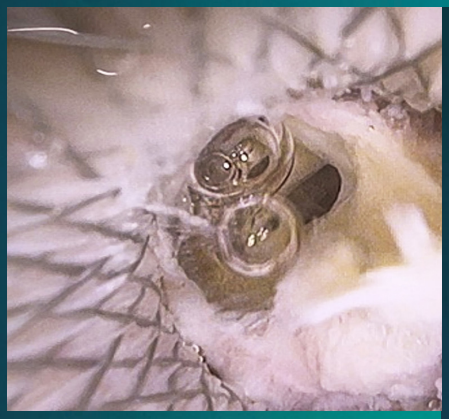
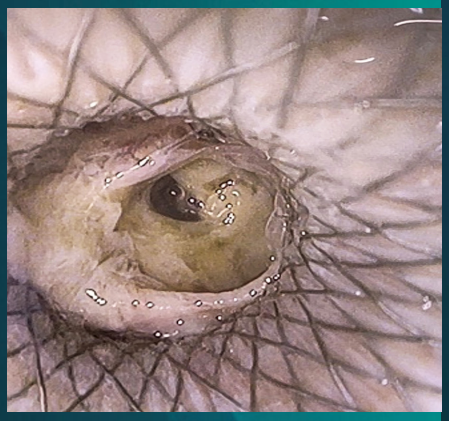
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Editorial

The Mental Health of Gastroenterologists: How Well Do We Take Care of Ourselves?

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Today, gastroenterologists aspire to comprehensive, high-quality training. We stay current with scientific knowledge through conferences and research, renew our technology, and implement clinical practice guidelines with the aim of improving our patients' clinical outcomes. In this relentless pursuit of efficiency—often self-imposed and pushing us to our limits—when do we stop to think about ourselves? Do we assess how these high-performance demands affect our mental health and quality of life?

Worldwide, physicians' mental health has become an increasingly important concern, encompassing stress, anxiety, depression, and burnout, all of which pose risks to healthcare professionals, patient safety, and the sustainability of healthcare systems[1,2]. It is common to hear exhausted colleagues say, "I'm ready to throw in the towel today," "I desperately need a vacation," or "If one more patient arrives, I'm running away." These colloquial expressions conceal a deeper reality of occupational exhaustion.

Burnout syndrome is a state of physical, mental, and emotional exhaustion caused by chronic workplace stress, a concept first introduced by the American psychologist and psychoanalyst Herbert Freudenberger in 1974[2,3]. The World Health Organization classifies burnout as an occupational phenomenon in the International Classification of Diseases, 11th Revision (2019). In Colombia, it is recognized as an occupational disease. The WHO proposes three dimensions for its identification[4]:

- Emotional exhaustion: a sense of depleted energy or extreme fatigue.
- Depersonalization: negative feelings, persistent complaints about the work environment, and antipathy toward patients and colleagues.
- Reduced professional efficacy: feelings of ineffectiveness and a diminished ability to make decisions.

The figures are alarming. Dr. Ong's meta-analysis (2021) estimated an average burnout prevalence of 35% among gastroenterologists[5]. Dr. Shiha's systematic review (2025) found that 45% of gastroenterologists worldwide experience burnout; of these, 31% report emotional exhaustion, 23% depersonalization, and 25% low professional accomplishment[1]. Dr. Aourarh's survey (2025), which assessed the impact of the work environment on gastroenterologists in Morocco, showed that 87% suffer from musculoskeletal disorders, 70% report gastrointestinal symptoms, 46% experience depression, and 24% anxiety[6].

The consequences include reduced productivity, deterioration of the physician–patient relationship, medical errors, emigration, and abandonment of the profession. Other serious risks include family and social isolation, alcohol or psychoactive substance abuse, depression, and suicide[3,6–9].

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Women have a 50% higher risk of burnout (odds ratio [OR]: 1.5; $p < 0.01$)[5], attributable to factors ranging from motherhood to hostile work environments and sexual harassment. In addition, according to Dr. Ong, the current generation of young gastroenterologists was trained in an overprotective system that has reduced their resilience to criticism and failure, thereby affecting their sense of personal accomplishment. Finally, operational factors such as long hours of outpatient consultations and endoscopic procedures without breaks, poor ergonomics, and on-call availability for emergencies further exacerbate this problem[5–7].

According to the Colegio Médico Colombiano survey (2020), 35% of physicians in Colombia experience burnout[10]. The current period, marked by the aftermath of the 2019 coronavirus disease (COVID-19) pandemic, has dramatically increased stress among gastroenterologists. This situation is compounded by a structural crisis in the healthcare system that limits access to and continuity of treatment, generating an excessive workload further aggravated by the financial instability of Healthcare Service Provider Institutions (Instituciones Prestadoras de Servicios de Salud [IPS]) and delays in professional fee payments. Factors such as shortages of medical supplies, the risk of complications during endoscopic procedures, and potential medicolegal or reputational consequences arising from adverse events further intensify professional exhaustion. Added to this are the constant pressure to remain scientifically up to date (necessary to standardize the quality of care), as well as the growing bureaucratic burden associated with administrative documentation and the digitalization of clinical practice, all of which contribute to moral injury, in which physicians' values, ethical principles, and sense of professional purpose are compromised by organizational decisions that prevent them from providing safe and optimal care[2,5,11]. Other factors unrelated directly to medical practice, but that negatively affect the mental health of Colombians, include traffic congestion in major cities, insecurity during commuting, and difficulties in maintaining a balance between professional and personal life[8].

In accordance with the Political Constitution of Colombia (Section 25), which guarantees the right to dignified work, and in line with the standards of the Organisation for Economic Co-operation and Development, Law 2101 of 2021 was enacted to reduce the workweek to 42 hours. The law states that increased rest time reduces stress and, consequently, enhances productivity and improves quality of life[12]. Dr. Aourarh reported in his survey that gastroenterologists work an average of 50 hours per week[6]. In Colombia, it is common for physicians to work in multiple hospitals, far exceeding the legal limit on working hours. It is imperative that gastroenterologists accurately quantify their actual workload in order to assess how these extended work schedules affect their productivity and their physical and mental health.

Many physicians do not seek care for fear of jeopardizing their professional careers or being stigmatized. The problem lies not only in the existence of the syndrome itself, but also in the lack of self-awareness. Many physicians fail to recognize their own risk factors or to ask themselves whether they may already be affected. Likewise, as a professional community, we must ask ourselves: how much space do we create to discuss this issue with our colleagues?

The sustainability of gastroenterology care depends not only on technical innovation and the expansion of endoscopic services, but also on the psychological well-being of specialists. Caring for physicians' mental health is essential to safeguarding patient safety. The well-being of healthcare professionals should be regarded as a quality indicator of the healthcare system. Recognizing burnout is not a sign of weakness. In Colombia, Law 2460 (2025) strengthens the national mental health policy and establishes specific funding for this sector. I fully agree with Dr. Buscarini, an Italian gastroenterologist, in her publication *How to Manage and Prevent Burnout in Gastroenterologists* (2020), in which she recommends maintaining a balance between professional and personal life (including family and community life)[3].

The words *work* and *labor* derive etymologically from the Latin *tripaliāre* and *laborāre*, terms associated with physical sacrifice and fatigue[13], and for many people these words evoke stress. Today, this concept should be replaced by terms such as enjoy or rejoice, as gastroenterologists should practice their profession with passion and pride, integrating into their lifestyle the sense of well-being experienced in the hospital while caring for patients, in harmony with their personal time and relationships with family and friends.

The evidence suggests that organizational strategies are effective in reducing physician burnout[3,6,7]. Dr. Brian E. Lacy, an American gastroenterologist, has indicated that organization-level programs can systematically help physicians recognize the early signs of burnout, promote health and self-care, and restore well-being[14].

Leaders of gastroenterology services are encouraged to include mental health on their teams' agendas. To this end, protected spaces should be established to enable screening and diagnosis, thereby facilitating timely interventions to improve working conditions. Promoting more humane work environments that ensure autonomy and active participation in decision-making—while also fostering teamwork, redistributing workloads equitably, and strengthening social connections outside the workplace—are strategies that significantly reduce burnout and stress while enhancing resilience and team satisfaction among physicians[3,6,7]. Within this framework, workplace flexibi-

lity emerges as a fundamental pillar. Allocating "protected time" of at least 20% of the work schedule to activities that foster personal fulfillment, such as research, teaching, or social engagement, is recommended[6,7]. Leadership should also prioritize recognizing individual achievements, creating opportunities for constructive dialogue, and optimizing communication channels in operational processes to promote a better quality of work life.

In recent years, the *Revista Colombiana de Gastroenterología* has published several original articles on the mental health and quality of life of patients with digestive disorders. Although this issue has been examined in depth in other medical specialties in Colombia[15,16], obtaining local data on burnout syndrome in gastroenterology is imperative. Only then will it be possible to design effective strategies for intervention and prevention.

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Original article

Autoimmune Liver Diseases in Mexico: Clinical Characterization and Outcomes at a National Referral Center (2012–2022)

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Abstract

Introduction: Autoimmune liver diseases, including autoimmune hepatitis (AIH), primary biliary cholangitis (PBC), and primary sclerosing cholangitis (PSC), are uncommon, exhibit heterogeneous phenotypes, and remain poorly characterized in Latin American populations. **Objective:** To describe the clinical and sociodemographic characteristics, as well as the outcomes, of patients with confirmed diagnoses of AIH, PBC, and PSC treated at a national referral center in Mexico between 2012 and 2022. **Materials and methods:** A descriptive, cross-sectional observational study using secondary data sources was conducted. Adults with a confirmed diagnosis of autoimmune liver disease were included. Clinical, serological, and outcome variables were analyzed using descriptive statistics with Stata v.17. **Results:** A total of 303 patients were analyzed, of whom 77.9% were women, with a mean age of 50 years. Diagnoses included AIH (78.9%), PBC (46.5%), and PSC (8.2%), with 98 cases of overlap syndromes (AIH–PBC: 93; AIH–PSC: 7). The most frequent comorbidities were overweight, hypothyroidism, dyslipidemia, and ulcerative colitis. Treatment response was higher in PBC (88.6%) and AIH (84.9%), whereas PSC showed a greater need for transplantation (68%) and recurrence (100%). **Conclusions:** In this center, AIH was the most frequent entity, followed by PBC and PSC, with a considerable number of overlap syndromes, the most common being AIH–PBC. More favorable outcomes were observed in AIH and PBC, whereas PSC showed poorer clinical evolution. These findings provide relevant regional evidence and underscore the need for multicenter studies on autoimmune liver diseases in Latin America.

Keywords

Autoimmune hepatitis; primary biliary cholangitis; primary sclerosing cholangitis.

INTRODUCTION

Autoimmune liver diseases comprise a spectrum of potentially progressive idiopathic inflammatory disorders that are classically described in three clinical presentations: primary biliary cholangitis (PBC), primary sclerosing cholangitis (PSC), characterized by a predominantly cholestatic pattern of injury, and autoimmune hepatitis (AIH), characterized by predominantly hepatocellular injury, as well as overlap syndromes among these entities[1–3]. In recent years, other immune-mediated disorders have been proposed for inclusion within this spectrum, such as immunoglobulin G4-associated sclerosing cholangitis (IgG4-SC), and it has been suggested that some cases previously classified as PSC may actually correspond to this entity[1,4–6].

Significant changes in the epidemiology of these diseases have been described in recent years. In different regions of the world, an increase in the incidence and prevalence of autoimmune liver diseases has been observed, particularly for AIH and PSC in Europe and North America,

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whereas PBC has shown an increase in prevalence across various regions, including Asia and the Americas[1,2,7–9]. Population-based studies and multicenter cohorts have improved our understanding of the clinical course experienced by patients, highlighting variations in disease presentation according to geographic, demographic, and temporal factors[10,11]. The diagnosis of these diseases requires the integration of clinical, immunologic, radiologic, and histopathologic findings, reflecting the complexity of their clinical presentation and the heterogeneity of their phenotypes. In addition, some patients may present with overlap syndromes, in which features of more than one of these entities coexist, representing a diagnostic and therapeutic challenge in clinical practice[1,3,12].

Although autoimmune liver diseases are uncommon, they share the characteristic of imposing a high clinical burden relative to the incidence and prevalence of each condition in the population[10]. These disorders are characterized by phenotypic presentations that vary according to age, sex, and geographic context, variables that also influence clinical response and disease progression[1–3,13]. Autoimmune hepatitis (AIH) is a heterogeneous disease with two clinical forms: type 1 AIH, which affects both children and adults and is characterized by elevated antinuclear antibodies (ANA) and anti-smooth muscle antibodies (anti-SMA), and type 2 AIH, which is associated with positivity for liver kidney microsomal type 1 antibodies (anti-LKM1) and, in some cases, anti-liver cytosol type 1 antibodies (anti-LC1) [5,14–16]. Its estimated incidence is 1 case per 100,000 inhabitants per year, with a predominance in women[17–19].

