylated hemoglobin; OGTT: oral glucose tolerance test.

## PATHOGENIC MECHANISMS INVOLVED IN HCV DIABETOGENIC ACTION

### HCV Effects and Insulin Resistance

Hepatitis C is hepatotropic non-cytopathic virus whose genome has been identified in tissues beyond the liver including pancreatic acinar cells and epithelial cells of the pancreatic duct. (46) Post-mortem studies reveal that HCV replicates in the pancreas, and animal models suggest a direct effect of infection on insulin resistance in the liver. (47)

The virus has a 9.6 Kb ribonucleic acid (RNA) genome which encodes approximately 3,010 amino acids and is transported in structural proteins (core, E1, E2) and non-structural proteins (NS3-NS5B). These proteins play important roles in the development of insulin resistance and oxidative stress at the cellular level through reactive oxygen species. (48) The core protein, alone or in combination with other viral proteins, increases phosphorylation of the insulin receptor substrate-1 (IRS1) which is the basis of insulin resistance. (49) Phosphorylated IRS1 activates phosphatidylinositol 3 kinase (PI3K). Activation of PI3K and Akt is essential for many of the metabolic effects of insulin (Figure 2). (50) Therefore, defective association of PI3K with IRS1 and loss of activation of PI3K may contri-

bute to insulin resistance and increased prevalence of DM in subjects infected with HCV. Finally, this mechanism promotes translocation of glucose transporter 4 (GLUT4) to the plasma membrane to improve glucose uptake. (51) In addition, the core protein can directly activate insulin signaling inhibitors such as the mammalian target of rapamycin (mTOR), the suppressor of cytokine signaling 3 (SOCS3), and c-Jun N-terminal kinases (JNKs). (52) In addition, HCV increases stress on the endoplasmic reticulum which activates protein phosphatase 2 (PP2) which inhibits two adenosine monophosphate activated protein kinase (AMPK) and Akt which are key gluconeogenesis regulators. (52)

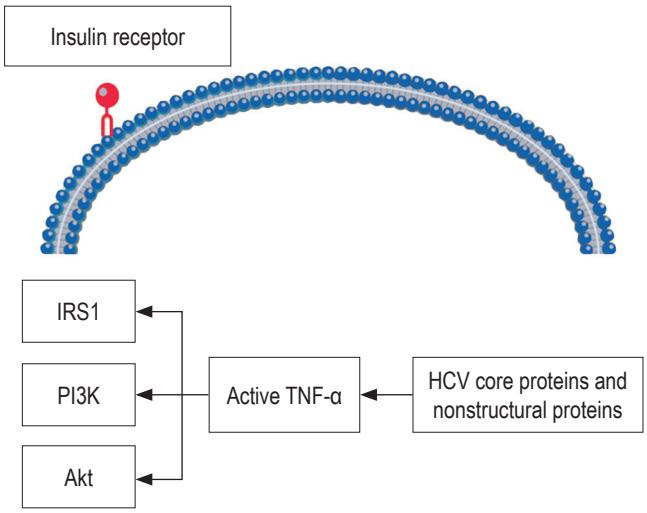


**Figure 2.** Mechanism by which HCV interferes with insulin signaling. TNF-α: tumor necrosis factor alpha.

Recent evidence supports the existence of a virus induced extrahepatic component of insulin resistance, an indication that the molecular pathogenesis of glucose metabolism abnormalities observed in HCV infections is much more complex than previously thought. (51)

## Inflammatory Cytokines

Innate viral evasion strategies and human genetic determinants are the basis of the transition from acute infections to viral persistence and chronic infection. Host genetic factors can influence infection outcomes and responses to antiviral therapy. Recent studies reveal a complex interaction between each patient's genetic context, viral factors, and host factors related to the innate immune trigger which dictates control of HCV infections and immunity. (53)

Beyond the direct effects of HCV on IRS1 and PI3K, the core protein can induce insulin resistance indirectly through stimulating secretion of inflammatory cytokines. In patients with chronic HCV, inflammation induced by the virus causes hypersecretion of insulin-resistant inflammatory cytokines such as interleukin 6 (IL-6) and TNF-α. (52, 54, 55) Inflammatory cytokines also regulate protein suppressors of the cytokine signal as part of a negative feedback circuit by attenuating their signal. (56) This phenomenon may contribute to increases in gluconeogenesis due to the loss of Akt-mediated inhibition of the expression of the phosphoenolpyruvate carboxykinase (PEPCK) gene. In this context, it is interesting to note that leptin can modulate the action of insulin in liver cells by antagonizing phosphorylation of insulin-stimulated IRS1. This increases expression of the FEPCK gene and decreases expression of glucokinase resulting in increased gluconeogenesis. (57) Increased gluconeogenesis after HCV infection results in increased production and accumulation of lipids mediated by inhibition of AMPK. (58) The lipolysis stimulating effect of TNF-α leads to elevated serum levels of free fatty acids which reduce insulin sensitivity. (59, 60)

Cytokines are intercellular mediators involved in viral control and HCV-induced liver damage. The complex cytokine network that operates during an initial infection allows coordinated and effective development of innate and adaptive immune responses, but the virus interferes with cytokines at various levels and escapes the immune response by inducing a $T_h2$ profile. Inability to control infection leads to recruitment of inflammatory infiltrates in the hepatic parenchyma by interferon gamma (IFN-γ) and induces chemokines CXCL9, CXCL10 and CXCL11 which results in sustained liver damage and eventually cirrhosis. (61, 62) Eslam et al. have found polymorphisms in the IFNL3 region (IL-28B) that are associated with spontaneous recovery and which were induced by treatment of infection. (63)

The most important extrahepatic systemic diseases related to HCV (mixed cryoglobulinemia, lymphoproliferative disorders, autoimmune thyroid diseases, and Type 2 DM) are associated with alterations in the complex regulation of the cytokine/chemokine network involving inflammatory chemokines and the $T_h1$ response. (61, 62)

## HCV and Type 1 DM

Various mechanisms have been postulated. Although HCV can infect extrahepatic tissues, its participation in the onset of type 1 DM has not yet been clarified. (64) Aside from direct mechanisms which have not been demonstrated, HCV infection initiates or accelerates an immune reaction against β cells. HCV β cell infection can regulate the expression and secretion of the CXCL10 gene and recruitment of Th1 lymphocytes which secrete IFN-γ and TNF-α. They induce secretion of CXCL10 by β cells and thus perpe-

tuate the immune cascade. This cascade can lead to β cell dysfunction in genetically predisposed subjects (Figure 3). (65) In addition, molecular mimicry with an HCV-related autoimmune trigger involving glutamic acid decarboxylase (GAD), which shares a similar 65 amino acid sequence with antigenic regions of the virus polyprotein, has been suggested. (66) Another possibility is induction of antibodies that react against GAD and the development of DM mediated by interleukin 18 (IL-18) and other inflammatory cytokines. (67) IL-18 plays a pathogenic role in type 1 DM because it is involved in acceleration of the development of manifest disease. It can induce $T_h1$ and/or $T_h2$ responses depending on the surrounding cytokines. In addition, it plays a pathogenic role in various diseases including acute liver failure. (67, 68) Other inflammatory cytokines such as TNF-α and IL-1B, which are elevated in patients with acute hepatitis, can also induce autoimmune diabetes. (69)

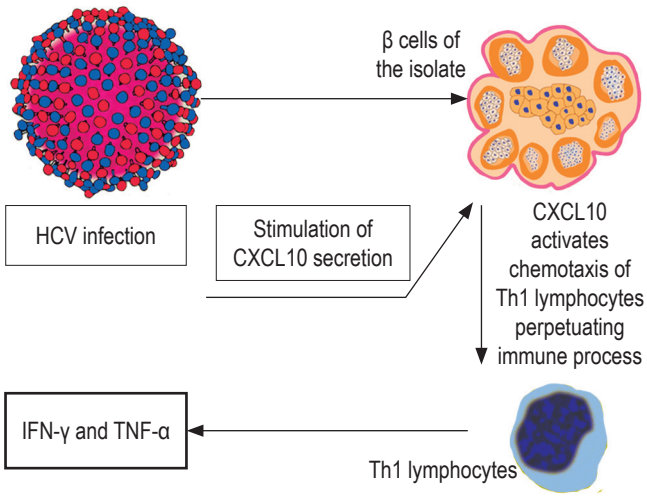


**Figure 3.** Potential regulation of endocrine manifestations of HCV in pancreatic islet β cells

## Iron Overload

High concentrations of ferritin are associated with insulin resistance and with increased risk of type 2 DM in healthy people, and increased ferritin levels have been reported in HCV patients. (70) Ferritin is an acute phase reactant that may be altered by inflammatory processes, and evidence suggests that there is a low degree of inflammation in type 2 DM. Patients with HCV infections without DM do not have high levels of ferritin, so it has been suggested that DM, and not the HCV infection, is a risk factor for high iron concentrations. However, more prospective studies are needed to evaluate this relationship. (70) In addition, hepatic iron deposits can cause insulin resistance by interfering with the ability of insulin to suppress hepatic glucose production. (70)

## Hepatic Steatosis

Hepatic steatosis occurs more commonly in HCV patients than in HBV patients: it occurs in more than 50% of chronic HCV patients. (71) Mild steatosis is associated with elevated BMI and visceral obesity while moderate to severe steatosis is directly caused by the virus. (52) Genotypic differences related to progression of liver disorders have also been described. Steatosis in HCV genotype 4 infection is an expression of metabolic syndrome caused by activation of inflammatory mechanisms as well as obesity and insulin resistance. The degree of steatosis in this genotype is independent of viral load and antiviral therapy does not improve it. (72) Genotype 3a is mainly related to severe steatosis. (52)

Hepatic steatosis may contribute to DM associated with HCV due to damage of the ability of insulin to decrease gluconeogenesis and promote liver fibrosis. (71)

## DM in HCV Infected Patients Treated with Interferon Alfa (IFN-α)

Some studies have shown a high prevalence of pancreatic autoimmune markers in patients with HCV during or after IFN-α therapy which is probably due to the immunostimulatory effects of these cytokines. (73) IFN-α has antiviral, antiproliferative and immunomodulatory activity. In predisposed individuals, it can induce a diabetogenic process. For this reason, islet cell and anti-GAD autoantibodies should be investigated before and during treatment to identify individuals who are at high risk of developing type 1 DM. (73) Some patients may develop de novo pancreatic autoimmunity and be at risk of developing DM. Patients who are initially positive for organ specific autoantibodies, especially specific pancreas and thyroid autoantibodies, and those who undergo seroconversion, are at high risk of developing clinical autoimmune disease after treatment. (74) IFN-α increases the expression of HLA class I antigens, activates natural killer cells and T lymphocytes and can be an important cofactor in the development of a $T_h1$ immune reactions. (75) Timely suspension of therapy is rarely accompanied by clinical regression of DM. (74)

## Cancer in HCV and DM infection

The main characteristic of diabetic patients is insulin resistance which is crucial for progression of fibrosis and which negatively impacts responses to antiviral treatment in sub-

jects with chronic HCV. (76) Reduced insulin sensitivity is the basis of compensatory hyperinsulinemia and elevated levels of insulin-like growth factor type 1 (IGF-1) which stimulates cell proliferation and inhibits apoptosis. This phenomenon has strong mitogenic effects on a wide variety of cancer cell lines. (77) At the same time, insulin activates the IGF-1 receptor which promotes growth and modulates cell cycle progression. Excess insulin can indirectly lead to the development of cancer by increasing the amount and bioavailability of circulating IGF-1. Obesity and physical inactivity also cause hyperinsulinemia and therefore are also associated with accelerated cancer progression. (78)

Chronic HCV is a progressive form of liver disease that leads to cirrhosis and HCC. (13) Patients with diabetes and HCV infections have higher risks of HCC than do non-diabetic individuals, so DM seems to have a selective impact on the development of HCC. (79) Patients with type 2 DM who achieve good glycemic control by reaching $HbA1_c$ levels of less than 7% can reduce the risk of HCC. (80)

## TREATMENT AND PREVENTION

Clinical studies of HCV patients have reported improvement in glycemic control and insulin resistance with direct-acting antiviral agents (DAA) in patients who have DM as well as in those who do not. (81-83) Diabetic patients who receive DAA should be strictly monitored so that diabetes medications, mainly insulin and sulfonylureas, can be reduced to avoid hypoglycemia. (84)

The advent of HCV therapies has helped us learn that the first interferon-based treatments acted as facilitators in the development of DM. (85) However, oral antiviral therapies have been accompanied by decreasing incidence of DM. A study of 5,127 patients treated for HCV found an incidence of 6.2% among those who achieved sustained virological response in contrast to 21.7 % of the patients who had therapeutic failure after 3.7 years of follow-up (adjusted hazard ratio: 0.79; 95% CI: 0.65-0.96). (86) Li et al. followed 1,395 HCV patients who also had type 2 DM who maintained sustained virological responses for an average period of 2.7 years. They found significant less complications such as acute coronary syndrome (Hazard ratio: 0.36; $p < 0.001$), terminal chronic kidney disease (Hazard ratio: 0.46; $p < 0.001$), cerebrovascular events (sub-hazard ratio: 0.34; $p < 0.001$), and retinopathy (sub-hazard ratio: 0.24; $p < 0.001$), when than in untreated patients. (87)

Other variables such as $HbA_{1c}$ that are related to DM have also been identified. Recent studies have shown that $HbA_{1c}$ decreased more in patients who achieved sustained virological response (0.6% to 0.98%) than in those for whom treatment failed. (88, 89) These endocrine benefits provide additional justification for considering antiviral treatment for all patients with HCV and DM. (89) In addition, the treatment of HCV in patients with DM could decrease the prevalence of complications including chronic nephrology. (90)

Various factors including viral genotype, host genetic factors and comorbidities can alter this response. (91) Some research has reported that obesity and hypercholesterolemia may interfere with the sustained viral response suggesting additional therapeutic options for HCV. These include dietary changes, antidiabetic medications and statins although it is not yet clear if biguanides such as metformin are the best oral diabetes treatments while statins have not been able to inhibit HCV replication in vivo even though they can in vitro. (92, 93, 94)

The potential relationship between HCV infections and the development of DM increases the need to implement prevention measures. These should be directed to lifestyle changes that can reduce the risk of developing DM and HCV infections, and should include regular screening for DM in patients with HCV infections plus analysis of other risk factors such as obesity, dyslipidemia and alcohol consumption that can accelerate the progression of both. (95)

Additional studies are necessary to improve prevention policies and promote adequate and cost-effective programs for monitoring and treating diabetic patients with chronic HCV. Multifactorial treatment should be implemented to cure two diseases: DM and chronic HCV.

## CONCLUSIONS

HCV and DM infection are two disorders which have large high impacts on health and health care throughout the world. The high prevalence of type 2 DM in HCV patients with chronic hepatitis correlates with the increasing amount of evidence that this infection is a risk factor for developing DM and other alterations in carbohydrate metabolism. The specific mechanisms through which HCV is associated with DM appear to involve direct viral effects, insulin resistance, inflammatory cytokines, chemokines, cytokine signaling suppressors and other immune mediated mechanisms. These mechanisms are initiated in the early stages of liver disease.

Age, obesity, family histories of DM, African-American origins and HCV-HIV coinfections are risk factors associated with the development of DM among people infected with HCV. Studies should be carried out to evaluate alterations in the carbohydrate metabolism of these patients. Data regarding associations of chronic HCV and type 1 DM are scarce, but it has been reported that IFN-α therapy can stimulate pancreatic autoimmunity and, in certain cases, lead to development of type 1 DM. Diabetic patients with chronic HCV have greater risks of developing cirrhosis and HCC than do non-diabetic patients with chronic

HCV. DAA treatment improves glycemic control and insulin resistance. Additional studies are needed to improve prevention policies and promote adequate and cost-effective programs for diagnosis, treatment and monitoring of diabetic patients with chronic HCV.