Primary sclerosing cholangitis (PSC) exhibits a broad clinical spectrum, ranging from asymptomatic cases to presentations with jaundice, pruritus, hepatomegaly, or splenomegaly[1,20,21]. Its prognosis has been associated with age, liver function, and the presence of inflammatory bowel disease[2,5,22], with a mortality rate three times higher than that of the general population[17,23]. Primary biliary cholangitis (PBC), formerly known as *primary biliary cirrhosis*, is defined by injury to the small- and medium-sized intrahepatic bile ducts, positivity for antimitochondrial antibodies (AMA-M2) in 90% of cases, and a predominance in women between 30 and 60 years of age[16,24]. Its diagnosis requires at least two of the following three criteria: positive AMA, elevated alkaline phosphatase for more than six months, and chronic cholangitis involving the intrahepatic bile ducts[3,15,25]. Overlap syndromes may be observed in all of these entities, particularly AIH-PBC overlap and, less frequently, overlap between PBC and PSC[3,4,17,20,26].

In Latin America, although the available information remains limited compared with other regions, several clinical series and cohort studies published in recent years have described the epidemiology and clinical characteristics of autoimmune liver diseases. In Mexico, for example, an approximate prevalence of 8.5% of these diseases has been reported in liver biopsy-based studies and up to 17% in cohorts of patients with cirrhosis, underscoring the growing relevance of these disorders in the region[27]. In addition, some studies have reported a high proportion of cirrhosis at the time of diagnosis among Latin American patients, suggesting delayed diagnosis and highlighting the need for better characterization of these diseases in regional populations. In Mexico, the published evidence remains relatively limited and is restricted primarily to studies with small sample sizes. A descriptive study conducted at the ISSEMyM Medical Center characterized the clinical features of 78 patients with primary biliary cholangitis treated between 2005 and 2012[23]. However, the available evidence remains fragmentary and derives mainly from single-center studies, limiting the understanding of the clinical behavior, comorbid associations, and outcomes of these disorders in Latin American populations[27,28].

In this context, the aim of the present study was to characterize the clinical and sociodemographic profile, as well as the outcomes, of patients diagnosed with AIH, PSC, and PBC who were treated at a national referral center in Mexico during the period from 2012 to 2022.

MATERIALS AND METHODS

A descriptive cross-sectional observational study was conducted using secondary data from patients diagnosed with autoimmune hepatitis (AIH), primary sclerosing cholangitis (PSC), and primary biliary cholangitis (PBC) who were treated at the Instituto Nacional de Ciencias Médicas y Nutrición Salvador Zubirán, a national clinical referral center in Mexico, between 2012 and 2022. All adult patients with a confirmed diagnosis of AIH, PSC, or PBC who were treated at the Instituto Nacional de Ciencias Médicas y Nutrición Salvador Zubirán during the study period were included. This population was characterized based on data extracted from the medical records in order to describe and analyze sociodemographic and clinical variables relevant to understanding these diseases in the Latin American context.

The diagnosis of AIH was established according to the criteria proposed by the International Autoimmune Hepatitis Group (IAIHG), considering both the original and simplified criteria, which integrate clinical, serological, and histopathological findings when available. PBC was diagnosed based on the presence of positive antimitochondrial antibodies (AMA) and persistent elevation of alkaline phosphatase, or on compatible histopathological findings. PSC was diagnosed based on characteristic cholangiographic findings and the exclusion of secondary causes of cholangiopathy[29,30]. In all cases, the diagnosis was esta-

blished by hepatology or gastroenterology specialists at the Institute and recorded as a confirmed diagnosis in the institutional medical record. Response to treatment was defined based on the clinical and biochemical improvement documented in the medical records, including normalization or a significant reduction in transaminase levels and cholestatic markers according to the underlying disease.

Information on sociodemographic and clinical variables was collected from the medical records of patients treated during the study period who had confirmed autoimmune liver disease, as documented in the medical record. A detailed descriptive analysis of the data was performed to obtain information on the distribution and characteristics of the variables. Measures of central tendency, frequencies, and proportions were calculated according to the type of variable, and the information was classified for each liver disease. Stata version 17 was used for the analysis.

RESULTS

Data from 303 individuals were analyzed, of whom 236 (77.89%) were female. The mean age was 50.03 ± 13.50 years (range: 21 to 77 years), and 52.15% belonged to the middle socioeconomic level. The sociodemographic characteristics of the sample are presented in **Table 1**.

Among the 303 patients included, 239 cases of autoimmune hepatitis (AIH) (78.88%), 25 cases of primary sclerosing cholangitis (PSC) (8.25%), and 141 cases of primary biliary cholangitis (PBC) (46.53%) were identified. Due to the presence of overlap syndromes, some patients were classified into more than one diagnostic category. A total of 98 overlap syndrome cases were identified. Of these, seven corresponded to AIH-PSC overlap (2.31% of all cases), 89 to AIH-PBC overlap (29.37% of all cases), and two to PSC-PBC overlap (0.66% of all cases). Regarding diagnostic confirmation, histopathological confirmation by liver biopsy was available in 232 of the 239 patients with autoimmune hepatitis (97.1%), whereas in the remaining cases the diagnosis was established based on clinical, serological, and imaging criteria. In the overall cohort, 96.0% of patients underwent histopathological liver evaluation, reflecting the diagnostic approach at this referral center based on clinicopathologic correlation.

The medical histories identified in the patients are described according to the diagnosed autoimmune disease in **Table 2**. The most frequent comorbidities among patients diagnosed with AIH were overweight (45.19%), dyslipidemia (20.50%), hypothyroidism (20.50%), diabetes *mellitus* (19.25%), and arterial hypertension (16.74%). Among patients diagnosed with PSC, the most frequent conditions were ulcerative colitis (80%), pancreatitis (40%), underweight (26%), depression (24%), overweight (20%),

Table 1. Sociodemographic Characteristics of Patients Diagnosed with Autoimmune Liver Diseases

Variable	n	%
Sex		
Male	67	22.11
Female	236	77.89
Socioeconomic Level		
High	37	12.21
Middle	158	52.15
Low	107	35.31
Missing data	1	0.33
Marital Status		
Single	82	27.06
Married	162	53.47
Common-Law Marriage	15	4.95
Divorced	28	9.24
Widowed	15	4.95
Missing data	1	0.33
Education Level		
Illiterate	1	0.33
Primary school	34	11.22
Secondary school	143	47.19
High school	1	0.33
Technical education	21	6.93
University	95	31.35
Postgraduate	4	1.32
Missing data	4	1.32
Occupation		
Homemaker	95	31.35
Retired	31	10.23
Salesperson	31	10.23
Unemployed	26	8.58
Bachelor's degree holder	16	5.28
Student	12	3.96
Secretary	9	2.97
Other occupations	80	26.40
Missing data	3	0.99
Religion		
Catholic	282	93.07
Evangelical	6	1.98
Agnostic	3	0.99
Jehovah's Witness	3	0.99
None	9	2.97

Author's own research.

and a family history of autoimmune disease (20%). In contrast, among patients with PBC, the most commonly reported conditions were overweight (49.65%), hypothyroidism (28.37%), Sjögren's syndrome (18.44%), underweight (16.31%), and dyslipidemia (15.60%).

With respect to clinical laboratory findings, the most representative results were antinuclear antibodies (ANA) and antimitochondrial antibodies (AMA). Regarding overlap syndromes, these were most frequent in primary biliary cholangitis, with a prevalence of 52.55%. AMA positivity was identified in 65 (29.55%) cases of autoimmune hepatitis, which may correspond to those associated with overlap with primary biliary cholangitis.

Among liver function test findings, autoimmune hepatitis showed a predominantly hepatocellular pattern, with greater elevations in aspartate aminotransferase (AST) levels (range: 0.56–4,086) than in alanine aminotransferase (ALT) levels (range: 0.44–2,664), as well as greater alterations in immunoglobulin G (range: 235–7,824) and immunoglobulin M (range: 65–2,252) levels. In primary biliary cholangitis, a mixed pattern of hepatocellular and cholestatic injury predominated, with more marked abnormalities in γ-glutamyl transferase (GGT) levels (range: 26–7,093).

Regarding patient outcomes, the highest treatment response rates were observed in patients with primary biliary

Table 2. Medical History of Patients According to the Diagnosed Autoimmune Liver Disease

Medical History	Autoimmune Hepatitis (n = 239)		Primary Sclerosing Cholangitis (n = 25)		Primary Biliary Cholangitis (n = 141)	
	n	%	n	%	n	%
Systemic lupus erythematosus	31	12.97	0	0	14	9.93
Autoimmune thyroiditis	5	2.09	1	4.00	2	1.42
Hypothyroidism	49	20.50	1	4.00	40	28.37
Arterial hypertension	40	16.74	2	8.00	15	10.64
Diabetes *mellitus*	46	19.25	2	8.00	12	8.51
Rheumatoid arthritis	8	3.35	1	4.00	6	4.26
Ulcerative colitis	9	3.77	20	80.00	4	2.84
Crohn's disease	0	0	0	0	0	0
Celiac disease	1	0.42	1	4.00	0	0
Sjögren's syndrome	18	7.53	1	4.00	26	18.44
Sicca syndrome	7	2.93	0	0	7	4.96
Scleroderma	15	6.28	0	0	21	14.89
Dermatomyositis	3	1.26	0	0	1	0.71
Psychiatric disorder	28	11.72	7	28.00	18	12.77
Depression	21	8.79	6	24.00	15	10.64
Anxiety	10	4.18	1	4.00	7	4.96
Normal weight	60	25.10	10	40.00	32	22.70
Underweight	34	14.23	9	36.00	23	16.31
Overweight	108	45.19	5	20.00	70	49.65
Obesity	34	14.23	1	4.00	16	11.35
Dyslipidemia	49	20.50	0	0	22	15.60
Alcohol consumption	10	4.18	0	0	2	1.42
Use of hepatotoxic medications	6	2.51	0	0	1	0.71
Smoking	14	5.86	0	0	5	3.55
Family history of autoimmune disease	12	5.02	5	20.00	4	2.84
Cytomegalovirus infection	11	4.60	1	4.00	4	2.84
Tuberculosis	6	2.51	0	0	1	0.71

Author's own research.

cholangitis and autoimmune hepatitis, at 89.05% and 84.94%, respectively. Remission was achieved in 74.48% of patients with autoimmune hepatitis, and recurrence occurred in 100% of patients with primary sclerosing cholangitis. Chronic hepatitis was present in more than 80% of patients across all three clinical forms of autoimmune liver disease. In addition, a substantial proportion of patients developed osteoporosis, and the need for liver transplantation was greatest among patients with primary sclerosing cholangitis (68%). Both acute and chronic transplant rejection were frequent in patients with autoimmune hepatitis, occurring in 25.45% and 21.82% of cases, respectively (**Table 3**).

DISCUSSION

This study, conducted at a national referral center in Mexico, represents one of the largest Latin American series on autoimmune liver diseases (AIH, PBC, and PSC). Our results confirm that AIH is the most frequent entity, followed by PBC and PSC, with a considerable proportion of overlap syndromes, mainly AIH-PBC overlap. This distribution is consistent with reports from other regions, where AIH represents the most common form within the spectrum of autoimmune liver diseases, particularly in Western populations[1–3,7,8,31]. Likewise, recent studies have reported a progressive increase in the incidence and prevalence of these disorders in different regions of the world, attributed both to improved diagnostic detection and to environmental and immunologic changes[7,8]. In Latin America, recent reviews have highlighted that the available evidence remains limited and derives mainly from clinical series from referral centers, making it difficult to establish comparable regional epidemiologic patterns[27,28].

Most cases corresponded to AIH, followed by PBC and PSC, with greater involvement of women in AIH and PBC, and of men in PSC, similar to what has been reported in the international literature. This sex-related difference is consistent with international studies demonstrating differences in presentation and prognosis according to sex, particularly in primary biliary cholangitis[16,24]. Overlap syndrome was observed, and the most frequent phenotype was PBC-AIH overlap, followed by AIH-PSC overlap, also in agreement

Table 3. Outcomes in Patients According to the Diagnosed Autoimmune Liver Disease

Medical History	Autoimmune Hepatitis (n = 239)		Primary Sclerosing Cholangitis (n = 25)		Primary Biliary Cholangitis (n = 141)	
	n	%	n	%	n	%
Treatment response	203	84.94	17	68.00	125	88.65
Remission	178	74.48	12	48.00	91	64.54
Recurrence	160	66.95	25	100	113	80.14
Chronic hepatitis	200	83.68	25	100	129	91.49
Cirrhosis	96	40.17	15	60.00	63	44.68
Liver failure	58	24.27	6	24.00	25	17.73
Osteoporosis	109	45.61	4	16.00	44	31.21
Need for transplantation	74	30.96	17	68.00	54	38.30
Acute transplant rejection	14	25.45	1	7.14	5	13.51
Chronic transplant rejection	12	21.82	0	0	4	10.53
Recurrence of autoimmune disease after transplantation	22	40.00	2	13.33	21	55.26
Hepatocellular carcinoma	3	1.26	1	4.00	2	1.43
Cholangiocarcinoma	0	0	0	0	0	0
Other cancers	1	0.42	1	4.00	1	0.71
Death	19	7.95	3	12.00	15	10.64

Author's own research.

with findings reported in the literature[3,4,17,20,26]. Patients with overlap syndrome were predominantly women and exhibited lower treatment response rates and more episodes of disease reactivation, as previously reported[1,17,21].

Regarding outcomes, the best treatment response and remission rates were observed in AIH and PBC, whereas PSC showed the greatest need for transplantation and the highest recurrence rates, consistent with international reports describing PSC as the entity with the poorest prognosis[14,17,18,21,32]. A relevant finding was the frequency of post-transplant rejection in patients with AIH, which raises questions regarding the difficulty of differentiating between disease recurrence and immunologic rejection. This issue has been highlighted in previous studies and underscores the need for meticulous clinicopathologic evaluation in this subgroup of patients[19,21]. Some authors have emphasized the importance of intrinsic donor characteristics, their associated risks, and the true presence of rejection or disease recurrence. This is particularly relevant in PSC cases, in which stenotic lesions of the biliary tract may be observed and can lead to confusion with ischemic cholangiopathy, disease recurrence, or rejection, making it difficult to determine whether the findings overlap or are associated with recurrence of the underlying disease[1,10,21].

These disorders are also well known to be associated with other autoimmune diseases, with coexistence reported in up to 20% of patients. Some of the autoimmune conditions associated with these disorders include systemic lupus erythematosus, autoimmune thyroiditis, hypothyroidism, rheumatoid arthritis, and inflammatory bowel disease. The latter is more strongly associated with PSC and contributes to disease recurrence and the need for transplantation, in addition to increasing the risk of developing colon cancer and cholangiocarcinoma[12,20,21,31,33]. In our study, a high prevalence of osteoporosis was observed, particularly in AIH, probably related to chronic corticosteroid use, disease recurrence, and the coexistence of other rheumatologic diseases[5]. This finding reinforces the importance of implementing prevention and follow-up programs for metabolic complications in this population[22,23].

Histopathologic findings continue to be of major importance for the clinicopathologic correlation of these disorders, especially in AIH and PBC, in which they may be decisive in guiding the diagnosis in some cases[34]. The predominant findings included interface hepatitis, lymphoplasmacytic infiltrates, and lobular involvement in AIH, whereas the presence of portal granulomas and bile duct injury suggested PBC involvement. Interpretation becomes more complex when a combination of these findings is observed, suggesting the diagnosis of overlap syndrome, which must always be corroborated with clinical findings. In only four cases, submassive hepatic parenchymal necrosis associated with acute liver failure and interface hepatitis was identified, suggesting AIH involvement, and two of these patients required transplantation. In this regard, the high proportion of histopathologic confirmation in our cohort strengthens the clinicopathologic correlation and constitutes an important diagnostic strength of the study.

Among the strengths of our study are the considerable sample size and the focus on a Mexican cohort, which remains underrepresented in the international literature. Recent studies have highlighted that autoimmune liver diseases represent a growing burden on healthcare systems in Mexico and other Latin American countries, particularly because of their chronic course, the need for prolonged immunosuppression, and the risk of progression to cirrhosis or liver transplantation[27,28]. In this regard, the findings of the present study contribute to expanding the available evidence in the region and to improving the understanding of the clinical profile and outcomes of these disorders in Latin American populations.

Among the identified limitations was the lack of information regarding the initial diagnosis and management of some patients, several of whom were referred in advanced stages of disease due to the need for inclusion in the liver transplantation program, or had been diagnosed during childhood and were referred to the Institute upon reaching adulthood. It should also be acknowledged that the Institute where the present study was conducted exclusively manages adult patients. Future studies should include the pediatric population, given the interest in phenotyping these diseases in this age group, in which greater variability has been described in the international literature[35]. Likewise, because of the retrospective nature of the study and the use of secondary clinical records, it was not possible to establish the follow-up time uniformly for all patients, which limits estimation of the cohort's median follow-up time. Finally, as this is a national referral center, the cohort likely includes a greater proportion of complex or advanced disease cases.

It is important to note that additional studies conducted in greater depth are needed to establish associations with the identified variables, as well as to further characterize the phenotypes of the Mexican population in order to improve understanding of autoimmune liver disease and thereby guide treatment and improve patient survival.

CONCLUSIONS

This study, conducted at a national referral center in Mexico, enabled the identification of the main clinical and epidemiologic characteristics of patients with autoimmune liver diseases over a 10-year period. Autoimmune hepatitis was the most frequent entity, followed by primary biliary cholangitis

and primary sclerosing cholangitis, with a relevant number of overlap syndromes, particularly AIH-PBC overlap.

Treatment response and remission rates were more favorable in AIH and PBC, whereas PSC showed a poorer prognosis, with greater recurrence and need for transplantation. These findings contribute to expanding knowledge regarding the clinical behavior of autoimmune liver diseases in the Latin American population and highlight the importance of continuing to develop regional studies that allow for a better understanding of their progression and optimization of management strategies.

Ethical Considerations

This research followed the principles of the Declaration of Declaration of Helsinki and the Belmont Report for research involving human subjects, as well as the Mexican Official Standard NOM-004-SSA3-2012 regarding medical records, emphasizing that "the information reviewed in the medical record shall be handled with discretion and confidentiality," and no personal data were published or disclosed. The study was considered research without biological, psychological, physiological, or social risk for the patients of the Institution, since the information was collected through anonymized secondary data and no individual-level intervention representing risk to the integrity of the study. The project was approved by the Research and Ethics Committee of the Instituto Nacional de Ciencias Médicas y Nutrición Salvador Zubirán.

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Conflict of Interest

The authors declare that there were no conflicts of interest in the conduct of the present study.

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Original article

Etiological Pattern of Liver Cirrhosis: Experience at a Hospital in Southwestern Colombia

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Abstract

Introduction: Liver cirrhosis is a leading cause of morbidity and mortality worldwide and in Colombia. Its most common etiologies have traditionally been chronic alcohol consumption and viral infections due to hepatitis B and C. However, recent decades have shown a shift in the etiological profile, with an increase in metabolic dysfunction–associated liver disease and autoimmune conditions. **Objective:** To determine the etiology of liver cirrhosis in patients treated at a tertiary care hospital (Nariño, Colombia) during the period 2022–2023. **Methods:** A cross-sectional descriptive observational study was conducted. Medical records of patients treated at Fundación Hospital San Pedro with a diagnosis of liver cirrhosis were reviewed. Statistical analysis was performed using Microsoft Excel 365, and approval was obtained from the hospital ethics committee. **Results:** A total of 120 patients were analyzed, with a mean age of 66.4 years; females predominated (52.5%), and most patients were from the department of Nariño (90.83%). Clinically, 49.2% presented with ascites, 42.5% with upper gastrointestinal bleeding, and 17.5% with hepatic encephalopathy. According to the Child–Pugh classification, 39.2% were stage B and 25.8% stage C. The most frequent etiology was cryptogenic (35.8%), followed by autoimmune (25.0%) and alcohol-related (15.0%). In-hospital mortality was 11.7%. **Conclusions:** Liver cirrhosis showed a predominantly cryptogenic etiological profile, with a high burden of advanced disease at diagnosis. The high frequency of autoimmune and steatosis-associated etiologies suggests a shift from the traditional etiological pattern observed in previous decades.

Keywords

Liver cirrhosis; causality; immunity; mordibity; prevalence.

INTRODUCTION

Cirrhosis is described as a chronic disease resulting from a persistent inflammatory process that leads to fibrosis of the hepatic parenchyma accompanied by injury to the vascular architecture due to multiple causes, among which alcohol consumption, viral infections—primarily hepatitis B virus (HBV) and hepatitis C virus (HCV)—autoimmune diseases, drug-induced liver injury, cholestasis, and metabolic disorders stand out, among others[1]. Only one in three individuals with cirrhosis is aware of having the disease, as most patients remain asymptomatic until the onset of decompensation, at which point liver disease is considered advanced[2].

Once symptoms, clinical signs, or abnormal liver function tests are identified, further evaluation is performed to determine the etiology of the disease, which will guide subsequent treatment[2]. Accurate identification of the etiology, together with staging of the degree of fibrosis, is essential for determining prognosis. Without a clear etiology that allows for targeted treatment, interventions

aimed at slowing the progression of tissue damage and preventing severe complications are limited.

Chronic liver disease is the leading cause of morbidity in approximately 844 million people and is also responsible for nearly 2 million deaths annually worldwide, half of which are due to complications related to cirrhosis and the other half to chronic HCV infection[3]. The epidemiology of the disease is heterogeneous and varies according to etiology, sex, geographic location, age, and individual-specific risk factors. This condition imposes a substantial public health burden in many countries and has shown a progressive worldwide increase since 1990, partly due to population growth and aging. In Latin America specifically, deaths from liver cirrhosis doubled between 1980 and 2010[4].

Several regional studies have been conducted to clinically and epidemiologically characterize cirrhosis and to determine its etiological profile. In Colombia, MA Luján and colleagues[5] conducted a retrospective observational study that included patients diagnosed with liver cirrhosis and bacteremia at a tertiary-level hospital in the city of Medellín and described cryptogenic etiology as the leading cause of cirrhosis at 30.8%, followed by non-alcoholic fatty liver disease at 19.3%. In the city of Bogotá, JE Prieto and colleagues[6] found that the leading cause of cirrhosis was non-alcoholic fatty liver disease, accounting for 25.5%, in line with the global trend of increasing prevalence of this condition as a cause of liver cirrhosis. Similar phenomena have been described throughout Latin America, where a transition from infectious etiologies toward metabolic and autoimmune causes has been observed[7].

The aim of the present study is to characterize a group of patients with liver cirrhosis and determine the different etiologies present in the population of the department of Nariño treated at a tertiary-level hospital in the region during the 2022–2023 period.

METHODOLOGY

An observational, descriptive, cross-sectional, and retrospective study was conducted. Medical records of patients older than 18 years treated at Fundación Hospital San Pedro (Pasto, Nariño, Colombia) between January 2022 and December 2023 with a confirmed diagnosis of liver cirrhosis were reviewed according to the following criteria: the diagnosis of liver cirrhosis was established using a multimodal approach in accordance with the guidelines of the European Association for the Study of the Liver (EASL) and the Baveno VII Consensus. Cirrhosis was defined by fulfillment of at least one of the following criteria:

- Histological: evidence of stage F4 fibrosis according to the METAVIR classification on liver biopsy.
- Elastography: liver stiffness >15 kPa, a value with high specificity for confirming compensated advanced chronic liver disease.
- Noninvasive biomarkers: biochemical indices of advanced fibrosis such as FIB-4 >3.25 or APRI >1.0.
- Imaging and clinical findings: presence of regenerative nodules on ultrasound, computed tomography, or magnetic resonance imaging associated with unequivocal signs of portal hypertension such as splenomegaly, ascites, or esophageal varices identified on upper gastrointestinal endoscopy.

In addition, alcoholic cirrhosis was defined based on the clinical record of chronic alcohol intake (consumption >20 g/day in women and >40 g/day in men):

- Autoimmune cirrhosis: suggested by positivity for antinuclear antibodies (ANA), anti-smooth muscle antibodies (ASMA), or antimitochondrial antibodies (AMA) (titers ≥1:40), elevated total immunoglobulin G (IgG), or compatible biopsy findings (interface hepatitis and predominance of plasma cell infiltrate).
- Metabolic dysfunction-associated steatotic liver disease (MASLD): presence of steatosis on imaging associated with metabolic comorbidities (type 2 diabetes *mellitus* [T2DM], obesity, dyslipidemia) in the absence of significant alcohol consumption.
- Compatible biopsy: presence of regenerative nodules surrounded by fibrous bands (METAVIR stage F4).
- Use of APRI/FIB-4: these indices were used as diagnostic support only when clinical and radiological correlation with portal hypertension was present.