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## Conflicts of Interest

None declared by the authors.


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# A case report of eosinophilic esophagitis

Pedro Rosales Torres,[1] Rafael Pila Pérez,[2] Rafael Pila Peláez,[3] Pedro León Acosta,[4*] Yudenia Toledo Cabarcos.[5]

1 First degree specialist in pathological anatomy and Instructor at the Manuel Ascunce Domenech Provincial Teaching Hospital in Camaguey, Cuba
2 Second degree specialist in internal medicine and tenured Professor at the Manuel Ascunce Domenech Provincial Teaching Hospital in Camaguey, Cuba
3 Second degree specialist in internal medicine and Assistant Professor at the Manuel Ascunce Domenech Provincial Teaching Hospital in Camaguey, Cuba
4 First degree specialist in internal medicine and Instructor at the Manuel Ascunce Domenech Provincial Teaching Hospital in Camaguey, Cuba
5 First degree specialist in pathological anatomy and Instructor at the Manuel Ascunce Domenech Provincial Teaching Hospital in Camaguey, Cuba

***Correspondence:** leon@mad.cmw.sld.cu

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## Abstract

**Objective:** We present the first case of eosinophilic esophagitis (EE) reported in our country in fifty-three years. **Clinical Case:** The patient was 28-year-old white woman with a personal history of atopy, allergic rhinitis, dermatitis and occasional diarrhea and asthma. She had relatives with bronchial asthma and had been admitted to hospitals several times previously. According to the patient, these alterations began at age 17, and she had seen several specialists since that time. Ten months prior to this admission, increasingly severe dysphagia accompanied by chest and abdominal pain, heartburn and weight loss began. Upon physical examination, wheezing was evident in both lung fields. The complete analytical study and imaging tests were all normal. Endoscopy and esophageal biopsy showed elements compatible with eosinophilic esophagitis. Excellent results were obtained from treatment with oral steroids, montelukast and proton pump inhibitors. **Conclusions:** EE is still poorly understood. It is more common in children and young white men, and there is usually a marked atopic component. In adulthood it is manifested by dysphagia and impaction of food. To diagnose EE there must be symptoms of esophageal dysfunction, more than 15 eosinophils per field, lack of response to proton pump inhibitors and exclusion of gastroesophageal reflux. Depending on the case, patients may require multidisciplinary treatment by gastroenterologists, allergists, immunologists and nutritionists.

## Keywords

Eosinophilic esophagitis.

## INTRODUCTION

Eosinophilic esophagitis is the result of inflammation of the esophagus due to eosinophils, a type of leukocyte involved in immunity against certain infections , especially of parasites, and in many allergic diseases such as bronchial asthma. (1) Although it is a rare disease, the frequency of eosinophilic esophagitis is increasing in many developed countries for reasons that remain unclear although it is known that all types of allergies now occur more frequently than in past generations. (2) In addition, there have been studies of other pathologies that have eosinophilic infiltration such as infectious esophagitis, Crohn's disease, hypereosinophilic syndrome, adverse drug reactions and connective tissue disease. (1) Various terms have been used to refer to this entity, but the most commonly accepted term is eosinophilic esophagitis. (3) The first case, an adult with a history of atopy who presented esophageal spasms, was reported in the literature by Dobbins et al. in 1977.

Eosinophilic esophagitis' impact is global since cases have been described on every continent except Africa. (5) It is estimated that its prevalence currently varies between 0.4% and 1.0% in adult patients and between 0.04% and 0.09% in children with an annual incidence of 1:100,000 in adults and 1:10,000 in children. Affected adults are most often young men between 20 and 50 years of age (average age of 38 years). The male to female ratio of cases is 3:1, but reported symptoms are similar for both sexes. (5)

 

The objective of this study is to present the first case of a patient with eosinophilic esophagitis in Colombia in 53 years.

## CLINICAL CASE

The patient was a 28 year old white woman who worked as a teacher, did not smoker, and had a family history of allergy and asthma. She said that she had suffered from allergic rhinitis, recurrent atopic dermatitis, occasional diarrhea and bronchial asthma from the age 17 and had been hospitalized several times. She had been examined by the pulmonology, immunology and allergy services. A skin prick test had shown sensitivity for lacticin, bread, beans, rice and tomatoes. An allergen-specific immunoglobulin E (IgE) test found elevated levels for these foods, so allergists treated her with multiple antihistamines and a diet. She improved for several months, but at 10 months she began to experience progressively increasing dysphagia, heartburn, chest pain and epigastric abdominal pain for which reason she came to the hospital.

### Physical Examination

The patient was depressed but not in poor general condition. She was hydrated, her skin and mucous membranes were normally colored, her hair and nails were normal, and she had no peripheral lymphadenopathy, edema or skin lesions. Her respiratory rate was 16 breaths per minute (rpm). She had a mild vesicular murmur with scattered wheezing in both lung fields, and her heartbeats were rhythmic and without murmurs. Her blood pressure was 110/70 mm Hg.

Her abdomen was soft and depressible to touch and without pain. There were no signs of visceromegaly. The rest of the physical examination, including the gynecological exam, found no alterations. The fundi of her eyes were normal.

### Tests

All biochemical and hematological studies were within normal limits and her chest, esophageal, stomach and duodenal x-rays and her electrocardiogram were normal. No abnormalities were found with abdominal and gynecological ultrasound or a CT scan.

Esophagogastroduodenoscopy found focal stenosis, superficial punctate papules with evident inflammation, and circumferential rings (feline esophagus) with abundant punctate exudates. Her stomach and duodenum were normal.

Histological study showed inflammation with numerous intraepithelial eosinophils with extensive granulation plus microabcesses on the surface (Figures 1-4). The intraepithelial eosinophils were most numerous in the upper half of the epithelium. The histological study of the stomach and duodenum was normal.

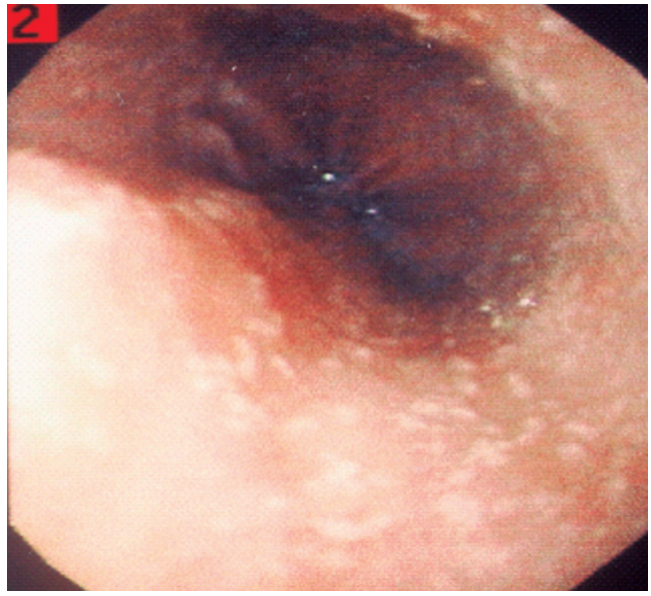


**Figure 1.** Esophagogastroduodenoscopy showing whitish punctate papules.

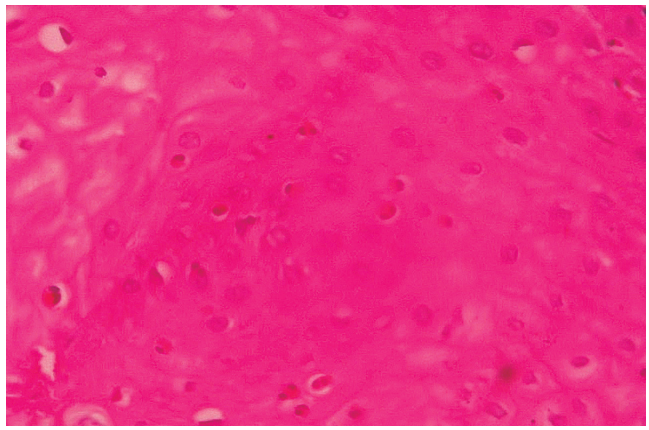

**Figure 2.** Photomicrograph showing the epithelium of the esophageal mucous with diffuse distribution eosinophils. H/E 20 x.

A soft diet of purees, broths, and soups, that eliminated all foods that had triggered her crises was initiated. Omeprazole, montelukast and prednisone were administered for eight weeks. Her response was favorable, and a follow-up esophagogastroduodenoscopy was normal.

## DISCUSSION

Under normal conditions, there are no eosinophils in the esophagus, so their presence is considered pathological.

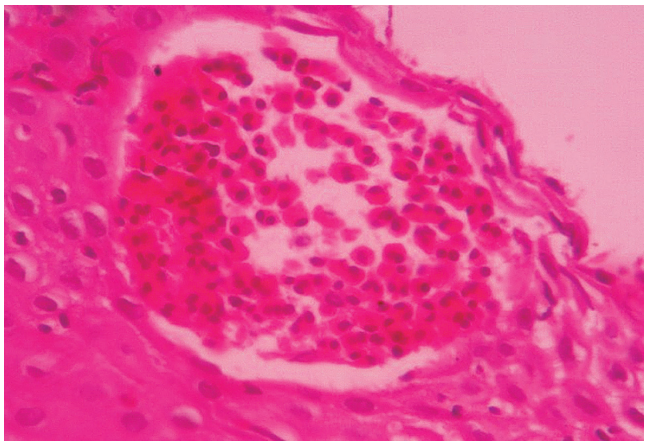

**Figure 3.** Histological field of whitish punctate papules. Note the formation of an eosinophilic abscess in the upper third of the epithelium. H/E 40 x.

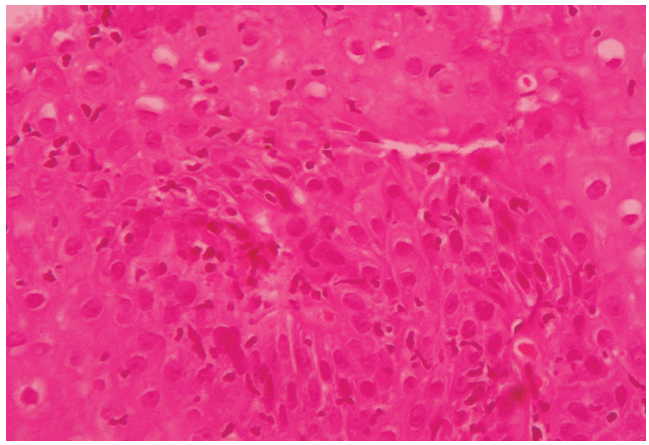

**Figure 4.** Histology shows distribution of eosinophilic cells is deeper and less regular toward the middle and lower third of the esophagus. H / E 40 x.

Until a few years ago, eosinophils in the esophageal mucosa was considered a marker of reflux. (1) In recent years, a large number of patients with symptoms of esophageal dysfunction and large eosinophilic infiltrations of the esophagus who do not respond to anti-reflux measures but have normal esophageal pH have been described. This combination corresponds to eosinophilic esophagitis. (3) Noel et al. conducted a study of 103 patients, 0 to 19 years of age, who had eosinophilic esophagitis. It reported a predominance of the male gender (71%). Half of them had histories of atopy, and 70% of them had family histories of atopy. Our patient had a personal and family history of atopy. Personal histories of atopy are found in 60% of cases while family histories are found in 20% to 40% of cases. (6) The pathophysiology of eosinophilic esophagitis includes atopy, eotaxin-3, and interleukins. Some foods and aeroallergens are indicated in atopy while eotaxin-3 implies a genetic component and interleukins are mediators of inflammation. Gastroesophageal reflux is a component that is under discussion. (3) It has been noted that the presence of eosinophils in the esophagus is pathological and prone to chronicity, but the cause of eosinophilic infiltration of the esophagus is currently ignored. (1) Manifestations vary greatly from patient to patient according to their ages. Some patients' symptoms are constant while other patients' symptoms appear intermittently or seasonally. (2) Dysphagia and food impaction occur more frequently in adults, followed by symptoms of gastroesophageal reflux, chest pain and abdominal pain. (1-3) A study by Desai et al. has found that eosinophilic esophagitis was responsible for 50% of esophageal food impacts in outpatient visits. (7) A significant delay in the diagnosis of the disease in the adult population is noted, with an average of 4.5 years from the onset of symptoms until the time of diagnosis. (1) In our case, the delay was even longer. In 50% to 80% of both adult and pediatric patients, one or more of the following atopic conditions occur: asthma, sinusitis, dermal lesions, food allergies and/or eczema. (1, 3, 5) They are often observed with seasonal changes as was the case with our patient, taking into account her genetic background. Complications include esophageal structural abnormalities, Boerhaave syndrome and nutritional deficiencies. (8)

The diagnosis is confirmed with endoscopy and biopsy when there are more than 15 eosinophils observed per field similar to findings for our patient. (1, 2) The most common endoscopic findings are esophageal grooves, esophageal rings, whitish granulations, esophageal strictures, whitish plaques associated with eosinophilic microabscesses, and areas of high density of eosinophil infiltrate. (2) Thirty percent of endoscopies may appear normal, but care should be taken due to the fragility of the mucosa. Five biopsies including one from the stomach and one from the duodenum are recommended in order to rule out other entities. (2) This was done in the case presented here.

Treatment of eosinophilic esophagitis is controversial, so no optimal therapy or even expected goals have been defined. (1, 5, 7). Liacouras et al. observed that the combination of steroids and diet significantly improved symptoms and histological findings, as in the case of our patient. (9) Teltelbaum et al. (10) and Konikoff et al. (11) recommend using steroids systemically or topically for four to six weeks. (10, 11) We administered steroids orally for eight weeks, and we progressively decreased them over six months.

The diet eliminates all solid foods and replaces them with appropriate nutritional formulas that avoid foods identified as allergens. (1-3, 6-10). Due to the relationship between

eosinophilic esophagitis and gastroesophageal reflux, the use of proton pump inhibitors has been considered as primary or adjuvant treatment, and we administered them in this case. The current recommendation is that proton pump inhibitors should not be considered primary therapy. (3) Leukotrienes are chemoattractants of eosinophils, and they have been postulated as another therapeutic option for improving symptoms. Nevertheless, since they do not improve histology, these medications are not recommended for eosinophilic esophagitis. (12)

More recently, therapies that act against specific substances identified within the inflammatory cascade have been proposed. These include mepolizumab, a humanized monoclonal antibody that blocks interleukin 5 (IL-5). (13) We used steroids together with a proton pump inhibitor and a leukotriene antagonist and obtained favorable results.

## CONCLUSIONS

Eosinophilic esophagitis consists of inflammation of the esophagus that is characterized by a large numbers of eosinophils in histological studies. It is an allergic disorder whose frequency is increasing in the population because knowledge about it has improved. Its pathophysiology is not known with certainty, and there is no definitive treatment. The diagnosis is confirmed with endoscopy including five biopsy samples including one from the stomach and one from the duodenum. Differential diagnosis should consider more frequent diseases that feature eosinophilic infiltration of the esophagus.

### Conflicts of Interest

The authors declare that this study has not been funded or influenced in any other way that could lead to a conflict of interest.

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# A case of heterotopic pancreas in a gastric polyp

Pedro Rosales Torres,[1*] Rafael Pila Pérez,[2] Pedro León Acosta,[3] Rafael Pila Peláez.[4]

1 First degree specialist in pathological anatomy and Instructor at Manuel Ascunce Domenech Provincial Teaching Hospital in Camaguey, Cuba
2 Second degree specialist in internal medicine and Associate Professor at Manuel Ascunce Domenech Provincial Teaching Hospital in Camaguey, Cuba
3 First degree specialist in internal medicine and instructor at Manuel Ascunce Domenech Provincial Teaching Hospital in Camaguey, Cuba
4 Second degree specialist in internal medicine and Assistant Professor at Manuel Ascunce Domenech Provincial Teaching Hospital in Camaguey, Cuba

***Correspondence:** rtpedro.cmw@infomed.sld.cu.

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**Abstract**
Pancreatic heterotopia is rare and is sometimes found accidentally. It can occur anywhere in the digestive tract and even outside of it. Heterotopic pancreas is congenital, but its pathogenesis is under discussion. Although it develops slowly and progressively, its behavior is benign and asymptomatic. Nevertheless, it can manifest in obstructions, hemorrhaging, inflammation and neoplasia. In the latter case, histopathological diagnosis is essential. We present the case of a symptomatic patient with pancreatic heterotopia at the gastric pylorus, a very uncommon location.

**Keywords**
Heterotopic pancreas, gastric polyp.

## INTRODUCTION

Pancreatic heterotopia (PH), also known as heterotopic pancreas and ectopic pancreas, is characterized by normal pancreatic tissue in a different anatomical structure or site without vascular, neuronal or anatomical continuity with the pancreas. (1) The authors consulted point to Shultz as the person responsible for the first description of PH in 1727. They also agree that, in 1859, Klob was the first to offer histopathological confirmation while in 1916 Otschkin first reported PH in the gallbladder. (2) The frequency of this finding is calculated at between 0.11% and 13.7%. It is usually an incidental finding of autopsies or surgical procedures and is rarely found intentionally. (3) Its most frequent sites are the duodenum (30.3%), stomach (26.5%), jejunum (16.3%), ileum (5.8%) and Meckel's diverticulum (5.3%). It also occurs in the gallbladder, extrahepatic bile ducts, the Ampulla of Vater, the mesentery, bladder, lung, esophagus, thyroid, colon and spleen. (3)

Von Heinrich (4) classified PH morphologically into three varieties:

- Type I has all the elements of a normal pancreas.
- Type II has no pancreatic islets.
- Type III has only ducts surrounded by entangled fascicles of smooth muscle. These lesions are known as adenomyomata or mucoepithelial hamartomata. (3)

Other classifications such as the 2010 effort of Bromberg et al. (5) have multiple adherents.

Although the typical endoscopic ultrasound features of the PH include heterogeneous echogenicity, indistinct borders and a location within two or more layers, it can also exhibit hypoechoic homogenous echogenicity and a distinct border within the fourth ultrasound (muscularis

 

propria) layer similar to the endoscopic ultrasound characteristics of gastrointestinal stromal tumors. (6)

Despite the development of modern diagnostic procedures such as endoscopic ultrasound, computed tomography (CT) and gastroduodenoscopy, diagnosis remains difficult.

Asymptomatic patients diagnosed with PH should remain under medical supervision with periodic follow-ups. Patients without symptomatic complications should have their lesions removed, preferably by local resection. In sites accessible to endoscopy, endoscopic excision can be performed successfully in experienced hands in selected patients at appropriate institutions. The use of endoscopic ultrasound in this type of intervention is essential. (7)

Complications in ectopic pancreatic tissue are similar to those that occur in a normal pancreas and include acute pancreatitis, pancreatic cancer, insulinomas, gastrinomas and cystic degeneration (2, 3, 8, 9).

The objective of this work is to present the extremely rare case of a patient with pancreatic heterotopia. After presenting upper digestive manifestations refractory to conventional treatment, digestive endoscopy found gastric polypoid thickening and histopathological studies confirmed pancreatic heterotopia.

## CLINICAL CASE

The patient was a 66-year-old retired man who had a history of degenerative osteoarthritis and was being treated with non-steroid anti-inflammatory drugs (NSAIDs) at maximum dosage. He came to the hospital after two months of burning abdominal pain in the epigastrium that was exacerbated by food consumption and was accompanied by retrosternal burning and gastroesophageal regurgitation. A gastroenterological assessment concluded with a diagnosis of NSAID gastropathy, so treatment with proton pump inhibitors (PPIs) and dopamine agonists was started. Twenty days later he returned because of persistent symptoms which had not improved.

### Physical Examination

Physical examination showed that the patient was obese, his skin and mucous membranes were without alterations, and subcutaneous cellular tissue had not been infiltrated.

#### *Cardiorespiratory System*

His respiratory rate was 19 breaths per minute. He had a normal vesicular murmur without rales, a central heart rate of 96 beats per minute (bpm) and blood pressure of 125⁄85.

#### *Digestive system*

His abdomen was globular, soft, and depressible. It was painful upon deep palpation in the epigastrium and mesogastrium, but there were no visceromegaly, abdominal masses, or abdominal murmurs.

Otherwise, the physical exam found no alterations.

#### *Blood Tests*

Blood tests found hemoglobin of 125 g/L, leucocytes of 9 × 109 g/L with normal differential formula, and a globular sedimentation rate of 55 mm/first hour. Cholesterol, triglycerides, blood sugar, uric acid, urea, creatinine, total and fractionated proteins, and liver functions were normal. In addition, hospital policies require a test for syphilis (VDRL) which was not reactive and ELISA for HIV which was negative.

Chest radiography was normal. Abdominal ultrasound found a diffuse, echogenic liver without dilated bile ducts. The pancreas had no alterations. The kidneys were normal size, without lithiasis or dilation. The bladder and prostate had no abnormalities. The x-ray of the esophagus, stomach and duodenum was inconclusive for the diagnosis.

#### *Esophagogastroduodenoscopy*

Stomach: A polypoid thickening of approximately 1.5 cm of the same color as the surrounding mucosa was found in the gastric antrum. It was exophytic, did not contain any erosions, and had a central depression through the duct exit (Figure 1). A biopsy of showed that it was pancreatic heterotopia type I (Figures 2 and 3).

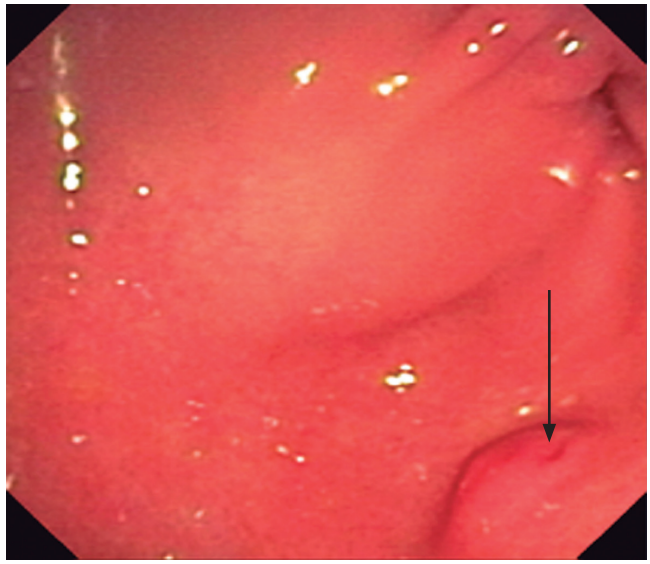

**Figure 1**. Endoscopic image of the antrum. Elevated submucosal lesion simulating a tumor in the antrum. Note the small depression at the exit of the duct.

Esophagus: The first and second portion of the duodenum were without alterations.

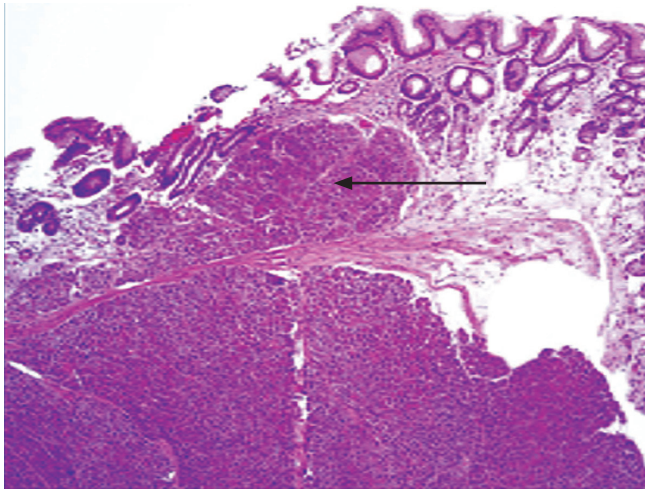

**Figure 2.** Panoramic image. Note the well-defined lesion in the submucosa and muscularis mucosae. H/E, 20 X.

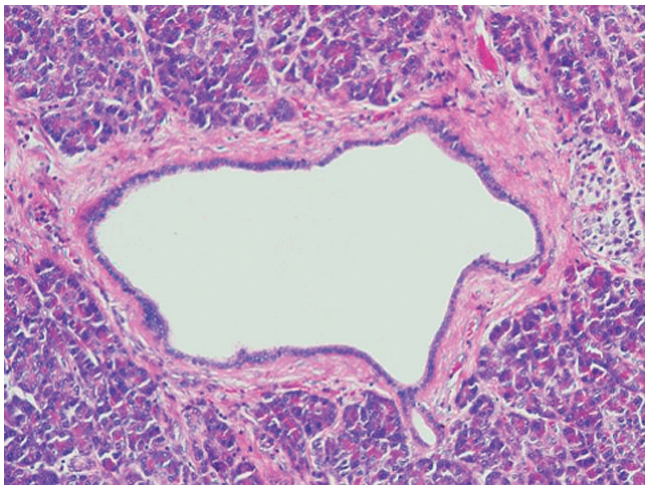

**Figure 3.** Image with higher magnification shows heterotopia type I. Note the ducts, acini and small islet nests to the right. H/E, 40 X.

After the diagnosis made, doses of the medications were modified, NSAIDs were suspended, and a date for surgery was scheduled. Given the histopathological result and the persistence of symptoms, the area of the gastric wall in which the ectopic tissue was implanted was excised. Three cm of healthy tissue surrounding the lesion were resected.

## DISCUSSION

Although PH is linked to organogenesis, it is usually discovered in adulthood. It is normally present as a benign and asymptomatic entity from birth. It is most common in males. Among females, it is found more often in girls and adolescents than in adult women. The most common form in female patients is gallbladder PH. (3, 5) This patient was a 66 year old man.

Several hypotheses have emerged to try to explain the pathogenesis of PH. They include origin as a hamartoma such as focal glandular hyperplasia, reactive changes in response to a persistent harmful stimulus, diverticular invagination and fibro-adenomatous involution associated with old age. (10)

Cytokeratins detected by immunohistochemistry in adenomyomata are similar to those exhibited by the normal biliary and pancreatic duct systems. They test positive for cytokeratin 7 and negative for cytokeratin 20 (CK 7 +/CK 20-). For this reason, comparisons of this expression profile with the expression profile of the intestinal epithelium show an inverted pattern (CK 7 -/CK 20+), as demonstrated by Takahashi and Fukusato based on previous work by Babal, Handra-Luca and Yao. (8-11) Macroscopically, PH can be found either as a unique, firm, well-defined nodule ranging in size from 1 mm to 5 cm, or in clusters. In our case, it was a unique mass measuring 1.5 cm. They can be located anywhere on visceral wall in the submucosa. They are either solid or cystic, and at their edges they are whitish to yellow and often have a duct (or ducts) leading to the lumen, as in our patient. This is more likely when PH is found in or near Meckel's diverticulum. (11) Histologically, the components of the exocrine and endocrine duct system are distinguished in different proportions and combinations, as in our patient.

Most asymptomatic cases of PH are not recognized prior to surgery. They are discovered during surgery, histological study of the anatomical piece, abdominal examination or during an autopsy. (12) In cases of confirmed diagnosis in asymptomatic patients, the recommendation depends on the lesion's location and resectability. Potential for malignancy must always be taken into account. (11) Sometimes, monitored waiting is indicated, but if an incidental surgical finding is treated, it is advisable to perform complete resection to avoid late complications and the need for reoperation. (12)

About 30% to 40% of PH cases have gastrointestinal symptoms, as in this case, or complications such as acute pancreatitis, pancreatic cancer, insulinoma, gastrinomas and cystic degeneration. (9) Differential diagnosis should be made for leiomyomas, lymphomas, neuroendocrine tumor, gastrointestinal stromal tumor and metastatic lesions. (2, 3)

Principal diagnostic studies include gastroduodenoscopy, CT scans and endoscopic ultrasound. The latter was not available to us at the time of the study, but it is usually a very useful resource for detecting tumors smaller than 2 cm even though it is not specific and cannot exclude other pathologies such as carcinoids, fibroids, eosinophilic granulomas and leiomyomas. In symptomatic patients, surgical examination is usually required to make a definitive

diagnosis and to exclude other types of lesions including neoplasia.

## CONCLUSIONS

PH is infrequently diagnosed but is most often discovered in the duodenum, stomach, jejunum, ileum and Meckel's diverticulum. It may also be found in locations outside the digestive tract. A definitive diagnosis is often difficult. In this case, it was confirmed by histopathological studies.

### Conflicts of Interest

The authors declare that they have not received any financial assistance of any kind for this work.

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# Case report and literature review of Budd-Chiari syndrome during the puerperium

Gabriel Sebastián Díaz,[1] Carlos Alberto Salgado,[2] Adolfo Zuluaga,[3] Estefanía Orozco,[3] Juan Ignacio Marín.[4*]

1 Internist and Clinical Hepatology Fellow at the University of Antioquia in Medellín, Colombia
2 Physician, surgeon and Internal Medicine Resident at the Universidad Libre in Cali, Colombia
3 Undergraduate student at the Universidad Pontificia Bolivariana in Medellín, Colombia
4 Hepatology and liver transplant unit at Hospital Pablo Tobón Uribe and Professor at the Universidad Pontificia Bolivariana in Medellín, Colombia

***Correspondence:** marinji@hotmail.com

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## Abstract

Budd-Chiari syndrome is defined as obstruction of hepatic blood outflow. This obstruction can be located anywhere from the small hepatic veins at the entrance of the inferior vena cava to the right atrium. Most cases are primary Budd-Chiari syndrome which is caused by endoluminal thrombosis. Secondary Budd-Chiari syndrome occurs as the result of extrinsic compression associated with space-occupying lesions such as malignant tumors. Hereditary thrombophilic states are the main risk factors, but since pregnancy and the puerperium are hypercoagulable states, they can be associated with Budd-Chiari syndrome. Nevertheless, the prevalence of this type of case in the literature varies according to the population studied. There have been no studies on the incidence or prevalence of this disease in Colombia. The small number of case reports here have not been related to pregnancy.

We report the case of a patient who developed Budd-Chiari syndrome 12 weeks postpartum. Our report includes management and clinical evolution as well as a review of the literature of cases associated with pregnancy.

## Keywords

Budd-Chiari syndrome, postpartum period, venous thrombosis.