Patients with etiological profile results that included hepatitis B and C virus testing (hepatitis C virus antibodies [anti-HCV], hepatitis B surface antigen [HBsAg], antibodies against hepatitis B surface antigen [anti-HBs], antibodies against hepatitis B core antigen [anti-HBc], hepatitis B e antigen [HBeAg], viral load for HBV and HCV), autoimmunity markers (ANA, ASMA, AMA, IgG), alcohol use (clinical record and chronic intake criteria), metabolic/MASLD profile (body mass index [BMI], T2DM, dyslipidemia, hypothyroidism, liver ultrasound), storage diseases (ceruloplasmin, ferritin, transferrin saturation, total iron), and other etiologies (history of hepatotoxic drug exposure) were included. Pregnant women and patients with metastatic liver tumors were excluded. Sociodemographic, clinical, laboratory, and etiological variables were collected. Patient care was provided in the outpatient and emergency settings by hepatology, gastroenterology, and internal medicine services. Statistical analysis was descriptive, calculating measures of central tendency, means, and absolute and relative

frequencies. The study was approved by the institutional ethics committee.

RESULTS

A total of 120 medical records were analyzed. The mean age was 66.4 years with a standard deviation (SD) of 11.4 (minimum age: 28 years; maximum age: 92 years), with a slight predominance of females (52.5%). Of the patients, 90.8% were from the department of Nariño and 56.67% from the city of Pasto; 49.17% had completed only primary school education (**Table 1**). The most frequent complications were ascites (49.1%), upper gastrointestinal bleeding (42.5%) secondary to esophageal varices (75%), and hepatic encephalopathy (16.6%) (**Table 2**). According to the Child-Pugh classification, 39.2% were classified as stage B and 25.8% as stage C, reflecting a high proportion of advanced disease (**Figure 1**).

Table 1. Sociodemographic Characteristics of the Population Included in the Study

Variable	n	Mean ± SD
Age	120	66.4 ± 11.4
Sex	**n**	**%**
Female	63	52.50
Male	57	47.50
Origin	**n**	**%**
Nariño	109	90.8
Cauca	1	0.8
Putumayo	10	8.3
Comorbidities	**n**	**%**
Type 2 diabetes *mellitus*	36	30
Arterial hypertension	28	23.3
Hypothyroidism	28	23.3
Obesity	6	5

Author's own research.

In the prognostic evaluation using the MELD-Na score, the population was stratified according to 90-day mortality risk: 55.8% of patients presented a low risk (6% mortality), 15% an intermediate risk (19.6% mortality), and 5% were within the highest severity range (52.6% mortality) (**Figure 2**). In-hospital mortality was 11.7%; among deceased patients, 50% presented with two complications at admission, 28.57% with three complications, and 21.43% with four complications, including ascites, encephalopathy, upper or lower gastrointestinal bleeding, or spontaneous bacterial peritonitis. No outpatient follow-up data after discharge were available.

Table 2. Clinical Characteristics of the Population Included in the Study

Variable		
Laboratory Tests	**n**	**Mean ± SD**
Total bilirubin (mg/dL)	118	2.66 ± 2.97
ALT (U/L)	119	68 ± 100
AST (U/L)	119	82 ± 74.2
Alkaline phosphatase (U/L)	115	263 ± 223
GGT (U/L)	94	233 ± 334
Albumin (g/dL)	115	3.16 ± 0.89
INR	119	1.37 ± 0.5
Creatinine (mg/dL)	120	1.1 ± 1.06
Platelets (10^3/µL)	118	125.934 ± 79.661
Sodium (mEq/L)	102	137 ± 5.43
Imaging Studies	**n**	**%**
Liver ultrasound	51	42.5
Cholangiography	50	41.7
Computed tomography	13	10.8
Elastography	1	0.8
Not reported	5	4.2
Imaging Findings	**n**	**%**
Liver cirrhosis	65	54.2
Chronic liver disease	47	39.2
Hepatic steatosis	3	2.5
Not reported	5	4.2
Complications		
Ascites	59	49.1
Upper gastrointestinal bleeding	51	42.5
Hepatic encephalopathy	20	16.6

ALT: alanine aminotransferase; AST: aspartate aminotransferase; SD: standard deviation; GGT: gamma-glutamyl transferase; INR: international normalized ratio. Author's own research.

Regarding the diagnosis of cirrhosis, the predominant method was imaging studies (87.5%). Liver ultrasound and magnetic resonance cholangiography were the most frequently performed studies (42.5% and 41.7%, respectively). Elastography was performed in only 0.8% of patients, reflecting the limited availability of advanced diagnostic methods. Liver biopsy was performed in 15.8% of cases

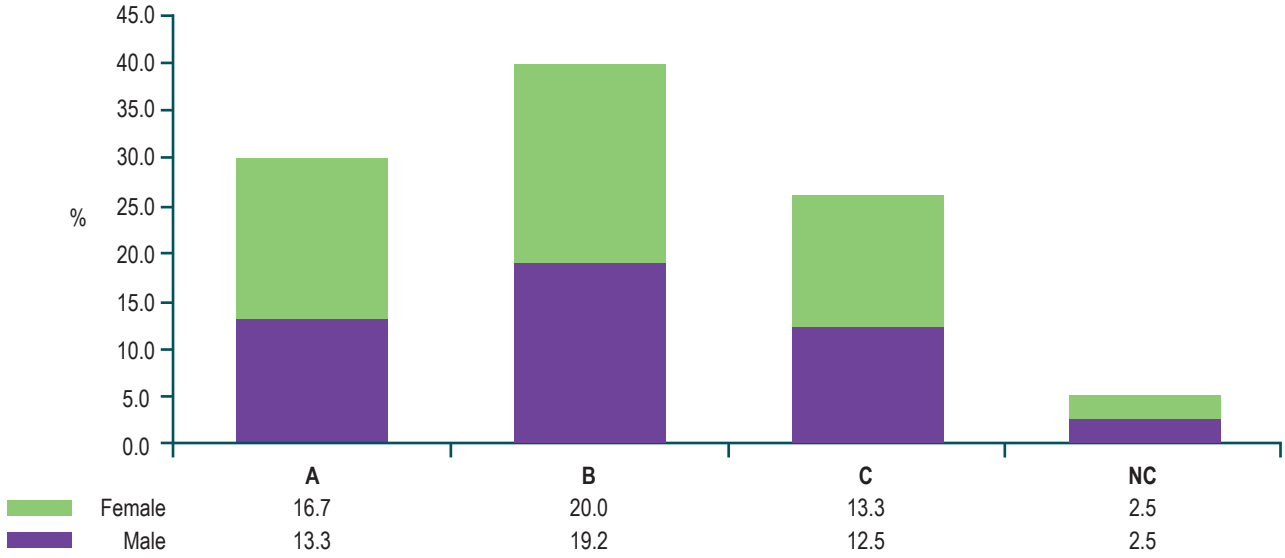


Figure 1. Percentage Distribution according to Child-Pugh Classification Stage Author's file.

(**Table 3**). In the etiological profile, the most frequent cause was cryptogenic cirrhosis (35.8%), followed by autoimmune (25.0%) and alcoholic etiologies (15.0%). Metabolic hepatic steatosis accounted for 9.2% of cases, whereas viral etiologies due to HBV and HCV were uncommon (approximately 3% to 4%). Two cases of cardiac origin and one case due to storage diseases were also identified (**Table 3**). Distribution by sex is presented in **Figure 3**.

DISCUSSION

The present study revealed a predominance of females (52.5%), a finding consistent with national reports in which the high prevalence of autoimmune diseases shifts the distribution toward this population group[5]. The mean age of 66.4 years reaffirms that cirrhosis is usually diagnosed at advanced stages due to its silent progression, with a significant impact on morbidity and mortality[1]. The high frequency of complications at admission, such as ascites (49.1%) and gastrointestinal bleeding (42.5%), demonstrates an advanced presentation of the disease. Progression to decompensated states significantly increases the risk of hospitalization and mortality[8]. These findings are consistent with the literature emphasizing that such complications reflect clinically significant portal hypertension and are associated with a greater need for early interventions. Ascites constitutes the most frequent complication of portal hypertension and is associated with poorer prognosis and increased risk of spontaneous bacterial peritonitis and hepatorenal syndrome[9,10].

Table 3. Variables related to the Etiology of Liver Cirrhosis

Variable	n	Positivity (%)
HBsAg	111	3.33
Anti-HBc	71	7.5
Anti-HBs	46	4.17
HBeAg	4	0.83
HBV viral load	4	3.33
Anti-HCV	110	4.17
ANA	75	12.5
ASMA	77	15
AMA	77	12.5
Total IgG	61	15
Ceruloplasmin	53	1.67
Ferritin	77	5.83
Transferrin saturation	62	5.83
Serum iron	69	2.5
Alcohol consumption	18	15
Liver biopsy	19	15.8

HBeAg: hepatitis B virus e antigen; AMA: antimitochondrial antibodies; ANA: antinuclear antibodies; ASMA: anti-smooth muscle antibodies; anti-HBc: antibodies against hepatitis B core antigen; HBsAg: hepatitis B surface antigen; anti-HBs: antibodies against hepatitis B surface antigen; total IgG: total immunoglobulin G; HBV: hepatitis B virus; anti-HCV: antibodies against hepatitis C virus. Author's own research.

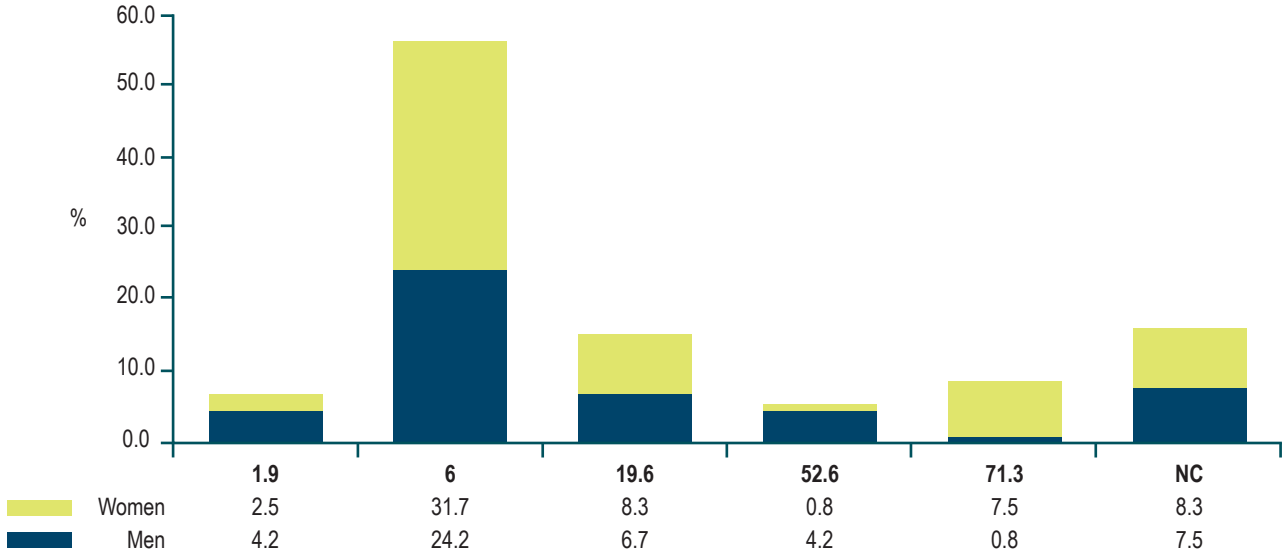


Figure 2. Percentage of 90-day mortality determined by the MELD-Na score. NC: not classifiable. Author's file.

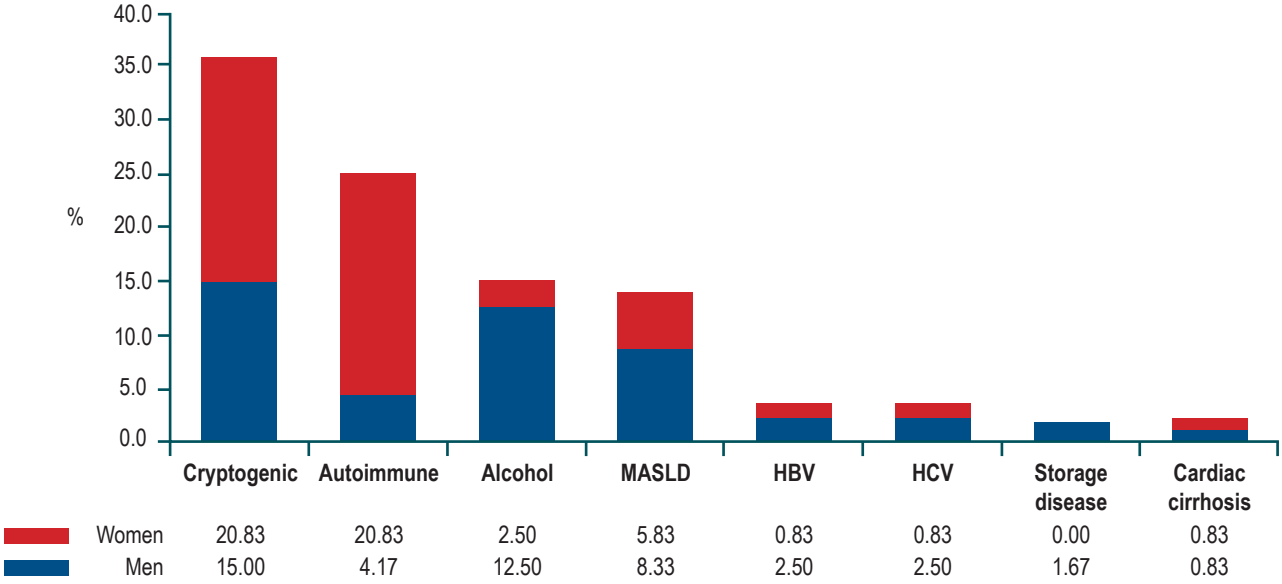


Figure 3. Etiology of Liver Cirrhosis in Patients Treated at FHSP During the 2022–2023 Period, Stratified by Sex Author's file.