## INTRODUCTION

Budd-Chiari syndrome is a condition in which hepatic venous flow is obstructed anywhere from the hepatic veins to the site of attachment to the inferior vena cava and the right atrium. (1) It can be divided into primary and secondary. Primary Budd-Chiari syndrome is intraluminal vascular compromise usually due to thrombosis while secondary Budd-Chiari syndrome is due to extrinsic compression of the venous bed. Accepted causes of secondary obstruction include liver transplantation, liver resection, cardiac surgery, extrinsic compression and tumor invasion. (2) Epidemiology varies greatly throughout the world: in Denmark there is an incidence of 0.5 cases/million people/year while in Japan the prevalence reaches 2.4/million people with approximately 20 new cases each year. (3, 4) Established risk factors are include myeloproliferative syndromes, antiphospholipid syndrome, nocturnal paroxysmal hemoglobinuria, hyperhomocysteinemia, mutations of Factor V Leiden, mutations of the prothrombin gene (G20210A), deficiencies of C and S proteins, pregnancy, the puerperium, poverty and family history. (2) Pregnancy, a particularly hypercoagulable physiological state in preparation for childbirth, increases the risk of thromboembolic events with an incidence that is 7-10 times higher than in controls of the same age. (5, 6)

Similarly, there is clinical evidence that the risk continues during postpartum with a much higher incidence than among non-pregnant controls. (7) The literature on Budd-Chiari syndrome's relation to pregnancy and the puerperium reports rates of prevalence that vary greatly. (8) This article reports a case of postpartum Budd-Chiari

 

syndrome. We highlight the importance of taking into account pregnancy and the puerperium as risk factors in this group of patients.

## CLINICAL CASE DESCRIPTION

Our patient was a 14-year-old Afro-Colombian patient from the urban area of Quibdó, Chocó who had had a spontaneous term delivery without complications followed by postpartum contraception with depot medroxyprogesterone acetate. She had no other relevant medical history. In the second postpartum month, she developed generalized abdominal pain, increased abdominal perimeter and jaundice, but she did not consult until one month after the onset of symptoms at which time she had an episode of hematemesis.

Physical examination found that the whites of her eyes were jaundiced, and she had ascites and a palpable hepatomegaly four centimeters from the right costal edge. Digestive endoscopy showed hypertensive gastropathy and esophageal varices grade II. They were ligated endoscopically. She required paracentesis twice to evacuate ascitic fluid (5,000 and 7,000 mL) which had a high albumin gradient. The Doppler study of hepatic circulation showed an absence of flow in the suprahepatic veins. An abdominal CT scan showed portal hypertension (collateral circulation and ascites) with extensive thrombosis of the suprahepatic veins and hepatomegaly compressing the vein cava (Figure 1). This confirmed the diagnosis of subacute postpartum Budd-Chiari syndrome. Laboratory studies are described in Table 1. The Rotterdam score, a prognostic index for

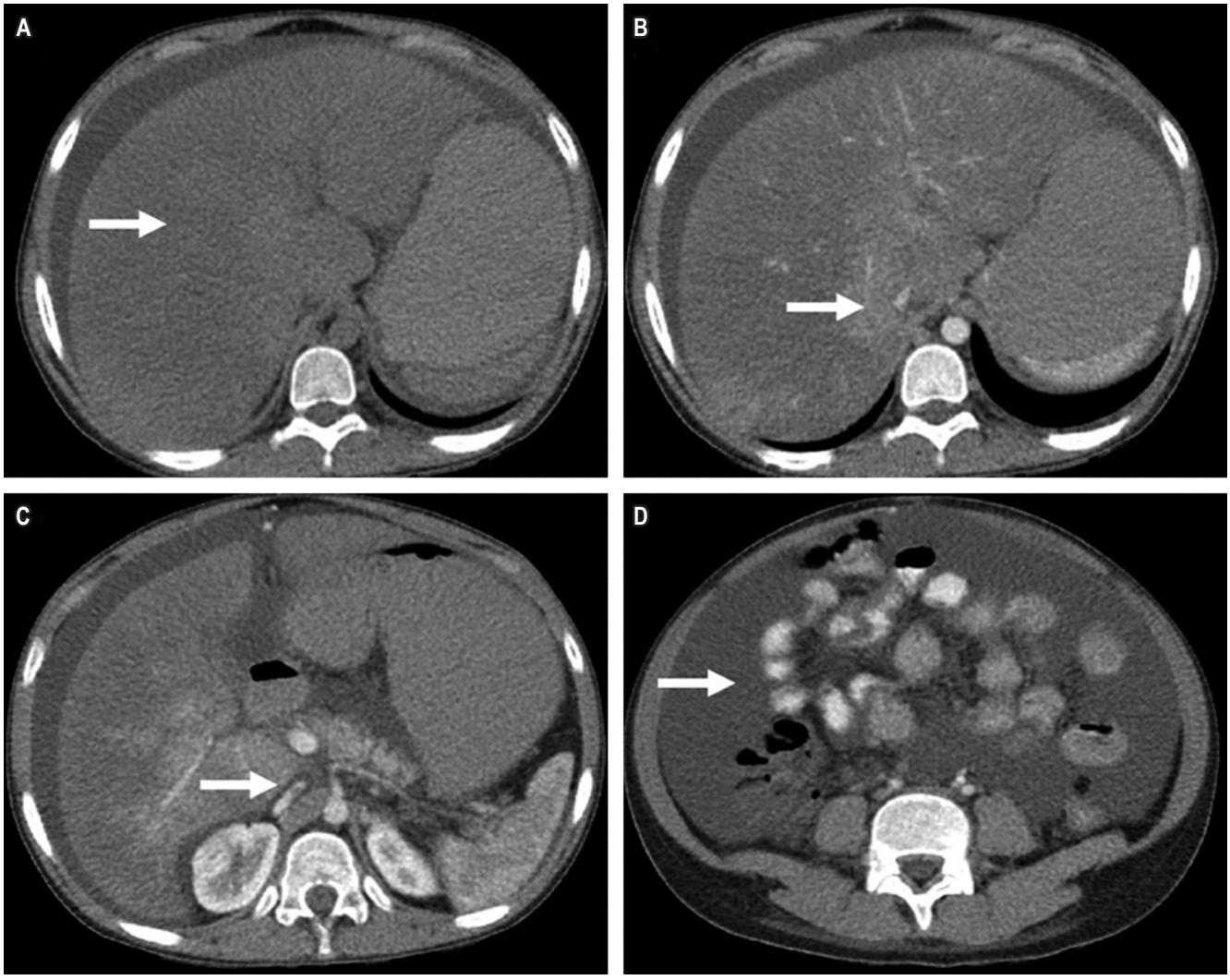


**Figure 1.** CT scan of the abdomen and pelvis. **A.** Phase without contrast shows hepatomegaly. **B.** Contrasted phase shows absence of suprahepatic vein flow. **C.** Contrasted phase shows compression of the inferior vena cava. **D.** Contrasted phase shows ascites.

Budd-Chiari syndrome, was 1.16 which placed her at intermediate risk. Studies were extended in search of thrombophilia to explain the etiology of the clinical picture, but none of these tests were positive. This confirmed the causal relationship between the hypercoagulable state of the puerperium as and Budd-Chiari syndrome. We considered that the use of medroxyprogesterone had probably enhanced the thrombotic condition.

**Table 1.** Laboratory Test Results

| Tests | Results | Reference values |
|---|---|---|
| ALT | 11 | 0 to 35 U/L |
| AST | 27 | 0 to 35 U/L |
| Total bilirubin | 2.82 | 0.3 to 1 mg/dL |
| Direct bilirubin | 1.92 | 0.1 to 0.3 mg/dL |
| Alkaline Phosphatase | 53 | 30 to 120 U/L |
| GGT | 72 | Up to 40 U/L |
| Creatinine | 0.79 | <1.5 mg/dL |
| Sodium | 140 | 136 to 145 mEq/L |
| Potassium | 3.47 | 3.5 to 5 mEq/L |
| Albumin | 6.1 | 3.5 to 5.5 g/dL |
| Leukocytes | 7700 | 4,500 to 11,000/mm$^3$ |
| Hemoglobin | 9 | 12 to 16 g/dL |
| Hematocrit | 27 | 36 to 46 % |
| Neutrophils | 50 % | 40 to 70 % |
| Lymphocytes | 34 % | 22 to 44 % |
| Platelets | 238,000 | 150,000 to 350,000/mm$^3$ |
| PT | 21.1 | 11.1 to 13.1 sec |
| PTT | 42 | 22.1 to 35.1 sec |
| INR | 1.99 | 0.9 to 1.2 |
| AgsHB | Negative | NR |
| HCV antibody | Non- reactive | NR |
| ANA | Negative | Negative |
| IgG anticardiolipin antibody | 1.5 | 0 to 15 U |
| IgM anticardiolipin antibody | 13.5 | 0 to 15 U |
| DRVVT | <1.10 | <1.10 |
| Anti β2 glycoprotein antibody | <20 U | <20 U |
| IgM-IgG-IgA | Negative | Negative |
| Leyden Factor V | Negative | Negative |
| Prothrombin gene mutation | Negative | Negative |
| JAK-2 Mutation | 0.9 IU/mL | 0.8 to 1.2 IU/mL |

HCV: hepatitis C virus; AgsHB: hepatitis B virus surface antigen; ALT: alanine aminotransferase; ANA: antinuclear antibodies; AST: aspartate aminotransferase; dRVVT: dilute Russell's viper venom time; GGT: gamma glutamyl transpeptidase; IgA: immunoglobulin A; IgG: immunoglobulin G; IgM: immunoglobulin M; INR: International Normalized Ratio; NR: not reactive; PT: prothrombin time; PTT: partial thromboplastin time.

The patient's hepatic hemodynamics were measured, and angiography of the vena cava was performed. Total chronic occlusion of hepatic outflow was found. Blood flow had been diverted through a collateral and hepatic venous pressure gradient (GPVH) of 22 mm Hg with no possibility of management through stenting. Consequently, a 10 x 70 mm Viatorr transjugular intrahepatic portosystemic shunt (TIPS) was placed. This required a 10 x 60 mm proximal stent extension. Angiographic monitoring revealed disappearance of varicose veins, and post-TIPS GPVH was 8 mm Hg (Figure 2). After the procedure, the patient began to progressively improve. Abdominal pain diminished, ascites was brought under control with diuretics, and there was no need to perform paracentesis again. In addition, aminotransferase and bilirubin levels decreased. The patient was discharged with a prescription for anticoagulation with low molecular weight heparins. Two subsequent follow-up examinations found that the patient had no ascites, her hepatomegaly had resolved, and her liver profile was normal. Doppler studies during follow-ups confirmed permeability of the TIPS.

## DISCUSSION

The postpartum period is associated with increased risks of thrombotic events. (9) Although the puerperium is currently definition as the six weeks following delivery, some studies indicate that high risk of thrombosis continues as long as 12 weeks after giving birth. (9) Various studies have reported thrombotic complications such as myocardial infarction, stroke and venous thromboembolism during the puerperium. (10-12) Nevertheless, reports of Budd-Chiari syndrome related to pregnancy and the puerperium are very variable. (8) A recent systematic review that brought together 120 patients with Budd-Chiari syndrome related to pregnancy found the prevalence of this syndrome to be 6.8%. (6) This places pregnancy as a hypercoagulable state with an associated prevalence similar to those of other known risk factors such as the Leiden V mutation, the prothrombin gene G20210A and other types of thrombophilia. Therefore, when the etiology of a case of Budd-Chiari syndrome is evaluated, pregnancy should be considered a risk factor.

The systematic review described brings together patients from 20 countries, predominantly from Asia and Europe. (6) Although the report of this case is important, information about the real prevalence of risk factors for Budd-Chiari in Colombia requires a collaborative study of the referral centers where we patients with hepatic vascular pathologies are evaluated. There are even cultural differences in the management of the puerperium. In India, where reported prevalence of Budd-Chiari syndrome related

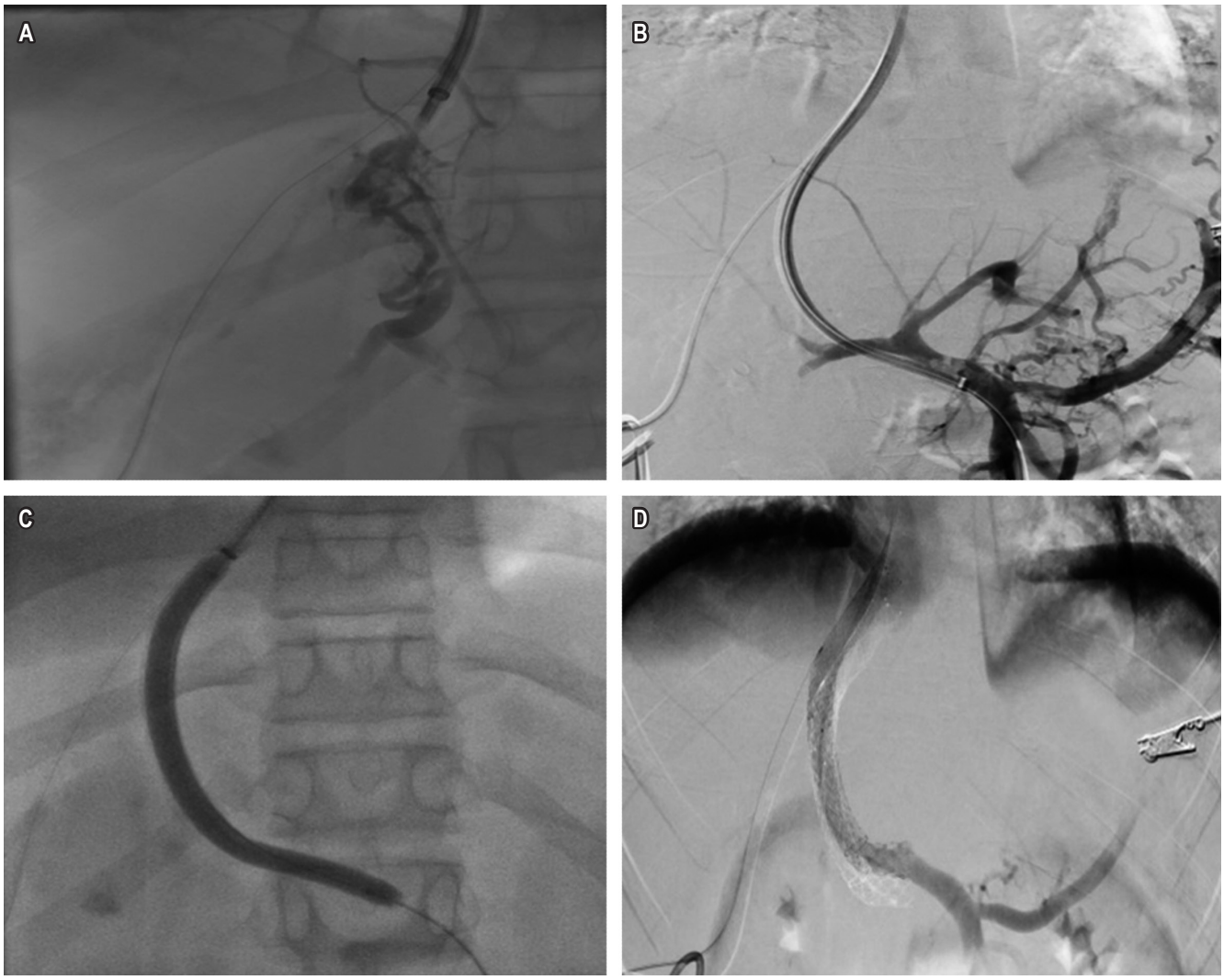


**Figure 2.** TIPS implant. **A.** Complete obstruction of suprahepatic veins with collateral flow bypass. **B.** Permeability of the portal vein and its branches, esophageal varices. **C.** Balloon dilation of the TIPS path. **D.** GORE® VIATORR® TIPS Endoprosthesis with proximal extension (10 x 60 mm self-expanding stent), disappearance of esophageal varices.

to pregnancy is as high as 13.1%, occurrence seems to be related both to the puerperal hypercoagulable state and to postpartum rest with limited access to good hydration of between 30 and 40 days. (13) A similar belief still exists in Colombia, especially in rural areas.

Most commonly, the clinical presentation of Budd-Chiari syndrome associated with pregnancy is acute and is due to thrombosis of the suprahepatic veins with obstruction of the outflow tract. (14) This was the case in our patient although the patient consulted late due to social difficulties.

Better understanding of this disease combined with development of new treatments has made it possible to modify the natural history of patients with Budd-Chiari syndrome. Depending on the situation of each particular patient and the hepatic hemodynamics findings, the step-by-step treatment algorithm validated in a number of cohorts proposes initial management with anticoagulation, followed by angioplasty or placement of a stent with thrombolysis, followed by placement of a TIPS. Performance of liver transplantation is necessary in cases of acute liver failure, chronic liver failure or when the Rotterdam score is adverse. (15, 16) In the case we have reported, the hemodynamic findings of chronic thrombosis with complete occlusion of the outflow tract indicated placement of a TIPS. Thanks to the availability of this device, decompression of the hepatic outflow tract and clinical recovery were achieved.

Finally, with this case we want to highlight that pregnancy and the puerperium should be understood as hypercoagu-

lable states that are risk factors for hepatic vascular events in this specific population group.

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# Ancylostomiasis: a rare cause of gastrointestinal bleeding and severe anemia

Edwar Jassir Rozo O.,[1] Ledmar Jovanny Vargas R.,[2*] Jessica Paola Jiménez W.,[2] Erika Tatiana Szemmelveisz N.[3]

1 Specialist in internal medicine in the department of internal medicine at the Regional Hospital of Chiquinquirá in Chiquinquirá, Boyacá, Colombia
2 General Practitioner at the University of Boyacá
3 Specialist in internal medicine in the department of internal medicine at the Regional Hospital of Chiquinquirá and 12th semester at the Universidad Juan N. Corpas in Chiquinquirá, Boyacá, Colombia

***Correspondence:** lejovaro@gmail.com.

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**Abstract**

Anemia is characterized by low levels of hemoglobin. In Colombia, anemia affects 27.7% of the population. The most seriously affected populations are preschool children, women of reproductive age, pregnant women and the elderly. **Clinical case:** Upon admission, the 58-year-old patient was found to have a condition compatible with cardiomegaly and redistribution of blood flow and required a blood transfusion. Additional studies suggested that digestive hemorrhaging due to ancylostomiasis could be the cause. Treatment with anthelmintics was begun and had good clinical and paraclinical results. **Discussion:** Acquisition of this parasite, considered to be a forgotten cause of digestive bleeding, is associated with multiple risk factors. In some cases, there are severe consequences such as cardiomegaly and redistribution of blood flow. The effectiveness of treatment with anthelmintics ranges between 62% and 92%.

**Keywords**

Ancylostomiasis, anemia, iron deficiency, helminths, intestinal parasitosis.

## INTRODUCTION

Anemia is characterized by low levels of hemoglobin, the protein that is the main component in erythrocytes. It is essential for their proper functioning and is synthesized in the bone marrow. (1)

Epidemiologically, it is estimated that 1.6 billion people in the world have anemia. (2) In Colombia, it affects 27.7% of the population: about 15 million people out of the country's population of 48,700,000 have some degree of anemia. (3)

The most severely affected populations are preschool children, women of reproductive age, pregnant women and elderly people. (1, 3, 4) Anemia's multiple causes include malnutrition, micro nutrient and macronutrient deficiencies, iron deficiency, plant-based diets, hemoglobin pathologies, (5) malaria, intestinal parasitosis, and gastrointestinal bleeding. (6)

In this article, we present the clinical case of a patient who presented severe anemia secondary to gastrointestinal bleeding due to ancylostomiasis.

## CLINICAL CASE

A 58-year-old farmer came to the hospital after five days of moderate to severe abdominal pain located in the mesogastrium associated with hyporexia, asthenia and adynamia but which did not radiate. He also reported that he had suffered trauma to his lower right leg which had caused pain and limited his ability to walk.

Vital signs found during physical examination were as follows: heart rate (HR): 125 beats per minute, respiratory rate (RR): 24 breaths per minute (BPM), blood pressure: 130/87, temperature: 36.7, and body mass index (BMI): 18.3 kg/m$^2$. The patient was pale and had intercostal retractions and rales in his lung segments. On superficial palpa-

 

tion of the mesogastrium, he experienced pain with voluntary muscular defense. Patient had no signs of peritoneal irritation, erythema, or edema. He also had no sign of heat in the internal malleolus of his lower right leg.

Paraclinical tests performed at admission (Table 1) showed hypochromic microcytic anemia with anisocytosis. His clinical picture suggested cardiomegaly and redistribution of blood flow. After reviewing the results, it was decided to transfuse two units of red blood cells.

**Table 1.** Paraclinical tests performed at admission

| Diagnostic test | Result | Reference |
|---|---|---|
| Leukocytes | 10.4 × 109/L | 4.5 to 11.0 × 109/L |
| Neutrophils | 80 % | Up to 85 % |
| Eosinophils | 3 % | Up to 5 % |
| Hemoglobin | 6.0 g/dL | 13 to16 g/dL |
| Hematocrit | 17.5 % | 36% to 52 % |
| MCV | 60 fL | 80 to 100 fL |
| MCHC | 23.3 g/dL | 27 to 32 g/dL |
| RDW | 20.30 % | 0% to 16 % |
| Platelets | 356 × 109/L | 150 to 450 × 109/L |
| Creatinine | 0.93 mg/dL | Up to 1.2 mg/dL |
| PT | 16 s | 9 to 16 s |
| PTT | 33.4 s | 25 to 35 s |

MCHC: mean corpuscular hemoglobin concentration; PT: prothrombin time; PTT: partial thromboplastin time; RDW: red blood cell distribution width; MCV: mean corpuscular volume.

The next day the patient's condition improved with vital signs within the normal range: HR: 90 bpm, RR: 18 bpm, and BP: 122/72. His post-transfusion blood count showed an increase in serum hemoglobin values. Complementary studies were then done to determine the cause of anemia (Table 2).

**Table 2.** Follow-up paraclinical tests and extension studies

| Diagnostic tests | Results | Reference |
|---|---|---|
| Hemoglobin | 8.4 g/dL | 13 to 16 g/dL |
| Hematocrit | 25% | 36% to 52% |
| MCV | 62.2 fL | 80 to 100 fL |
| MCHC | 26.4 g/dL | 27 to 32 g/dL |
| RDW | 22.30% | 0% to 16% |
| Peripheral blood smear | Normal | Normal |
| Ferritin | 82 ng/mL | 12 a 150 ng/mL |
| Transferrin | 400 mg/dL | 170 a 370 mg/dL |
| Fecal occult blood | Positive | Negative |
| Direct Coombs test | Negative | Negative |
| Reticulocyte count | 3.36% | 0.3% to 4.5% |

A colonoscopy was normal, and the only finding from a total abdominal ultrasound was a moderate splenomegaly (160 x 92 mm). Upper endoscopy found a hiatal hernia without esophagitis and duodenal ancylostomiasis ( Figure 1).

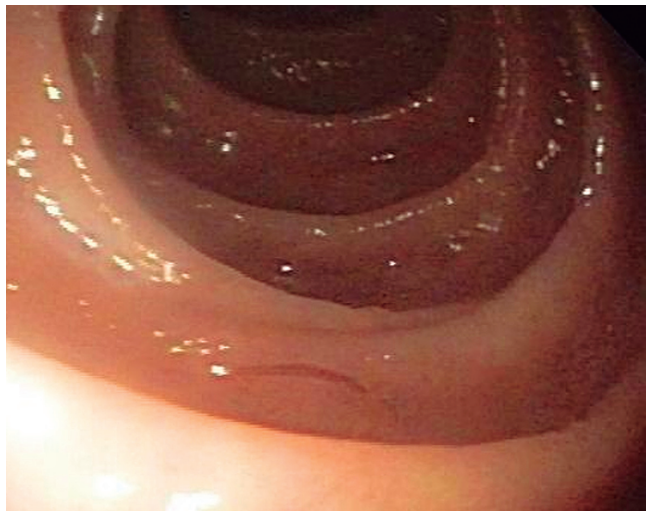

**Figure 1.** Upper digestive endoscopy shows duodenal ancylostomiasis.

When the patient was questioned about risk factors, he mentioned that his drinking water came from a deep well, he did not have adequate hand hygiene, and his socioeconomic condition was irregular because he was living in a rural area.

We considered that the patient was suffering from iron deficiency anemia secondary to hemorrhaging of his digestive tract due to ancylostomiasis. We decided to treat him on an outpatient basis with two 400 mg doses of albendazole supplemented with 300 mg of ferrous sulfate every 12 hours and 500 mg of cephalexin every 6 hours to treat the infection in his lower right leg.

At his one month follow up the patient's conditi0on had improved. Physical examination showed adequate general conditions with vital signs within the normal range, no signs of anemia, and normal hemoglobin values in the control blood count.

## DISCUSSION

Ancylostomiasis can be caused by either ancylostoa duodenale (old world hookworm) or necator americanus (new world hookworm), the latter of which is typical of tropical areas. Approximately 31% of the people who live in these areas have intestinal parasitosis. (7) This tropical disease's economic burden ranges from 7.5 to 138.9 billion pesos per year. (8)

Risk factors associated with the acquisition of these parasites include personal hygiene, consumption of contamina-

ted water, housing in rural areas, being barefoot, engaging in agricultural work, malnutrition and blood type A. (9, 10) The patient in the case presented here had several of these risk factors.

The parasite can enter the body in either of two ways. Most often its larvae penetrate the skin, migrate through the circulatory system to the lungs, and ascend through the respiratory tract until they reach the digestive tract. However, they can also be acquired orally. When they are, there is no associated pulmonary cycle so they affect only the small intestine. (11) Once the parasites are in the small intestine, they cause blood loss due to suction or intestinal ulcers. (6) These losses amount to 0.3 to 60 mL per day which is why ancylostomiasis is considered to be a cause of digestive bleeding. (12, 13)

Twenty-two percent of ancylostomiasis patients may have anemia. Of these, only 1.9% develop severe anemia (<7 mg/dL) which is why it is considered infrequent. (14)

The clinical picture of ancylostomiasis can include abdominal pain, hyporexia, asthenia, adynamia, malnutrition, drum stick fingers and anemia. (15) Anemia decreases oxygen transport capacity which results in activation of compensatory mechanisms such as increase production of 2,3-Bisphosphoglyceric acid and overproduction of erythropoietin to conserve tissue oxygenation. When levels fall below 10 g/dL, increased sympathetic activity produces an increase in cardiac output, which can result in tachycardia and hypertension, and a decrease in blood viscosity which can cause pleural effusions and eventually produce respiratory distress. In the long term, this leads to a remodeling of the left ventricle, and it can trigger heart failure. These changes are included in the concept of cardiomegaly and redistribution of blood flow. (16)

Splenomegaly can occur as a result of hyperplasia of cells of the mononuclear phagocyte system (MPS) associated with the infectious process or secondary to cardiomegaly and redistribution of blood flow. (17)

This entity should be suspected in patients from rural areas, especially if they have digestive symptoms, eosinophilia (present in 30% to 50% of cases) or anemia. (18) The latter is characterized by microcytosis, hypochromia, anisocytosis and elevated reticulocytes, (15) all of which were found in the tests performed on our patient.

Diagnosis requires clinical suspicion and is made by identifying the parasites' eggs in a stool test. Nevertheless, a direct stool exam has low sensitivity, so analysis of three samples for three consecutive days is recommended. On rare occasions including this case, the parasite can be visualized in the small intestine during the performance of standard endoscopic studies. (19)

The use of albendazole in doses of 400 mg/day is effective for community deworming which reduces the prevalence of helminthiasis. (20) Mebendazole in 100 mg doses twice a day for 3 days can also be used. The success of the treatment varies between 69% and 92% depending on the regimen used. (21)

## CONCLUSIONS

Ancylostomiasis is an important cause of gastrointestinal bleeding that has been forgotten. One fifth of these patients have iron deficiency anemia, but only 2% have severe clinical pictures. The diagnosis is made by viewing the parasite either through microscopic analysis of stool samples or through endoscopy. Treatment uses anthelmintics which are highly effective for deworming.


### Acknowledgements

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### Conflicts of Interest

The authors have no conflicts of interest.

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# Transcatheter venous coil embolization of gastric varices

Oscar Rivero Rapalino,[1] Camilo Barragán Leal,[2] Diego Salcedo Miranda,[3*] Laura Quintero Rojas.[3]

1 Interventional radiologist at Hospital Universitario fundación Santa Fe and Universidad El Bosque in Bogotá, Colombia
2 Radiologist at Hospital Universitario fundación Santa Fe and Universidad El Bosque in Bogotá, Colombia
3 General Surgery Resident at Hospital Universitario fundación Santa Fe and Universidad El Bosque in Bogotá, Colombia

***Correspondence:** dsalcedo_ub@hotmail.com

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**Abstract**

Coils and microcoils, the most commonly used embolization agents, have reported technical success rates ranging from 81% to 100% of cases. The spirals or coils are available in a wide variety of configurations and sizes which fit into vessels of different calibers. They have good radiopacity allowing for accurate release. Coils are the analogue of a surgical arterial ligation, because they produce mechanical occlusion due to their positioning in the vascular lumen. This decreases blood flow while their synthetic fibers have an additional thrombogenic effect. **Case:** We present four cases of coil embolization treatment of gastric varicose veins at our institution. All procedures were successful and had good technical results. We also present a review of the literature.

**Keywords**

Digestive bleeding, gastric varices, embolization, coils.