The etiological distribution identified demonstrates a changing pattern in southwestern Colombia. Although cryptogenic cirrhosis was the most frequent cause (35.8%), this high percentage suggests limitations in prior comprehensive diagnostic evaluation. In the current literature, studies with rigorous follow-up usually report cryptogenic cirrhosis rates below 10%[13]. In our setting, this may be explained by the limited availability of advanced diagnostic tools: elastography was performed in only 0.8% of cases and liver biopsy in 15.8%. It is highly likely that a considerable proportion of these cryptogenic cases actually correspond to metabolic or autoimmune forms not confirmed through noninvasive tests (NITs) or histology. NITs have demonstrated diagnostic and prognostic utility in advanced fibrosis and cirrhosis, particularly in settings where biopsy is not widely available[11].

Regarding MASLD etiology, an apparent contradiction was observed: although 30% of patients had T2DM, only 9.2% were etiologically classified as MASLD. This phenomenon is characteristic of advanced stages of cirrhosis (Child-

Pugh stages B and C, which represented 65% of our sample), in which hepatic fat tends to disappear as fibrosis progresses, a phenomenon known as burnt-out NASH, making imaging or histological identification more difficult[12,15].

Autoimmune etiology accounted for 25% of cases. However, this value should be interpreted with caution; antibody positivity (ANA/ASMA) ranged from 12.5% to 15%, and only a minority of patients had biopsy confirmation. In biopsied cases, findings of interface hepatitis and hepatocyte rosettes are pathognomonic, but their absence in most of the cohort suggests that autoimmune etiology may be overestimated if based solely on limited clinical criteria[13,14].

Regarding alcohol consumption (15.0%), underreporting of intake is likely due to socioeconomic factors and the educational level of the population, in which 49.1% had only primary school education. Finally, the frequent use of magnetic resonance cholangiography (41.7%) as a diagnostic method in our cohort reflects the clinical need to rule out obstructive biliary diseases or sclerosing cholangitis in the presence of cholestatic biochemical patterns, favoring its use over computed tomography because of its greater sensitivity in evaluating the biliary tract in cases of unclear etiology.

This study has limitations inherent to its retrospective design and the limited availability of elastography. Nevertheless, it confirms an epidemiological transition toward metabolic and autoimmune causes in the region, similar to what has been observed in other developing countries, where infectious causes are being displaced[16].

CONCLUSION

This study identified a shift in the etiological pattern of liver cirrhosis in southwestern Colombia, with predominance of cryptogenic and autoimmune cases. These findings suggest the need to strengthen timely etiological diagnosis and to implement preventive strategies focused on emerging trends in chronic liver disease.

Author Contributions

NVIO: designed the research protocol, conducted data collection and analysis, and drafted the final version of the manuscript. JABM: participated as methodological advisor in the study design and critical review of the manuscript. DFTG and MBR: served as scientific advisors, providing conceptual guidance and content review. SDMM and AJVR: collaborated in data collection. All authors reviewed and approved the final version of the manuscript.

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https://doi.org/10.22516/25007440.1511

Original article

Germline Variants in Patients with Sporadic Gastric Cancer from Southwestern Colombia

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Abstract

Introduction: Gastric cancer (GC) is a major public health problem worldwide, and Colombia is among the regions with the highest incidence. Multiple factors contribute to its development, including germline mutations (hereditary disease), which influence individual susceptibility. **Objective:** To identify germline variants in the exome of patients diagnosed with sporadic GC from regions of high and low incidence in Colombia. **Materials and methods:** Four blood samples were collected from patients with GC in the department of Nariño, Colombia, for whole-exome sequencing (WES). Bioinformatic analysis included raw data quality control, alignment of reads to the human reference genome, variant calling, annotation, filtering and prioritization, data visualization, and functional pathway analysis of genes harboring deleterious variants. **Results:** A total of 1,800,145 germline variants were identified in the analyzed patients. Five of these variants were reported in ClinVar as pathogenic, and these genetic alterations have not been previously described in patients with GC. The variants were identified in the genes *ACADS* (rs57443665), *BRCA1* (rs55688530), *FLNC* (rs200502811), *MCCC2* (rs757052602), and *ACSS2* (rs59088485), which have been previously reported and studied by The Cancer Genome Atlas (TCGA). **Conclusions:** Rare pathogenic molecular variants associated with susceptibility to GC were identified. Further studies are encouraged to validate these findings.

Keywords

Neoplasms; germline mutation; exome sequencing; genetic variation.

INTRODUCTION

Gastric cancer (GC) is the fifth most common type of cancer worldwide and one of the leading causes of cancer-related mortality, with approximately 968,000 new cases and more than 660,000 deaths estimated in 2022[(1)]. In Colombia, this neoplasm represents a major public health problem and ranks among the leading causes of cancer mortality, with an estimated mortality rate of 9.9 deaths per 100,000 inhabitants. Likewise, GC is among the neoplasms with the greatest disease burden in the country, with an approximate incidence rate of 12.8 new cases per 100,000 inhabitants[(1)]. However, the risk and incidence of GC are higher in certain regions of the country, such as the Andean region, where incidence rates reach 26.1 and 14.8 cases per 100,000 inhabitants in men and women, respectively[(2,3)].

The development of the disease can be explained by the interaction of multiple risk factors, including environmental factors, chronic infection with the bacterium *Helicobacter pylori*, diet, alcohol consumption, smoking, socioeconomic conditions, genetic factors, the presence of molecular

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variants, and epigenetic alterations, all of which together play a predominant role in the pathophysiology of GC[4].

In recent years, the search for molecular variants in different genes has intensified through the use of next-generation sequencing (NGS) technologies[4]. These high-throughput technologies enable the detection of genetic alterations associated with an increased risk of disease development[5,6]; however, sequencing may focus exclusively on protein-coding regions of the genome, given that approximately 85% of cancer-causing mutations are estimated to occur within coding regions. The technology used to analyze genetic alterations in coding regions is known as whole-exome sequencing (WES)[6–8].

Using whole-genome and whole-exome sequencing data, together with bioinformatic analyses, it has been possible to detect both somatic and germline genetic variants[9]. The latter have been less extensively studied and have been identified in approximately 10% of sporadic cancer cases; nevertheless, this type of mutation often goes unnoticed[10–12]. These mutations may interact at different stages of cancer development, acting synergistically to promote disease progression[13,14]. Furthermore, studying the interaction among cancer-associated germline variants provides deeper insight into aberrant pathways that may constitute potential therapeutic targets[15].

Therefore, the aim of this study was to characterize germline genetic variants in the exome of patients diagnosed with sporadic gastric cancer from two regions of high and low incidence in Colombia.

MATERIALS AND METHODS

Study Type

A quantitative, observational, and analytical study was conducted using available whole-exome sequencing data from patients with a histopathological diagnosis of GC.

Patients and Samples

Four Colombian patients older than 18 years with a histopathological diagnosis of intestinal-type GC were included. All patients had no family history of GC, tested negative for *H. pylori* infection, and had no comorbidities associated with other types of cancer or HIV infection. Blood samples were obtained by venipuncture under aseptic and fasting conditions. Sample collection was performed by healthcare professionals.

Genomic DNA Extraction

DNA was isolated using the DNA Isolation Kit Ultra Clean Blood Spin (MOBIO, Mobio Technologies Inc., San Diego, United States). DNA quantity and quality were determined quantitatively and qualitatively using the NanoDrop-2000 system and electrophoresis.

Whole-Exome Sequencing

Library enrichment for the capture of coding regions was performed using the Agilent SureSelect V5 kit. Sequencing of exonic regions was carried out on the Illumina HiSeq 2500 platform with 100–150 bp paired-end reads and 100× coverage. Raw sequencing data were obtained in FASTQ format, which includes read quality scores according to the Phred scale. Raw data quality was assessed using FastQC[16].

Low-quality sequence filtering and adapter trimming were performed using the BBMap package[17]. Reads were aligned to the human reference genome hg19/NCBI using the Burrows-Wheeler Aligner (BWA) software version 0.7.17, with the BWA-MEM algorithm and default parameters[18]. Alignment files were processed using SAMtools[19]. As part of the post-alignment processing, PCR duplicates were marked using the Picard MarkDuplicates.jar tool and removed from subsequent analyses (Broad Institute, Cambridge, Massachusetts).

Variant calling was performed using two programs:

- The "HaplotypeCaller" module from GATK (Broad Institute, Cambridge, Massachusetts), which simultaneously identifies germline SNPs and INDELs through local *de novo* haplotype assembly in active regions[20,21].
- FreeBayes, a complementary program based on a Bayesian model for SNP and INDEL detection. FreeBayes is haplotype-based and uses short-read alignments together with a reference genome to determine the most probable genotype combinations in the analyzed samples[22].

The hard filters recommended by the Broad Institute for SNPs and INDELs were applied to reduce false positives in the initial set of variants detected by HaplotypeCaller. These filters use properties or statistics describing, for each variant, the sequence context surrounding the variant site, the number of reads covering the site, the number of reads per allele, the proportion of reads in forward and reverse orientation, among other parameters. The raw set of variants generated with FreeBayes was filtered using the vcffilter tool with a quality score greater than 20.

The variants obtained by both algorithms were merged into a single file. Variant annotation was performed using the ANNOVAR software[23]. Subsequently, a filtering cascade was applied to prioritize variants potentially involved in the etiology of GC:

- Nonsynonymous exonic variants, variants involving gain or loss of the start or stop codon, and frameshift variants.

- Rare variants (MAF <0.01) according to the ExAC database[24].
- Single-nucleotide variants predicted to be deleterious according to SIFT[25] and MutationTaster[26].
- INDELs with high or moderate impact on protein coding according to SnpEff[27].
- Clinical significance information reported in ClinVar[28] and allelic frequencies across different populations according to the 1000 Genomes Project[29].

Subsequently, functional enrichment analysis was performed using the genes containing prioritized single-nucleotide variants through the DAVID 6.8 annotation database[30], employing the updated Kyoto Encyclopedia of Genes and Genomes (KEGG) and Gene Ontology (GO) databases.

Statistical Analysis

Statistical analysis was performed using licensed SPSS Statistics v27 software. A univariate descriptive analysis was conducted for the sociodemographic variables sex and age. In addition, a frequency distribution was established to determine the absolute frequency, defined as the total number of times a variant was repeated. A bar graph was generated to show the number of SNPs and INDELs with functional relevance within the exome of patients with GC.

Ethical Considerations

The study was approved by the Bioethics Subcommittee (INV 2084-I), under Approval Certificate No. SCBE06-17.

RESULTS

Four exomes from individuals without *H. pylori* infection diagnosed with intestinal-type GC were analyzed: three men and one woman, with an age range between 54 and 79 years and a mean age of 64 years (**Table 1**).

Table 1. Sociodemographic and Clinical Information of the Study Patients

n	ID	Sex/ Age	Diagnosis Lauren/de Borrmann Classifications	Access Number
1	SP03	M/79	Intestinal-type gastric cancer/Type 0	SAMN20956683
2	SP05	M/54	Intestinal-type gastric cancer/Type 0	SAMN20956684
3	SP06	F/62	Intestinal-type gastric cancer/Type V	SAMN20956685
4	SP07	M/63	Intestinal-type gastric cancer/Type V	SAMN20956686

F: female; M: male. Author's own research.

Between 42 and 69 million paired-end sequencing reads were obtained; sample SP03 showed the highest number of reads, with a total of 69,534,672. High sequencing quality scores were obtained, and more than 99% of the reads from all samples mapped to the human reference genome (hg19) (**Table 2**).