## INTRODUCTION

Embolization is the endovascular treatment of choice for acute bleeding of the upper gastrointestinal tract, hepatobiliary bleeding and lower digestive tract bleeding. Superselective arterial catheterization or venous catheterization using a microcatheter with a caliber less than 3 French (F) is generally required. The catheter is advanced coaxially through a diagnostic catheter (usually 5 F) to those distal vascular segments or as close as possible to the site that is bleeding. This technique allows more selective embolization and avoids other vascular territories which decreases the risk of intestinal ischemia. (1, 2)

Arterial embolization is a feasible treatment of upper gastrointestinal bleeding because it carries no significant risk of ischemia due to the wide network of collateral arteries that supply the upper gastrointestinal tract. The arterial segments proximal and distal to the hemorrhage should be embolized to prevent retrograde irrigation of the artery and new episodes of bleeding. This is known as closing the front and back doors of the bleeding site. (2)

Even though some cases of intermittent gastrointestinal bleeding cannot be identified during arteriography, blind embolization of the bleeding vessels is possible. Due to the rich vascular irrigation of the upper gastrointestinal tract, the segment where the bleeding is probably located can be guessed and targeted. It has been reported that this type of empirical embolization can be performed in up to 46% of all cases, and it has been shown that there are no statistically significant differences in the clinical outcomes of these patients. (2-4). It is even possible to embolize branches of the hepatic artery without a significant ischemic risk due to dual irrigation of the liver (75% through the portal vein and 25% through the hepatic artery). (2)

For 25 years gastric varices have also been managed with balloon-occluded retrograde transvenous obliteration (BRTO) which requires a sclerosing agent and a permanent balloon to retain the sclerosing agent in the gastric

 

varice, to prevent it from going into systemic circulation, and to optimize the sclerosis of the vessels causing local early thrombosis. Numerous variables involved in this technique have been described. In fact, variations of it do not require balloon occlusion which can be replaced with a wide variety of embolization materials. Nevertheless, there is no conclusive evidence showing that any single embolization agent is better than the others. In practice, use of these techniques depends on the experience and preference of the operator and the availability of the product. The most commonly used embolic agents are spirals or coils. Others include absorbable gelatin sponges (Gelfoam®), particles and liquid embolic agents. (2, 5)

Embolization spirals (coils or microcoils) have reported technical success rates ranging from 81% to 100% of cases. Coils are available in a wide variety of configurations and sizes that can be used in different calibers vessels. Because they have good radiopacity, they can be released accurately. These coils are the analogues of surgical arterial ligation because they produce mechanical occlusion due to positioning in the vascular lumen which decreases blood flow. In addition, their synthetic fibers provide a thrombogenic effect. (1, 5, 6 )

Gelfoam® sponges, polyvinyl alcohol particles, and trisacryl gelatin microspheres have all been used successfully, but controlling their release is more difficult and less precise than controlling coil release. Another disadvantage of embolization particles is that they can reach the blood circulation of the distal intestinal wall which increases the risk of ischemia potentially compromising circulation in vascular territory. To avoid this risk, larger particles measuring more than 500 microns (μ) should be used. Gelfoam® sponges produce temporary occlusion which has the theoretical advantage of allowing recanalization of embolized vessels within two to six weeks. Nevertheless, intestinal ischemia occurs in the first eight to twelve hours after interruption of blood flow, so these sponges have this risk. (1, 5, 7)

Technical success of embolization is close to 100%, and it can satisfactorily control digestive hemorrhaging in 80% to 90% of patients. Recurrent bleeding is uncommon except in cases of angiodysplasia, arteriovenous malformations and inflammatory lesions. It has been reported in approximately 15% of patients. New bleeding episodes may require a second performance of arteriography and embolization, but this does not increase the risk of intestinal ischemia. (1, 5, 8, 9)

Major complications related to arterial embolization include intestinal ischemia and contrast-induced nephropathy. Today, clinically relevant ischemic complications occur in less than 2% of patients thanks to the development of microcatheter technology and improvement of embolization materials. Most complications are insignificant and do not require additional treatment. (2, 5)

In addition, gastric varices' pathological and hemodynamic characteristics are slightly different from those of esophageal varices. Most gastric varices are secondary to portal hypertension. Other causes include varicose veins secondary to thrombosis of the splenic vein. BRTO is another highly effective minimally invasive procedure for treating isolated gastric varices, especially in patients with poor functional hepatic reserve who are not candidates for TIPS. This technique uses a catheter with a distal balloon that obstructs blood flow during injection of the sclerosant through portosystemic veins (usually a gastrorenal shunt) to adequately fill the varicose veins with enough time for sclerotherapy to be effective while preventing reflux of the sclerosant into the systemic or portal circulation. (2)

We replaced the balloon used in BRTO with coils and obtained good results and good bleeding control. We present a series of four cases of control of upper gastrointestinal hemorrhaging due to gastric varices with gastrorenal shunt in our institution that we treated with transcatheter venous embolization with coils. We obtained good technical results and good bleeding control in all four patients.

## CASE SERIES

### First case

This patient was a 74-year-old man who had a history of metastatic hepatocellular carcinoma, cirrhosis, and tumor invasion of the portal vein who came to the hospital after two days of bloody stools. Upper digestive tract endoscopy found small esophageal varices with no signs of bleeding. A subcardial varice was found. It extended approximately 15 mm towards the gastric fundus and had signs of bleeding with red signs at the level. In addition, an ulcerated area on the surface without active bleeding was found. We concluded that the patient had upper digestive bleeding from a large varicose vein in the fundus that was secondary to portal hypertension. Because he was not a candidate for endoscopic management, interventional radiological evaluation was requested. They performed an abdominal CT scan which found tortuous varices adjacent to the lower curvature of the stomach (Figure 1A). Selective venography was used to make the tortuous varices in the lesser curvature, some paraspinal drainage veins, and a gastrorenal shunt opaque. (Figure 1B) Coil embolization (Figure 1C) was used to occlude the flow in the varicose veins. The procedure was performed without complications, and the patient was discharged two days later.

### Second Case

This patient was a 60-year-old man who had previously undergone the Puestow procedure to treat pancreatic neo-

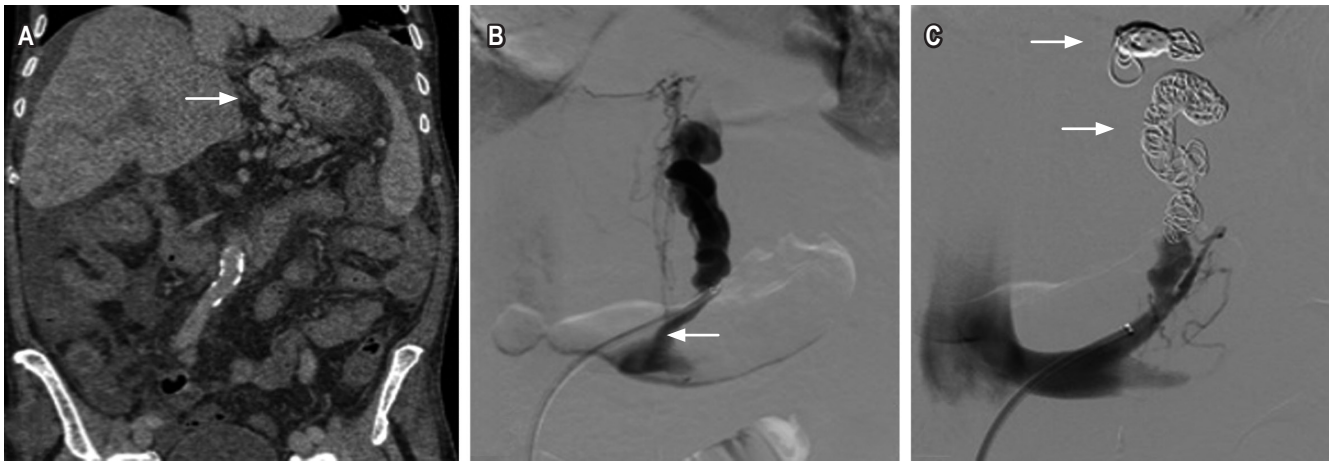


**Figure 1.** 74 year old man. Cirrhosis, gastric varices with gastrorenal shunt. **A.** Contrast abdominal CT scan shows coronal cut with soft tissue window showing tortuous varices adjacent to the lower curvature of the stomach (arrow). **B.** Selective venography opacifying tortuous varices in lesser curvature, with some paraspinal drainage veins and gastrorenal shunt (arrow). **C.** Coil embolization (arrow) occluding the flow in varicose veins.

plasia. He came to the hospital because of melena and anemia with a hemoglobin level of 7 g/dL. Upper endoscopy found blood in the gastric cavity. A large clot was found in the posterior wall of greater curvature of the stomach, but it was not removed because bleeding was observed from the tissue below it. Sclerotherapy with adrenaline solution was performed. An endoscopic follow up examination found two large groups of varices that were not actively bleeding in the fundus of the stomach. Because of their sizes, it was not possible to ligate them, so embolization was required. An abdominal CT scan showed the tortuous varices in the lower curvature of the stomach (Figure 2A). Selective venography was used to opacify the tortuous varices in the lesser curvature and a gastrorenal shunt (Figure 2B). Coil embolization (Figure 2C) was used to occlude the flow of blood in the varicose veins. The procedure was performed without complications, and the patient was discharged the next day.

## Third Case

This 66-year-old woman had a history of primary biliary cirrhosis and portal hypertension. She came to the hospital after two episodes of hematemesis. Upper endoscopy found four dilated varices in the distal third of the esophagus occupying 25% of the esophageal lumen. There were no signs or stigmas of recent or old acute bleeding. Remains of

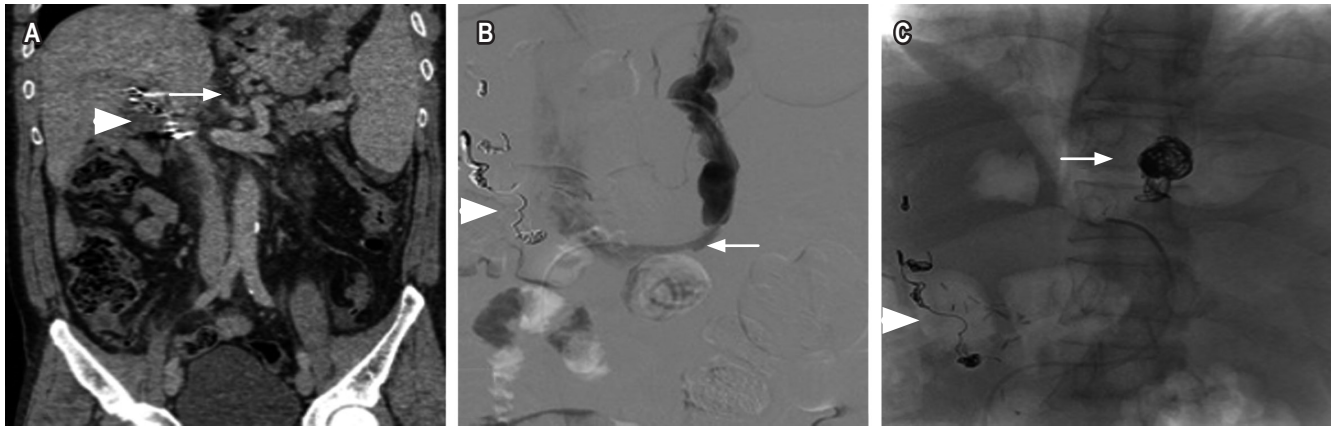


**Figure 2.** A 60-year-old man who had undergone pancreatoduodenectomy had developed a hepatic artery pseudoaneurysm with gastric varices and gastrorrenal shunt which were embolized with coils (triangles A, B and C). **A.** Contrast abdominal tomography shows coronal cut with soft tissue window showing tortuous varices in the lesser curvature of the stomach (arrow). **B.** Selective venography opacifying tortuous varices in the lesser curvature and gastrorenal shunt (arrow). **C.** Coil embolization(arrow) occluding the flow in varicose veins.

old blood were found in the gastric lake, but there was no evidence of active bleeding. A large subcardial varice was found near the greater curvature but there were no stigmas of acute, recent or old bleeding. An abdominal MRI found tortuous varices and a gastrorenal shunt adjacent to the lower curvature of the stomach (Figure 3A). The patient was considered to have a high risk of bleeding, so she required embolization. Selective venography opacified the tortuous varicose vein in the lesser curvature, and the gastrorenal shunt (Figure 3B). Coil embolization(Figure 3C) occluded the flow in the varicose veins. This procedure was performed without complications and the patient was discharged early.

## Fourth Case

This 69-year-old woman had a history of Child Pugh C alcoholic liver cirrhosis. She came to the hospital because of bleeding esophageal and gastric varices that were difficult to treat endoscopically. The patient required protection of the airway due to the risk of bronchoaspiration, and she received multiple transfusions and vasopressor support. Embolization by way of the route through the abdominal wall and the parenchyma of the liver was considered. An abdominal CT scan showed tortuous varices adjacent to the lower curvature of the stomach (Figure 4A). Selective retrograde portal access venography opacified the tortuous

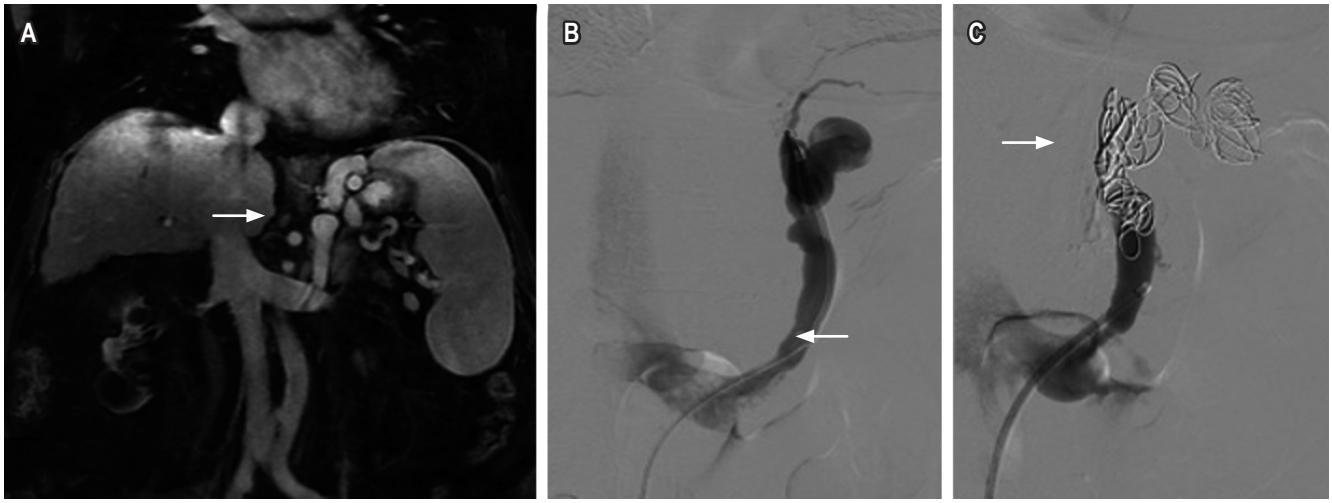


**Figure 3.** 66 year old woman with liver cirrhosis. **A.** Contrast abdominal magnetic resonance, T1 coronal section with fatty saturation, tortuous varices adjacent to the lower curvature of the stomach and gastrorenal shunt (arrow). **B.** Selective venography opacifying tortuous varice in the minor curvature and gastrorenal shunt (arrow). **C.** Coil embolization (arrow) occluding the flow in varicose veins.

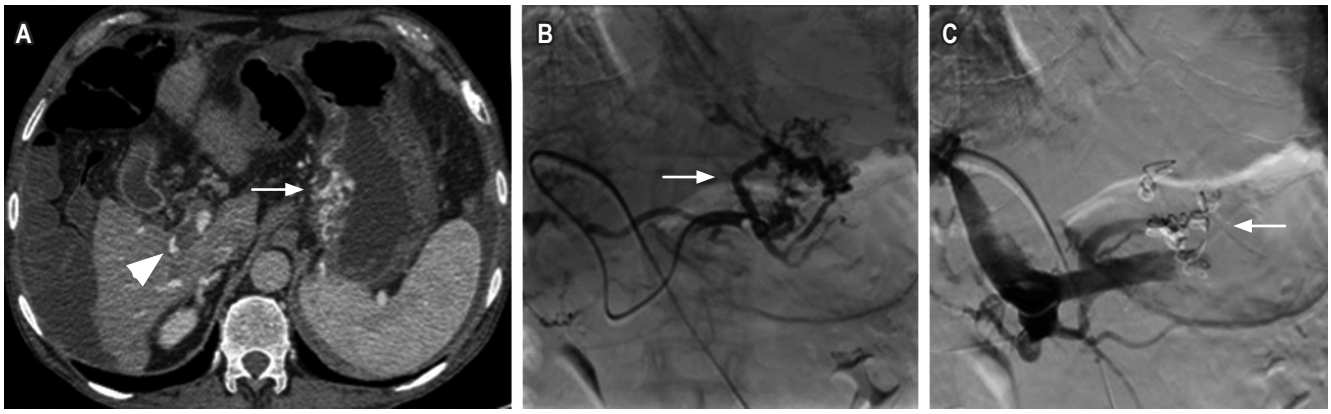


**Figure 4.** 66-year-old woman with liver cirrhosis who was not a candidate for TIPS due to portal thrombosis (triangle A). **A.** Abdominal CT scan shows axial cut with soft tissue window and tortuous varices adjacent to the lower curvature of the stomach (arrow). **B.** Selective retrograde portal venography opacifying tortuous varices in the lower curvature of the stomach (arrow). **C.** Coil embolization (arrow) occluding the flow through varices.

varices in the lower curvature of the stomach (Figure 4B), and coil embolization and Gelfoam® (Figure 4C) were used to occlude the flow of blood through the varices. The procedure was performed without complications and the patient's bleeding was controlled.

## DISCUSSION

Upper gastrointestinal bleeding secondary to gastroesophageal varices is a major complication in patients with cirrhosis and portal hypertension: Its reported incidence is between 4% and 14%. It is increasingly common due to increase number of patients with liver pathologies. In turn, it indicates portal vein hypertension of which cirrhosis is the most frequent cause. (10, 11) Varices are the source of approximately 59% of the cases of upper gastrointestinal bleeding in cirrhotic patients. Peptic ulcers, the second leading cause, account for only 16% of cases. (12, 13)

A gastric varicose vein system is defined as a gastrorrenal shunt, gastric varices in the submucosa, extragastric varices, and the veins, especially the portal vein. Between 60% and 80% of gastric varices are associated with spontaneous portosystemic communication on the left side, including especially gastro-splenic shunts. (14) These have been associated with a higher mortality rate. Endoscopic treatment of them is not always very effective, (12, 14) so angiography and embolization of bleeding gastric varices is indicated in these cases. This subgroup of patients requires angiographic intervention to locate the source of the bleeding. Treatment should be done by the endovascular route. (2, 5, 15, 16) For this reason, transcatheter venous coil embolizations were performed on the four patients in this series.

The current technique of coil embolization for treatment of acute gastrointestinal bleeding successfully controls bleeding in approximately 80% to 90% of patients. (8, 9) It is a safe technique in which the coil's fibers cause thrombosis of the vessel while the coil itself functions as a scaffold for the thrombus. Significant adverse events occur in less than 2% of patients. (2) One disadvantage of this mechanism is that it prevents future endovascular access to the specific lesion, but the rates of new hemorrhaging after coil embolization are between 0% and 40%. (6) Some embolized patients very selectively develop minor, asymptomatic and self-limiting ischemic changes such as small ulcers. In addition, very selective coil embolization is unlikely to cause a delayed infarct since this complication typically occurs within the first 48 hours after the embolization procedure. Coil embolization of blood vessels that are not targeted is rare since coils are introduced only after a microcatheter has been successfully inserted into the target vessel. For this reason, one must carefully choose the appropriate coil size since an oversized coil can displace the microcatheter from its superselective position. This could lead to coil deployment in a vessel other than the one chosen for embolization. Similarly, insufficiently large coils may not adequately occlude the target vessel or they may lodge distally to the lesion to be treated thereby decreasing the procedure's success rates. (5) Nevertheless, because of the large caliber of the left gastric vein and gastric varices combined with the high rate of blood flow through the splenic-renal shunt, some authors such as Ford et al. prefer to oversize coils used in in the venous system by at least 15% to 20% to minimize the probability of migration. (17). In our cases there were no major or minor complications during or after transcatheter venous coil embolization, and there were no subsequent migrations of coils.

BRTO is a highly effective, minimally invasive treatment of isolated gastric varices especially for patients with poor functional hepatic reserve who are not candidates for TIPS such as some of our patients. This technique uses a catheter with a distal balloon that obstructs blood flow during injection of the sclerosant through the veins of the portosystemic communication (usually gastrorenal). It allows adequate filling of the varicose veins with enough time for sclerotherapy to be effective while preventing reflux of the sclerosing substance into systemic or portal circulation. (2) Nevertheless, we consider, as do some reviews in the literature, that transcatheter venous coil embolization has tended to replace the BRTO because the logistic load that can wear out the interventional radiology team and increase expenditure of hospital resources. In addition, since replacement of the balloon with coils is technically feasible, (18) we use transcatheter venous coil embolization. To date, we have obtained good results.

## CONCLUSION

Transcatheter venous coil embolization is an effective and safe alternative to emergency surgery in patients with hepatobiliary pathologies for whom surgery could increase morbidity and mortality. Technical advances and increasing availability of diagnostic angiography and transcatheter embolization have strengthened this option for treating bleeding gastric varices that are refractory to medical and endoscopic therapy.

### Ethical Approval

Informed written consent was obtained from all patients for publication of this document.


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# An endoscopic videocapsule finding of heterotopia of the gastric mucosa of the small intestine

Santiago Castaño Quintero,[1*] Natalia Calvache,[2] Mauricio Sepúlveda,[3] Catalina Maldonado,[3] Pedro Tomás Argüello,[4] Juliana Escobar,[5] Carlos Arturo Rojas.[3]

1 Resident in internal medicine at Universidad CES and Fundación Valle del Lili in Cali, Colombia
2 Physician in the Gastroenterology and Endoscopy Service of Fundación Valle del Lili in Cali, Colombia
3 Gastroenterologist in the Gastroenterology and Endoscopy Service of Fundación Valle del Lili in Cali, Colombia
4 Gastrointestinal surgeon in the Gastroenterology and Endoscopy Service of Fundación Valle del Lili in Cali, Colombia
5 Pathologist in the Pathology Service of Fundación Valle del Lili in Cali, Colombia

***Correspondence:** santiagocasta1989@gmail.com.

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## Abstract

**Introduction:** Heterotopia of the gastric mucosa refers to an ectopic location of gastric mucosa in any part of the gastrointestinal tract. It is a rare cause of gastrointestinal ulcers and occult digestive bleeding. Endoscopic videocapsules have become fundamental tools for study of the small intestine. **Methods:** This is a descriptive case study based on information from the medical history, pathology report and endoscopic studies extracted from the databases of the Fundación Valle del Lili in Cali, Colombia. **Results:** An endoscopic videocapsule was used to examine a 71-year-old male patient who suffered from occult digestive bleeding. Segments of stenosis and ulcers were found in the jejunum and histopathology revealed heterotopic gastric mucosa. **Conclusion:** Heterotopy of the gastric mucosa should be thought of as a possible cause of bleeding in the small intestine.

## Keywords

Gastric heterotopy, occult digestive bleeding, endoscopic videocapsule.

## INTRODUCTION

Ulcers rarely occur in the small intestine, but endoscopic techniques such as videocapsules and enteroscopy have allowed this type of lesions to be identified more frequently. Intestinal ulcers can manifest clinically with anemia, episodes of abdominal pain, bleeding, obstruction or perforation. (1) Heterotopic gastric mucosa (HGM), the presence of gastric mucosa in an abnormal location, can cause intestinal ulcers although it is rarely found below the Ligament of Treitz. It is difficult to differentiate heterotopia from gastric metaplasia which is associated with Crohn's disease. (2)

We present the case of the endoscopic videocapsule study of a male patient who had been suffering from digestive bleeding. Multiple ulcers plus stenosis in were found in several of his small intestine. Histological study revealed the presence of pyloric glands with gastric foveolar epithelium.

## CLINICAL CASE

The patient was a 71-year-old man who had a history of hypertension and diverticular disease. He had been referred to the endoscopy unit of the Fundación Valle del Lili as an outpatient for endoscopic videocapsule diagnosis following two years of abdominal pain, colic and the sensation of a mass in the right iliac fossa that were associated with abdominal distension and episodic constipation alternating with occasional aqueous diarrhea. Paraclinical studies had found fecal occult blood and iron deficiency anemia refractory to administration of ferrous sulfate. He said that he did not use non-steroidal anti-inflammatory drugs (NSAIDs) and said that he was allergic to them. Reports of upper gastrointestinal endoscopy and total colonoscopy conducted elsewhere were normal. He was considered to have digestive bleeding, probably originating in the small intestine.

The patient provided and informed consent and was properly prepared prior to placement of the videocapsule. Erosions and small isolated ulcers were observed in the proximal jejunum. Erosions and deep ulcers with fibrin, retraction of folds, and mucosal edema which appeared to be chronic were found in the middle jejunum together with segments with partial stenoses. The capsule was retained by an ulcerated stenotic lesion in the distal jejunum (Figure 1).

One week after the study, the patient returned with symptoms of an intestinal obstruction. Fluoroscopy documented the capsule in the lower left quadrant of the small intestine. Exploratory laparoscopy found a flange of the omentum causing partial obstruction in the distal ileum of the small intestine. The loop was dilated with thickened and congestive serosa distal to the obstruction. The capsule was trapped in the stenotic segment which required a 6.5 cm resection of the intestine (Figure 2).

The surgical piece contained two ulcerated lesions (1.5 cm x 1 cm and 1 cm x 1 cm) which were reported macroscopically. A microscopic examination showed that the small intestine had areas of mucosal ulceration with granulated tissue and fibrin deposits. Foci were found in which foveolar gastric epithelium was observed as well as pyloric glands without cytological atypia in the mucosal and submucosal regions. Inflammatory lymphoplasmocytic infiltrate with formation of hyperplastic lymphoid nodules was observed. Surgical margins had adequate viability. Immunohistochemical PAS (periodic acid-Schiff) staining was used to check for the MUC-5AC mucin marker. The interpretation of the results indicated that neutral mucin was present in the gastric mucosa represented by the foveolar epithelium and the pyloric glands (Figure 3).

Omeprazole was prescribed for the patient during a postoperative follow-up appointment. Subsequent appointments documented improvement of gastrointestinal symptoms and resolution of anemia. Complementary studies of antineutrophil cytoplasmic antibodies (ANCA), anti-Saccharomyces cerevisiae antibodies (ASCA), rheumatoid factor, the erythrocyte sedimentation rate (ESR) and qualitative C-reactive protein (PCR) tests were done. The rheumatoid factor test was negative while the C-reactive protein (PCR) test was positive. It was decided to continue clinical follow-up with quarterly laboratory tests.

## DISCUSSION

The development and use of the endoscopic videocapsule has enabled diagnosis of various lesions in the small intestine that were previously difficult to identify. (3) This study has become a primary tool for evaluating hemorrhagic lesions, ulcers and tumors in this organ. (4) It is currently considered a first-line study for what was previously called occult digestive bleeding, a term that has changed to possible bleeding of the small intestine. This accounts for 5% to 10% of patients who consult for gastrointestinal bleeding. (5-7)

A study by Pandey et al. of patients who were diagnosed by endoscopic videocapsule has shown that the most frequent causes of bleeding in the small intestine were angiodysplasia in up to 23.5% of these patients, Crohn's disease in 14.7%, and NSAID enteropathy in 11.76%. Ulcers do not commonly cause bleeding in the small intestine although they have been reported in up to 5.8% of the cases. (8) In general, these ulcers are secondary to Crohn's disease or NSAID enteropathy and are less frequently associated with entities such as Celiac's disease, Behcet's disease, unspecified jejunoileitis, vasculitis, gastrointestinal stromal tumors, intestinal adenocarcinoma, lymphoma, multiple myeloma, Meckel's diverticulum, infections and HGM. (9)

HGM is gastric mucosa in an ectopic location in any part of the gastrointestinal tract. HGM is identified most frequently in the esophagus, followed by the duodenum. (10-12) With the exception of Meckel's diverticulum, locations below the Ligament of Treitz are extremely rare. There are only a few cases of HGM in the jejunum, ileum, colon and rectum

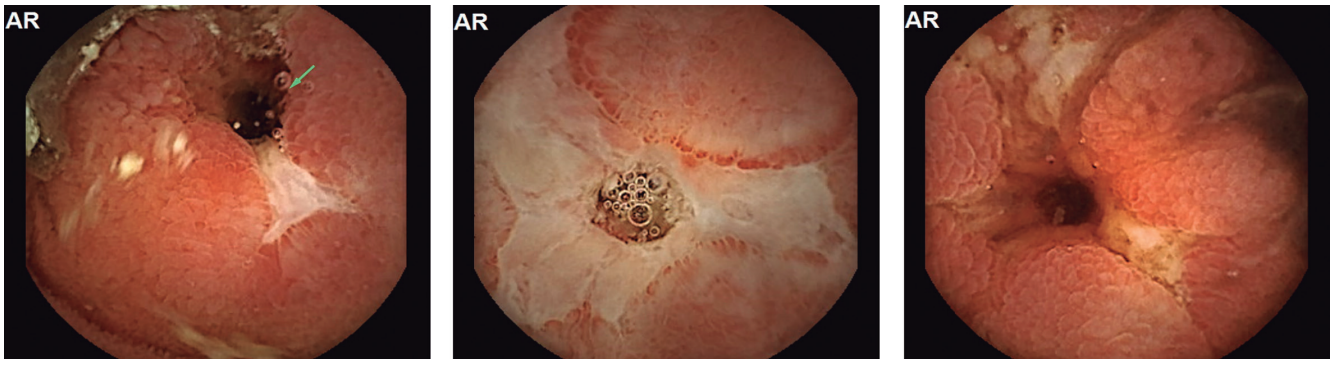


**Figure 1.** Endoscopic videocapsule. Concentric ulcerated stenosis, surrounded by mucosal edema.

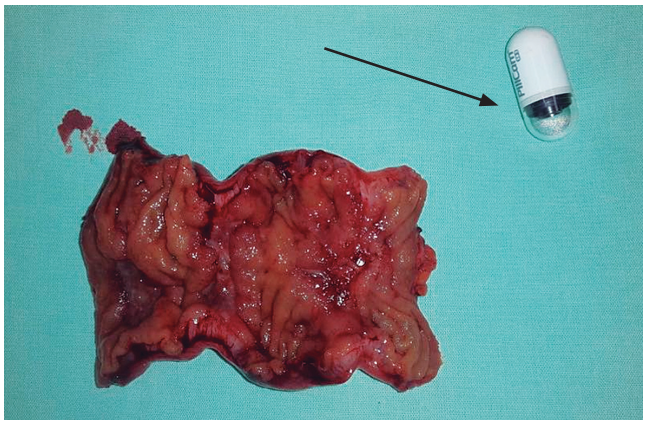

**Figure 2.** Surgical piece. Stenotic segment of 6.5 cm of small intestine (ileum). Endoscopic videocapsule (arrow).

in the medical literature. (13, 14) Most reports involving the small intestine present asymptomatic patients whose HGMs were identified by histopathological studies of samples obtained surgically. Nevertheless, associated symptoms of gastrointestinal bleeding, (15, 16) intussusception, (17) ulceration, perforation and intestinal obstruction have been described. In addition, there are cases in which HGMs have become malignant. (14, 18-20) In our patient, the symptoms were abdominal pain and anemia with a bowel obstruction after the endoscopic videocapsule was retained. Findings of multifocal compromises of the small intestine due to several ulcers resulting in various segments of stenosis are very rare situations. There are only two similar cases reported in the literature. One was a 42-year-old patient who had episodes of recurrent abdominal pain, and the other was a 24-year-old