Table 2. Sequencing Quality Scores and Alignment Statistics

n	ID	Total Reads	Q30 (%)	Average Read Quality	Duplication (%)	Mapped Reads (%)
1	SP03	69.534.672	93.1	Q40	8.8	99.90
2	SP05	51.400.046	95.5	Q36	9.0	99.94
3	SP06	50.193.962	95.3	Q36	8.5	99.93
4	SP07	42.933.884	95.5	Q36	8.0	99.93

Author's own research.

Germline Variants in Gastric Cancer

A total of 1,800,141 germline variants were identified across the four exomes from patients with GC. Of these, 101,902 corresponded to coding regions (5.7%); 40,130 were nonsynonymous SNPs (39.4%), 230 were stop codon gain or loss variants (0.6%), and 1,783 were INDELs (4.4%). **Table 3** shows the frequency of SNPs and INDELs by variant type within the exonic region in the four samples analyzed.

During prioritization, germline variants were filtered by selecting only exonic variants with a frequency below 1% and classified as deleterious. Genes harboring these prioritized variants were considered for the functional enrichment analysis (**Figure 1**).

Biological Pathways Involved in Gastric Cancer

A total of 630 genes were included in the functional analysis. Functional pathways involving genes with deleterious variants revealed 20 significant biological pathways with p <0.05 (**Figure 2**). Likewise, five genes of biological relevance (*BRCA1*, ACADS, FLNC, ACSS2, and MCCC2) were prioritized, as they harbored single-nucleotide variants with clinically significant pathogenicity according to the ClinVar database (**Table 4**).

Mutations in the BRCA1 (rs55688530) and ACADS (rs57443665) genes were identified in sample SP03 from a patient originating from a coastal region of Colombia. According to the 1000 Genomes Project database, these two molecular variants have previously been reported in

the African population, with frequencies of 0.01 and 0.008, respectively.

Patient SP07, from an Andean region of Colombia, presented three variants: FLNC (rs200502811), previously reported in African (C: 0.009) and American (C: 0.001) populations; and ACSS2 (rs59088485) (C: 0.016) and MCCC2 (rs757052602) (T: 0.003), which have been reported exclusively in the American population (**Table 4**).

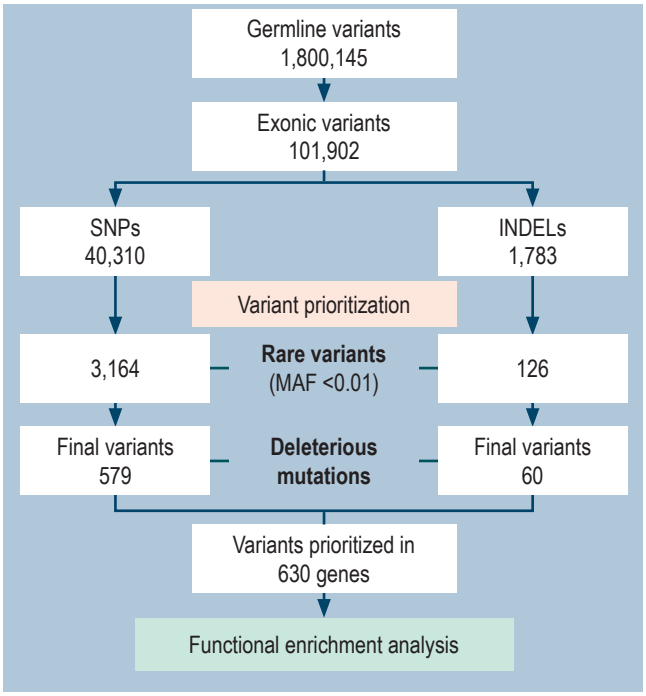


Figure 1. Workflow for the identification and prioritization of germline variants from whole-exome sequencing data of four patients with gastric cancer. Author's file.

DISCUSSION

GC is a complex and heterogeneous disease with high incidence and mortality rates, representing a serious threat to affected patients. Therefore, identifying relevant biomarkers for the diagnostic and prognostic assessment of the disease is essential[31,32].

In the present study, the results of the GO enrichment analysis showed that the genes were mainly associated with pathways previously described in GC, such as oxidation-reduction processes, the Wnt signaling pathway, sensory perception of sound, and endocytosis (**Figure 2**). An imbalance in the oxidation-reduction process may generate excessive levels of reactive oxygen species (ROS), which directly react with nucleic acids, causing both mitochondrial and nuclear genomic instability, thereby promoting carcinogenesis[33]. Wnt signaling regulates cell proliferation, differentiation, migration, and pluripotency; however, hypo- or hyperactivation of this pathway due to genetic alterations has been shown to promote the development of multiple solid tumors, including GC[34]. Endocytosis, in turn, plays an important role in the regulation of tumor metastasis[35]. KEGG pathway analysis showed that the genes were mainly enriched in glycolysis/gluconeogenesis, butanoate metabolism, and fructose and mannose metabolism (**Figure 2**), metabolic pathways that may be crucial in cancer research[36-38].

Furthermore, this study identified germline variants reported in ClinVar with clinically significant pathogenicity. These single-nucleotide variants had not previously been reported in patients with GC and were identified in the BRCA1, ACADS, FLNC, MCCC2, and ACSS2 genes (**Table 5**), which have already been described and stu-

Table 3. Frequency of Germline Alterations Identified by Whole-Exome Sequencing in Four Patients with Gastric Cancer

Sample	Intronic	Intergenic	Exonic	SNVs*			INDELs		
				Non-synonymous	Stop Codon Gain	Stop Codon Loss	Frameshift Substitution	Frameshift Deletion	Frameshift Insertion
SP03	194,300	162,423	28,321	10,042	87	22	9	150	186
SP05	274,587	322,622	24,337	10,076	100	12	9	144	117
SP06	262,971	300,106	24,528	10,078	101	13	5	130	80
SP07	233,732	244,789	24,716	10,116	87	14	9	126	98

*Includes mutations and polymorphisms. Author's own research.

Table 4. Reported Pathogenic Alterations and Their Frequency in Different Geographic Regions

Gene	Nucleotide Change	RefSNP	ClinVar	Allelic Frequency — 1000 Genomes
BRCA1	C → T	rs55688530	Conflicting interpretations of pathogenicity	Africa: T = 0.01
ACADS	T → C	rs57443665	Pathogenic/likely pathogenic	Africa: C = 0.008
FLNC	T → C	rs200502811	Conflicting interpretations of pathogenicity	Africa: C = 0.009 — America C = 0.001
ACSS2	T → C	rs59088485	Pathogenic	America: C = 0.016
MCCC2	A → T	rs757052602	Pathogenic/likely pathogenic	America: T = 0.003

Author's own research.

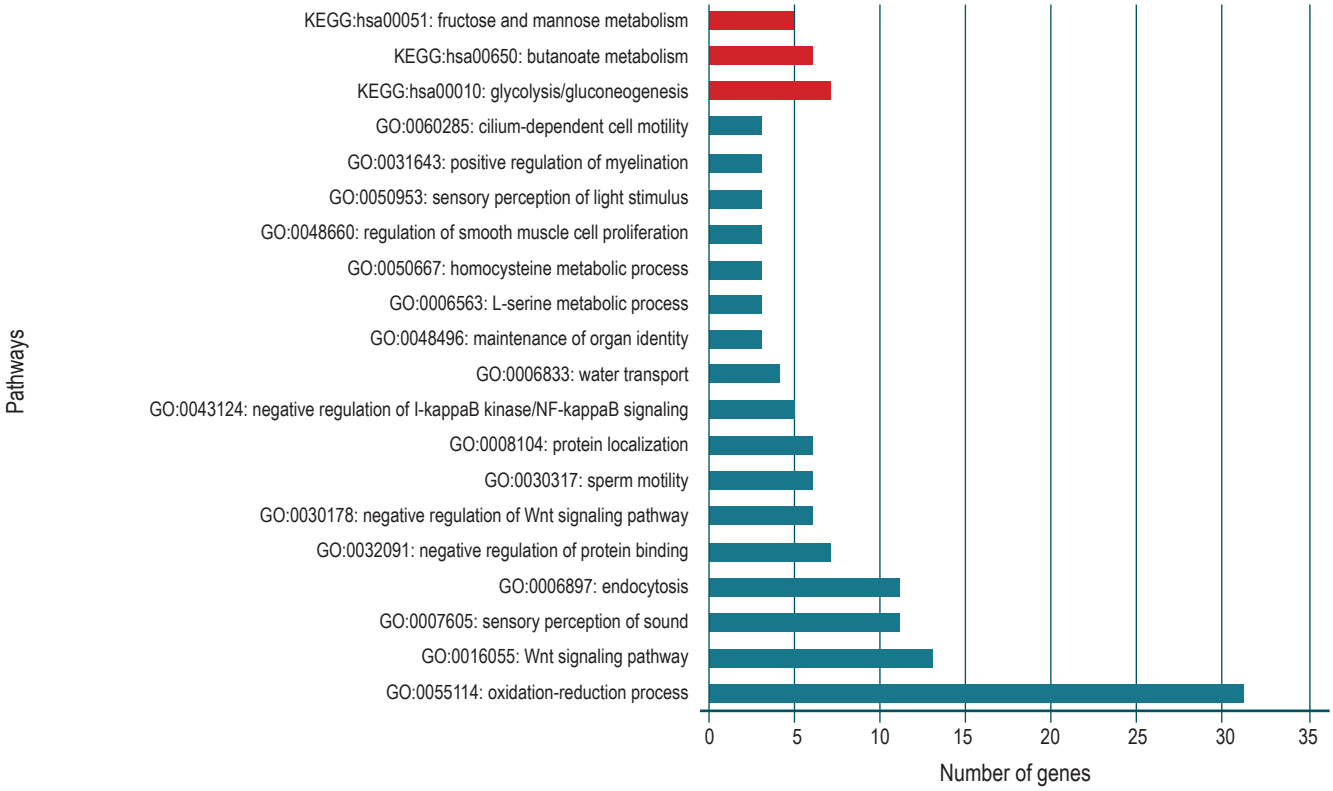


Figure 2. Biological processes (GO) and mutated KEGG pathways in patients with gastric cancer ($p < 0.05$, Fisher's exact test). Author's file.

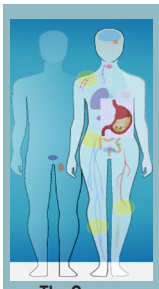
died within the framework of The Cancer Genome Atlas (TCGA) cancer genomics program[39].

The breast cancer 1 (BRCA1) gene plays a fundamental role in DNA repair as a cell-cycle checkpoint and functions as a regulator of epithelial cell growth[38]. Kim and collaborators[39] explained that carriers of germline BRCA1 mutations may have a four- to sevenfold increased risk of developing GC compared with the general population.

Regarding the ACADS gene, no reports of cancer-associated variants have been described; however, based on our findings, further investigation into the role of the rs57443665 variant is recommended, since according to ClinVar its significance is classified as pathogenic/likely pathogenic. In addition, this gene participates in the butanoate metabolic pathway. Han and colleagues[40] reported that this pathway could be crucial in cancer research, given

that butyrate inhibits histone deacetylases, thereby increasing the expression of genes that slow the cell cycle and induce apoptosis.

Table 5. Data on the Studied Genes Reported in The Cancer Genome Atlas



Gene	Cases by Sex		Vital Status		SNVs
	Male	Female	Alive	Deceased	
BRCA1	40	16	27	29	16
ACADS	29	8	22	15	16
FLNC	15	13	13	14	16
ACSS2	21	9	18	12	16
MCCC2	34	13	31	16	16

SNV: single-nucleotide variants. Adapted from: Kim H and colleagues. Oncol Lett. 2019;17(5):4383-92[39].

The FLNC gene encodes an actin-binding protein and has been reported by Slavin and collegues[41] as a candidate gene in GC research due to the presence of specific variants in a patient with the disease. The present study may support the conclusions of Slavin and colleagues[41], since the rs200502811 variant was identified in patients with GC with a deleterious prediction for protein coding and clinically significant pathogenicity according to ClinVar. This gene is part of the proteoglycan pathway in cancer, which is associated with cell proliferation, adhesion, angiogenesis, and metastasis[42].

With respect to the MCCC2 gene, this is the first report of a pathogenic variant (rs757052602) in a patient with GC. Caltabiano and colleagues[43] pointed out that few studies have associated MCCC2 with cancer; however, the authors identified that the gene is overexpressed in prostate cancer tumor tissues.

The ACSS2 gene has not been reported in GC studies or in publications implementing whole-exome sequencing (WES), and Hur and collegues[44] indicated that its role in the pathology remains unknown. Nevertheless, further investigation of this gene is necessary, since in the present study the rs59088485 variant was reported as pathogenic according to ClinVar.