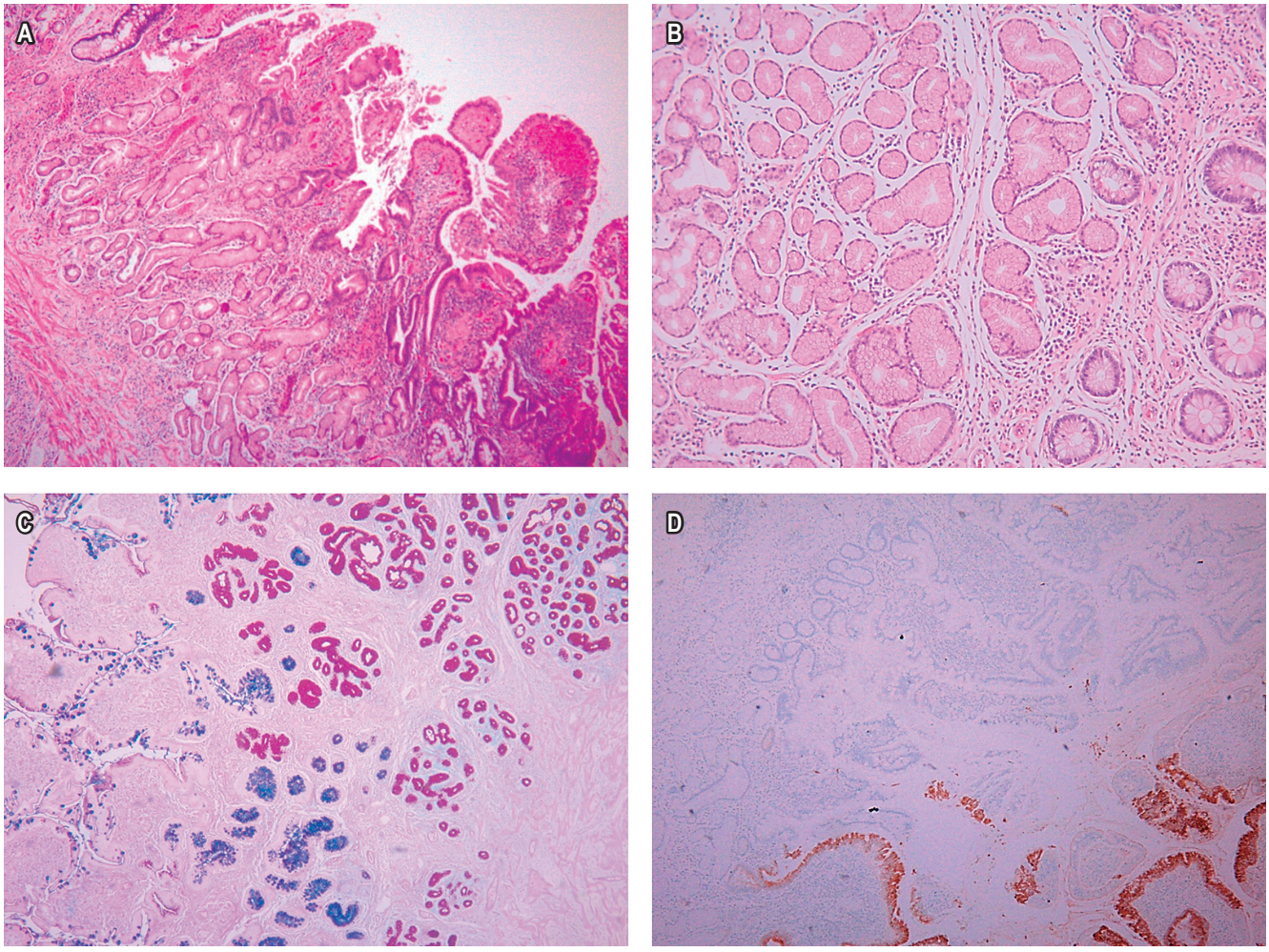


**Figure 3.** Histopathological study. **A.** Areas covered by the foveolar gastric epithelium (H-E x 10). **B.** Pyloric glands in the mucosa and submucosa (H-E x 40). **C and D.** PAS staining with immunohistochemical study with MUC-5AC showing the presence of neutral mucin of the gastric mucosa represented by the foveolar epithelium and the pyloric glands.

patient who had abdominal pain and intestinal perforation. (2, 21) Lesions were identified by endoscopic videocapsule in only one case. (14)

Two types of HGM have been characterized in relation to histological findings. The first has both gastric glands and gastric foveolar epithelium as in our patient. The second has only gastric foveolar epithelium. It is believed that the former has its origin in a congenital abnormality of the gastrointestinal tract, while the latter could be acquired through a metaplastic process the mechanism of which remains unknown. (11, 15, 22) There is a possibility that these types of histological lesions are related to Crohn's disease since outbreaks of pyloric metaplasia have been identified in patients with ileum ulcers and this disease. (23) Koukoulis et al. evaluated 45 biopsies of the terminal ileum of different patients and identified pyloric gland metaplasia in 10 (22.2%) specimens. These findings were observed in patients with terminal ileitis and were located below regeneration crypts and close to granulation and ulceration tissue. No granulomas were observed in any of the pieces. The meaning of this type of lesions is not entirely clear and has been considered a non-specific finding. (24) Agarwal et al. conducted a retrospective study which found that pyloric metaplasia in patients with inflammatory bowel disease who had ileoanal anastomoses with ileal pouches were more likely to have Crohn's disease than ulcerative colitis. In addition, pyloric metaplasia was associated with postoperative complications such as chronic pouchitis. (25) Although there was not enough evidence to suggest Crohn's disease in our patient, this possibility cannot be completely ruled out, which makes clinical, paraclinical and imaging follow-up necessary.

## CONCLUSION

Endoscopic videocapsules have made it possible to obtain images of the small intestine that were previously not possible. Heterotopic gastric mucosa is a condition that had traditionally been considered to be congenital, one that very rarely compromised the gastrointestinal tract below the Ligament of Treitz. It is very rare to have a multifocal condition in the small intestine, as in the case of this patient. Distinguishing HGM from pyloric metaplasia is difficult and still remains a point of discussion. This situation requires that patients diagnosed with this condition be strictly monitored clinically, paraclinically and with imaging.

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# Letter to the Editor

Valeria Atenea Costa Barney,[1*] Alexander Castañeda Ladino.[2]

1 Gastroenterologist at the Hospital Universitario San Ignacio and Honorary Professor at the Pontificia Universidad Javeriana in Bogotá, Colombia
2 Second year Gastroenterology and Digestive Endoscopy Fellow at the Hospital Universitario San Ignacio in Bogotá, Colombia

***Correspondence:** atenea.costa@gmail.com

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Dear Editor:

We would like to respectfully make a series of contributions regarding the original article "Diagnosis and treatment of patients with hereditary hemorrhagic telangiectasia (Osler-Weber-Rendú syndrome) at a university hospital in Colombia" by Dr. Mosquera et al.. Our contributions are on genetic diagnosis, clinical manifestations, medical management and endoscopic management.

Osler-Weber-Rendú syndrome, also known as hereditary hemorrhagic telangiectasia (HHT), is a disease with an autosomal dominant inheritance pattern characterized by telangiectasias and arteriovenous malformations. (1)

To date, the Curaçao criteria remain the parameters to be considered for diagnosis. It has been reported that these criteria are particularly useful in two situations: unaffected older adults, and young adults and children. This is where genetic testing plays an important role even though it is not widely available and is expensive. It should not be underestimated for making an accurate diagnosis. The alterations described related to endoglin (ENG for type 1 HHT) and the activin type A receptor gene (ACVRL1 for type 2 HHT) genes that account for the majority of HHT cases. They generate protein products that influence signaling TGF-β in vascular endothelial cells. The reported data show detection rates with sensitivity of up to 75% for mutations of ENG and ACVRL1 sequences. (1, 2) We also believe that these tests are relevant because of the different degrees of severity associated with different genotype alterations. Patients with HHT type 1 genotype are more serious and have a higher prevalence of pulmonary arteriovenous malformations and more severe episodes of gastrointestinal bleeding than do patients with HHT type 2. However, no significant changes in the severity of epistaxis, age of presentation and mortality rates have been demonstrated. (3)

On the other hand, more detailed descriptions of clinical manifestations and their frequencies seem relevant since they are data that can help a clinician suspect this disease which otherwise might initially be classified as an orphan disease. At least 90% of patients present nosebleeds, and 80% of HHT patients have gastric or small intestine telangiectasias although only 25% to 30% develop overt bleeding which tends to occur in the fifth to sixth decade of life (rarely before 40 years). (1, 4) These data are similar to those found in the study of Dr. Mosquera et al. It is also important to take into account other manifestations. Cardiac manifestations (acute myocardial infarcts and arrhythmia) have low prevalences. Arrhythmia is the most frequent cardiac manifestation. (5)

 

There is also evidence that these patients have a higher prevalence of hepatic focal nodular hyperplasia. (6) We point out these clinical data to complement the article since they were not discussed in the patients of the published series.

As part of the review of the available literature, we would also like to complement the article in regard to clinical and endoscopic management. According to reports in the literature, oral or parenteral iron supplements may be sufficient treatment for mild anemia and chronic bleeding of patients with HHT and could even be defined as the first-line. (1) Among the pharmacological treatments described is hormonal therapy (estrogen/progesterone or danacrine preparations). (7) As a second line, antifibrinolytics (aminocaproic acid or tranexamic acid) have been used, (8) and there are also reports of the use of tamoxifen, interferon, thalidomide and sirolimus. (9)

In endoscopic therapy, Nd:YAG (neodymium-doped yttrium aluminum garnet; Nd:Y3Al5O12) lasers and argon plasma coagulation (APC) have been described. The latter is considered to be the most effective method available today. Multiple attempts at local endoscopic therapy are not recommended due to the additive risks of adverse events without additional benefit. (1, 7, 10) There are also data in favor of the use of N-acetylcysteine as an antioxidant. Although prospective controlled studies of its efficacy have yet to be done, it is considered to be a promising management possibility. (11)

We should not put aside recent guidelines which suggest an approach based on five specific measures to optimize care and reduce morbidity and mortality rates: detection of pulmonary arteriovenous malformations (AVM), advice regarding nasal bleeding, evaluation of iron deficiency, antibiotic prophylaxis before dental and surgical procedures, and pregnancy advice. It is known that most pregnancies in women with HHT develop normally. Major complications are rare, but survival is better if HHT is recognized and addressed prior to pregnancy. (10, 12)

The Mayo Clinic currently has the most experience managing HHT-related bleeding with intravenous bevacizumab. In general, it is well tolerated, but a relevant adverse effect is arterial hypertension. It is usually benign course and responds well to medical management. From a cost-benefit perspective that considers transfusions, hospitalization time and iron infusions, in the future biological therapy could become an earlier therapeutic approach. (4) There are reports of the use of pazopanib as an alternative for patients who are refractory to bevacizumab, but more controlled and prospective studies of its efficacy are still needed. (13)

Until 2011, there were no data that favored nutritional measures or lifestyle changes for managing this disease. (1) Despite this, in 2013, Silva et al. suggested that room humidification, nasal lubrication and saline treatments could be beneficial for controllin epistaxis associated with HHT. They also suggested that modifying the intake of foods high in salicylates and those with natural anti-platelet activity (including red wine, spices, chocolate, coffee, certain types of fruit, garlic, ginger, ginseng, and ginkgo biloba) could be beneficial. (14)

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# Reply to the letter to the Editor

Gabriel Mosquera-Klinger,[1*] Kenny Gálvez Cárdenas,[2] Alejandro Ocampo Hincapié.[3]

1 Internist and gastroenterologist in the Gastroenterology and Digestive Endoscopy Unit at the Hospital Pablo Tobón Uribe in Medellín, Colombia
2 Internist and hematologist at the Hospital Pablo Tobón Uribe in Medellín, Colombia
3 Coordinator of Non-medical Plan Services and Support in the Admissions Department of the Hospital Pablo Tobón Uribe in Medellín, Colombia

***Correspondence:** gami8203@yahoo.com

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Dear Editor:

We thank you in advance for the contributions received by from Dr. Costa Barney and Dr. Castañeda. We are pleased to know that our case series has been reviewed and analyzed by this honorable working group. Their valuable comments can certainly contribute to managing and monitoring these patients who suffer from such a complex condition, and perhaps interesting guidelines can be established for future studies in this field. For us, it is a pleasure that our work has raised concerns that can be discussed in the academic environment of this type of publication.

The Curacao criteria remain the diagnostic gold standard, especially when three or more of its criteria are present (*defined* diagnosis). (1, 2) Confirmation of a *defined* diagnosis is not required because current management recommendations remain unchanged except in the rare situation of the *SMAD4* mutation with the theoretical risk of its association with juvenile polyposis. (3) Incidentally, this is the rarest of the genetic mutations identified in this disease.

We agree that this disease is uncommon in our environment. In fact, it is one of the 2,271 diseases that are officially listed as orphan-rare diseases in Colombia. Because it is an orphan disease, it is mandatory to report all cases to SIVIGILA (Sistema de Información para la Vigilancia en Salud Pública - Public Health Surveillance Information System). This disease's code number is 844 while its ICD-10 code number is I780. Based on the provisions of current regulations regarding the national registry and notification of patients with orphan diseases, we want to clarify that when no confirmatory diagnostic test has been determined for an orphan disease, or when no such test is available in Colombia, notification will be made on the basis of the clinical diagnosis declared by one or more of the treating doctors. The declaration of a clinically confirmed orphan disease will be made based on scientifically accepted classifications, medical history and other patient records that confirm the presence of the orphan disease (Ministry of Social Protection, Resolution 946 of April 22, 2019). We make this clarification because, as mentioned in our study, all patients included therein were diagnosed on the basis of the Curacao criteria. Also, genetic tests are not often available in our environment even though they are part of the procedures of the health benefits plan.

Currently there are only 15 sites in Colombia that can do genetic and metabolic tests for this disease. They are mostly based in Bogotá, and none are in Medellín. In addition, although these sites collect the samples, they are processed in laboratories in the United

States. The confirmatory genetic tests for this disease available in these centers and suggested by the Ministry are for ACVRL1, ENG, SMAD4, MADH4, GDF2. Each test has an estimated cost of 4 million pesos and average delivery time is 50 days. We reiterate that, in the absence of genetic confirmatory tests, a *defined* clinical diagnosis of Rendu-Osler-Weber syndrome on the basis of the Curaçao criteria is sufficient. Hopefully, a diagnosis will be endorsed by a multidisciplinary group. For this reason, our discussion cites Kjeldsen et al. At follow-ups of more than 7 years, they found no significant differences in the mortality rates of patients related to genetic diagnoses and/or establishment of disease subtype. (4) With the data described, we confirm that our position is only to request these tests in selected patients who do not meet the *defined* criteria of Curaçao. We believe that genetic tests can be useful and may also be requested for asymptomatic first-degree relatives without stigmata of the disease as an initial screening method.

We would like to take advantage of this space to suggest development of a multicenter study that can bring together the majority of patients with this disease in Colombia. Perhaps with more data we can propose a follow-up strategy based on the best currently available evidence.

Regarding clinical manifestations, we agree that extension of this description could be of interest to clinicians. The fact that the patients described in our series had no cardiac manifestations can be explained by the low prevalences described in other series. Four of the six patients with hepatic manifestations had vascular malformations while two had hepatic focal nodular hyperplasia.

We agree with what has been described about medical treatment. The data in our work reflect only the actions performed on the patients treated at our center. (5) For patients with very extensive disease who frequently consulted the emergency department due to bleeding, the approach was almost always to initially stabilize the patient. In cases of severe anemia, blood products were transfused. If endoscopy documented high-risk stigmas or recent bleeding, argon plasma therapy was administered, as described. A retrospective review found no data in the medical records that suggest complications during endoscopic procedures despite multiple interventions.

Regarding the general recommendations provided by the literature review by Dr. Costa Barney and Dr. Castañeda, we can only comment that patients with Rendu-Osler-Weber syndrome are complex and usually require multidisciplinary management. For this reason, any intervention aimed at improving the quality of life or increasing the life expectancy of these patients might be useful, but interventions should be individualized and should weigh risks against benefits. Of course, the context must be analyzed to be fair in terms of the costs and benefits of each intervention, since it is possible that one patient may require multiple interventions during the natural evolution of the disease.

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