Another interesting aspect to consider is the report of these variants in other populations, suggesting that the ethnic origin of patient SP03 (coastal region) is African, whereas patient SP07 (mestizo ethnicity) presented variants registered in both African and American populations. Genetic variation in Latin American populations could be explained by the convergence of Europeans, Amerindians, and especially Africans during the colonization process, which led to extensive genetic heterogeneity[45].

CONCLUSIONS

The results provide novel variants for investigation that may be associated with the development of GC and could explain part of the genetic component of this disease. It is important to note that this was an exploratory study with preliminary results; therefore, confirmation of the findings through validation studies, replication in samples from other populations, and more in-depth functional experiments is recommended. The need to include unaffected controls in exome sequencing studies is also emphasized in order to compare samples and filter variants with a higher likelihood of being pathogenic and involved in the development of GC. This will allow more precise identification of the genetic variants contributing to disease risk. Furthermore, the active search for variants and determination of their clinical impact will enable healthcare professionals to provide appropriate genetic counseling that contributes to timely decision-making in favor of patient health.

Informed Consent

Patients were informed verbally and in writing about the objectives, protocols, and characteristics of the study, and only those who signed the informed consent form were included.

Conflict of Interest

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

Funding Sources

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Use of Artificial Intelligence

The authors of this article declare that no artificial intelligence-assisted technologies were used.

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Original article

Comparison of Endoscopic and Histological Scoring Systems in Adults with Eosinophilic Esophagitis and Their Correlation with Inflammatory Activity

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Abstract

Background: Eosinophilic esophagitis (EoE) is a chronic inflammatory disease mediated by allergic mechanisms, with increasing prevalence in both adults and children. Disease activity is assessed using endoscopic (EREFS) and histological (PHEEo) scoring systems, although their concordance and discriminatory capacity remain under debate. **Objectives:** To evaluate the relationship between EREFS, PHEEo scores, and peak eosinophil count (PEC), and to develop a predictive model of EoE activity based on combined endoscopic and histological components. **Methods:** A multicenter study including 94 adult patients with confirmed EoE was conducted. Disease was classified as active (EoE-A; n = 49, ≥15 eosinophils per high-power field) or inactive (EoE-I; n = 45, <15 eosinophils per high-power field). Pearson correlation coefficients and receiver operating characteristic (ROC) curve analyses were applied, with 95% confidence intervals estimated using bootstrap techniques and comparison of areas under the curve (AUCs) performed using DeLong's method. **Results:** The diagnostic performance of the histological score PHEEo was superior to the endoscopic score EREFS (AUC: 0.90; 95% CI: 0.83–0.96 vs. 0.62; 95% CI: 0.52–0.74). The combined model (PEC) achieved an AUC of 1.00, indicating overfitting and the need for external validation. Correlation between EREFS and PHEEo was weak (r = 0.03; 95% CI: −0.18 to 0.23), whereas PHEEo and PEC showed a moderate association (r = 0.62; 95% CI: 0.48–0.73). These findings confirm that endoscopic and histological markers provide complementary, non-mutually exclusive, and non-redundant information. **Conclusions:** The histological score PHEEo more accurately discriminates inflammatory activity in EoE than the endoscopic score EREFS. An integrated model combining specific endoscopic and histological findings improves predictive performance and may optimize the assessment of active disease. However, the perfect performance of the combined model suggests overfitting and requires prospective validation before routine clinical implementation.

Keywords

Eosinophilic esophagitis; hypersensitivity; adult; endoscopy; methods; histological techniques.

INTRODUCTION

Eosinophilic esophagitis (EoE) is a chronic, inflammatory, recurrent allergic disease mediated by the immune system through activation of type 2 helper T (Th2) cells, and its main pathological feature is the predominant infiltration of eosinophils into the esophageal mucosa[1]. Clinically, EoE presents with symptoms related to esophageal dysfunction, such as dysphagia and episodes of food impaction, and it may affect individuals of all ages. Over recent decades, its prevalence has increased significantly[2]. The diagnosis of EoE is based on a consensus criterion requiring the presence of at least 15 eosinophils per high-power field (Eos/HPF) in esophageal biopsies, which is considered the diagnostic gold standard[3].

Although endoscopic findings such as edema, concentric rings, exudates, furrows, and strictures are suggestive of EoE, they are not entirely specific[4]. To standardize their assessment, the EREFS (Endoscopic REFerence System) endoscopic scoring system is used, providing a validated quantification of five key EoE features: edema, rings, exudates, furrows, and strictures[5]. Previous studies have demonstrated acceptable interobserver and intraobserver agreement for these endoscopic scores[6,7]. However, controversy remains regarding the relationship between endoscopic scores and eosinophil counts. While some studies have shown that endoscopic scores reliably predict both the diagnosis of EoE and histological response to treatment[8–10], others have indicated that these scores may not adequately reflect the histological activity of the disease[11,12].

Recently, a histological scoring system for EoE (EoEHSS) was developed and validated to comprehensively assess mucosal alterations through eight pathological features, including the severity of eosinophilic inflammation, measured by peak eosinophil count (PEC)[13]. This system has been shown to outperform PEC in distinguishing between treated and untreated patients with EoE, and some of its components have been associated with disease-specific endoscopic patterns[14]. Although both endoscopic and histological scores are validated tools for assessing EoE activity[15], the relationship between these two metrics and their combined value for predicting disease activity in adults has not yet been adequately documented. A strong correlation between these scores would allow them to be used as indirect markers of tissue pathology in EoE.

In this context, the aim is to establish the relationship between the endoscopic score (EREFS), the histological score (EoEHSS), and peak eosinophil count (PEC) in EoE activity, as well as how these parameters may be combined into a predictive model to more accurately assess the clinical activity of the disease.

PATIENTS AND METHODS

Study Participants and Case Definition

This multicenter retrospective cohort study included patients older than 18 years with a diagnosis of EoE who underwent endoscopic evaluation with biopsy sampling between January 2019 and December 2023. This cohort had previously been described in a larger study published recently[16]. The diagnosis of EoE was established according to the 2018 AGA Consensus recommendations[17], which require the presence of symptoms of esophageal dysfunction and significant eosinophilic inflammation in at least one esophageal biopsy sample following eight weeks of treatment with proton pump inhibitors, after excluding other causes of esophageal eosinophilia.

In this study, active eosinophilic esophagitis (aEoE) was defined as the presence of ≥15 eosinophils per high-power field (Eos/HPF), whereas inactive eosinophilic esophagitis (iEoE) was characterized by <15 Eos/HPF[18,19]. Patients were excluded from the analysis if they did not have at least six biopsy specimens adequate for histological evaluation, if proximal and distal esophageal biopsies were not differentiated, or if they had coexisting conditions that could interfere with the diagnosis, such as other eosinophilic gastrointestinal disorders (e.g., eosinophilic colitis or gastroenteritis), inflammatory bowel disease, connective tissue disorders, esophageal varices, or a history of esophageal surgery.

Data Collection

Demographic data (age, sex) and details regarding clinical presentation (initial symptoms), allergic comorbidities (eczema, allergic rhinitis, asthma), and exposure to ongoing treatments (such as proton pump inhibitors, oral and topical antiallergic agents, and topical corticosteroids) were collected. All information was recorded in a previously de-identified MS Excel database to ensure patient privacy.

Endoscopic Findings

During endoscopy, esophageal findings were evaluated using the EREFS scoring system, which includes the following parameters: edema (0–2), rings (0–3), exudates (0–2), furrows (0–2), and strictures (0–1). In addition, relevant secondary features, such as the appearance known as crepe-paper esophagus, were recorded. The total EREFS score was calculated by summing the individual values of each component, yielding a range from 0 to 10. Higher scores indicate greater severity of endoscopic findings (**Figure 1**).

Esophageal Biopsies and Histological Evaluation

At least six esophageal biopsy samples were obtained from each patient: three from the proximal esophagus and three from the distal esophagus. Sampling was prioritized in areas with features suggestive of EoE, such as furrows or exudates, and specimens were classified as proximal or distal according to their anatomical origin. All biopsies were processed using hematoxylin and eosin staining and evaluated for peak eosinophil count (PEC) and the degree of abnormality in eight pathological features according to the EoEHSS system: eosinophilic inflammation, basal zone hyperplasia, eosinophilic microabscesses, superficial layering of eosinophils, dilated intercellular spaces, surface

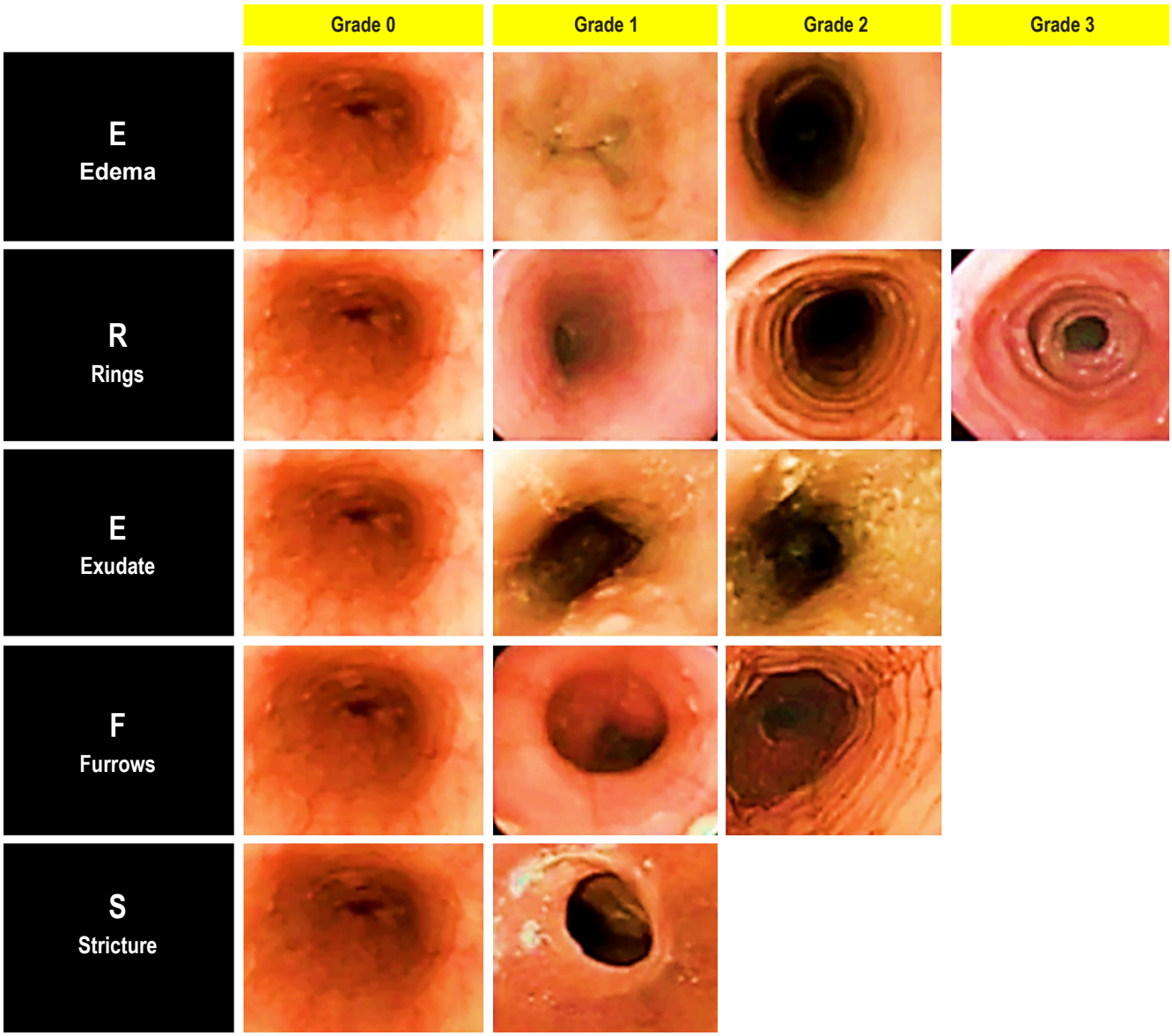


Figure 1. Endoscopic findings of eosinophilic esophagitis according to the EREFS classification and its progressive grades (0–3). Author's file.

epithelial alterations, dyskeratotic cells, and lamina propria fibrosis. Each feature received a score from 0 to 3, with a maximum score of 24 per biopsy. If any feature was not assessable (for example, fibrosis in the absence of lamina propria), the maximum score was adjusted proportionally. For instance, if the lamina propria was absent, the maximum score was reduced to 21. The final score for each biopsy was calculated as the quotient between the total sum of scores and the adjusted maximum score, thereby ensuring a standardized and comparable assessment (**Figure 2**).

Statistical Analysis

Descriptive statistical methods were used to characterize the study cohort. Correlations between endoscopic scores (EREFS) and peak eosinophil count (PEC), between endoscopic and histological scores (EoEHSS), and between histological score and PEC were assessed using Spearman's rho correlation coefficient (r). Both the total scores of the EREFS and EoEHSS systems and those of their individual components were analyzed. To adjust for

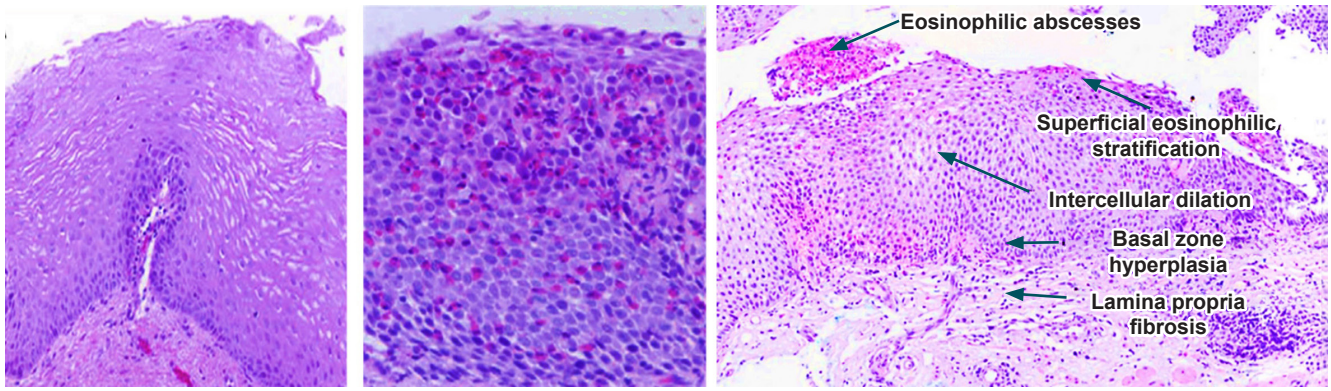


Figure 2. Histological findings in hematoxylin and eosin-stained biopsies, ranging from normal epithelium and eosinophilic infiltration (≥15 eosinophils per high-power field) to eosinophilic abscesses, basal hyperplasia, intercellular dilation, and lamina propria fibrosis, characteristic of the chronic inflammatory process. Author's file.

the effect of multiple comparisons, the Bonferroni correction was applied.

The magnitude of the correlation coefficient was interpreted as follows: 0.00–0.30 as negligible, 0.31–0.50 as weak, 0.51–0.70 as moderate, 0.71–0.90 as high, and 0.91–1.00 as very high. In addition, receiver operating characteristic (ROC) analysis was used to calculate the area under the curve (AUC) and generate plots representing sensitivity (true-positive rate) versus 1 – specificity (false-positive rate). Accuracy at different cutoff points for each component of the EREFS and EoEHSS systems was evaluated according to EoE activity status (active EoE versus inactive EoE).

Prospectively, it was planned to identify individual components with high AUC values (AUC ≥0.71) in order to develop an integrated panel of endoscopic and histological findings aimed at predicting EoE activity. For this combined panel, sensitivity, specificity, and correct classification rate values were calculated. All statistical analyses were performed using IBM SPSS software, version 26.0 (Armonk, New York).

RESULTS

Characteristics of Patients

A total of 94 adult patients with confirmed EoE were included (49 active EoE [≥15 eos/HPF], 45 inactive EoE). Mean age was 33 ± 8 years, and 69% were male. Fifty-three percent had atopic comorbidities (allergic rhinitis 20%, allergic conjunctivitis 19%). Dysphagia (18%) and reflux (16%) were the predominant symptoms. Ninety percent were receiving proton pump inhibitors (PPIs) (**Table 1**).

Endoscopic Findings (EREFS)

A total of 154 endoscopies were analyzed. Mean EREFS score was significantly higher in active EoE (4.5 ± 2.4) than in inactive EoE (3.5 ± 2.2; p = 0.016). Furrows were the most frequent finding (78% overall; 94% in active EoE versus 42% in inactive EoE, p <0.001). A normal endoscopic appearance (EREFS = 0) was observed in 6% of active EoE cases compared with 18% of inactive EoE cases (p = 0.07). The presence of friability, known as the crepe-paper sign, was also evaluated during biopsy collection, and no significant differences were found between the groups. The total EREFS score was significantly higher in patients with active EoE than in those with inactive EoE (4.5 ± 2.4 versus 4.2 ± 2.7; p ≤0.016) (**Table 2**).

Histological Evaluation (EoEHSS and PEC)

Mean peak eosinophil count (PEC) was 40 ± 12 eos/HPF in active EoE versus 4 ± 2 eos/HPF in inactive EoE (p <0.001). Mean EoEHSS score was 0.7 ± 0.1 versus 0.3 ± 0.2 (p <0.001). All histological features were significantly more prevalent in active EoE, particularly eosinophilic inflammation (96% versus 4%), eosinophilic abscesses (57% versus 7%), and epithelial stratification (35% versus 2%) (all p <0.001) (**Table 3**).

Correlations Between Scoring Systems

Peak eosinophil count (PEC) showed a high correlation with the EoEHSS histological score (r = 0.70; p <0.001), which remained significant after Bonferroni correction

Table 1. Demographic, Clinical, and Therapeutic Characteristics of the Cohort (n = 94)

Characteristics		Active EoE n = 49 (%)	Inactive EoE n = 45 (%)	Total n = 94 (%)
Age in years, mean ± SD		35 ± 8	31 ± 8	33 ± 8
Duration of symptoms, mean ± SD		21 ± 5	19 ± 5	20 ± 5
Eosinophil count, mean ± SD		37 ± 13	4 ± 2	21 ± 19
Sex	Female	14 (29)	15 (33)	29 (31)
	Male	35 (71)	30 (67)	65 (69)
Atopy	No	21 (22)	14 (15)	35 (37)
	Rhinitis	10 (11)	9 (10)	19 (20)
	Conjunctivitis	8 (9)	10 (11)	18 (19)
	Dermatitis	4 (4)	7 (7)	11 (12)
	Asthma	6 (6)	5 (5)	11 (12)
Symptoms	Asymptomatic	17 (35)	29 (64)	46 (49)
	Dysphagia	12 (25)	5 (11)	17 (18)
	Reflux	10 (20)	5 (11)	15 (16)
	Epigastric pain	7 (7)	3 (7)	10 (11)
	Food impaction	3 (3)	3 (7)	6 (6)
Management	PPI alone	23 (47)	22 (49)	45 (48)
	PPI plus diet	13 (27)	16 (36)	29 (31)
	PPI plus steroids	7 (14)	3 (7)	10 (11)
	PPI plus dilation	3 (6)	1 (2)	4 (4)
	No PPI	3 (6)	3 (7)	6 (6)

SD: standard deviation; EoE: eosinophilic esophagitis; PPI: proton pump inhibitors. Author's own research.

Table 2. Endoscopic Reference Score of the Cohort (n = 94)

Item		Active EoE n = 49	Inactive EoE n = 45	Total n = 94	*p*-Value
Exudates	0	9	12	21	0.622
	1	20	17	34	
	2	20	16	39	
Rings	0	11	8	19	**0.033**
	1	11	21	29	
	2	12	11	25	
	3	15	5	21	
Edema	0	14	13	25	0.576
	1	35	32	69	
Furrows	0	3	26	21	**0.001**
	1	46	19	73	
Strictures	0	47	44	91	0.532
	1	2	1	3	
Friability	0	21	19	40	0.558
	1	28	26	54	
EREFS	0-1	9	11	20	**0.013**
	2-3	6	8	13	
	4-5	15	17	23	
	>5	19	9	38	

EoE: eosinophilic esophagitis. Author's own research.

(p <0.001), whereas its correlation with the EREFS endoscopic score was weak (r = 0.21; p = 0.036) and lost significance after Bonferroni correction (p = 0.11) and Fisher's exact test (p = 0.31); the correlation between EoEHSS and EREFS was weak (r = 0.05; p = 0.629). Among individual components (versus PEC), strong correlations were observed with eosinophilic inflammation (r = 0.76), furrows (r = 0.45), and eosinophilic abscesses (r = 0.46) (all p <0.001); moderate correlations with dyskeratosis (r = 0.22) and fibrosis (r = 0.26); and weak or nonsignificant correlations with rings, edema, and strictures (**Figures 3–5**). Consequently, EoEHSS and PEC were strongly correlated with the inflammatory activity of EoE, whereas EREFS showed only a weak correlation.

Predictive Model for Active Eosinophilic Esophagitis

Whether the relationship between endoscopic findings (EREFS) and histological involvement (EoEHSS) was influenced by eosinophilic esophagitis activity (active EoE), defined according to the conventional PEC cutoff of ≥15 eos/HPF, was evaluated. The AUC of EoEHSS (0.90; 95% confidence interval [CI] 0.84–0.96) exceeded that of EREFS (0.62; 95% CI 0.52–0.72; p <0.001). A combined model (eosinophilic inflammation + furrows + eosinophilic abscesses + epithelial stratification + dyskeratosis) achieved:

- AUC: 0.93 (95% CI: 0.89–0.97).
- Sensitivity: 83% (95% CI: 74%–90%).
- Specificity: 95% (95% CI: 88%–98%).
- Accuracy: 90% (p <0.001) (**Table 4**, **Figures 6** and **7**).

Table 3. Histological Evaluation Based on the EoE Histological Scoring System and Peak Eosinophil Count

Evaluation		Active EoE n = 49 (%)	Inactive EoE n = 45 (%)	Total n = 94 (%)	*p*-Value
Eosinophilic inflammation	<15	2 (4)	43 (96)	45 (48)	**0.001**
	≥15	47 (96)	2 (4)	49 (52)	
Basal hyperplasia	No	4 (8)	13 (29)	17 (18)	**0.009**
	Yes	45 (92)	32 (71)	77 (82)	
Eosinophilic abscesses	No	21 (43)	42 (93)	63 (67)	**<0.001**
	Yes	28 (57)	3 (7)	31 (33)	
Eosinophil stratification	No	32 (65)	44 (98)	76 (81)	**<0.001**
	Yes	17 (35)	1 (2)	18 (19)	
Intercellular space dilation	No	4 (8)	12 (27)	16 (17)	**0.017**
	Yes	45 (92)	33 (73)	84 (83)	
Superficial epithelial alteration	No	33 (67)	42 (93)	75 (80)	**0.002**
	Yes	16 (33)	3 (7)	19 (20)	
Dyskeratosis	No	8 (16)	21 (47)	29 (31)	**0.001**
	Yes	41 (84)	24 (53)	65 (69)	
Lamina propria fibrosis	No	24 (49)	35 (78)	59 (63)	**0.004**
	Yes	25 (51)	10 (22)	35 (37)	
Histological score	Mean ± SD	0.7 ± 0.1	0.3 ± 0.2	0.5 ± 0.3	**<0.001**
Eosinophil count	Mean ± SD	40 ± 12	4 ± 2	23 ± 20	**<0.001**

SD: standard deviation; EoE: eosinophilic esophagitis; Eos: eosinophils. Author's own research.

In response to the second objective, the integrated panel of five markers (2 endoscopic + 3 histological) predicted active EoE with high accuracy, outperforming each system individually. In the diagnostic performance analysis (**Figure 6**), peak eosinophil count (PEC) achieved an area under the curve (AUC) of 1.00, followed by the histological score (EoEHSS) with 0.90 (95% CI: 0.83–0.96) and the endoscopic score (EREFS) with 0.62 (95% CI: 0.52–0.74). The difference between EoEHSS and EREFS was statistically significant (p <0.001), demonstrating the superiority of the histological component for identifying active disease.

In the analysis of individual components (**Figure 7**), eosinophilic inflammation showed the greatest discriminative capacity (AUC = 0.96), whereas longitudinal furrows (AUC = 0.76) and eosinophilic abscesses (AUC = 0.75) were the most relevant endoscopic findings. These results demonstrate that histological variables carry greater diagnostic weight than endoscopic findings, and that combining both domains could optimize the prediction of inflammatory activity in EoE.

DISCUSSION

The relationship between endoscopic scores (EREFS), histological scores (EoEHSS), and PEC was evaluated in 94 adults with EoE. In addition, selected components were integrated to develop a predictive panel for active EoE. The initial hypothesis—that EREFS, by capturing the most severe endoscopic findings, would closely correlate with histological changes—was not fully confirmed.

The correlation between EREFS and EoEHSS was poor, and the association observed with PEC was weak, ruling out the isolated use of endoscopy as a substitute for histo-

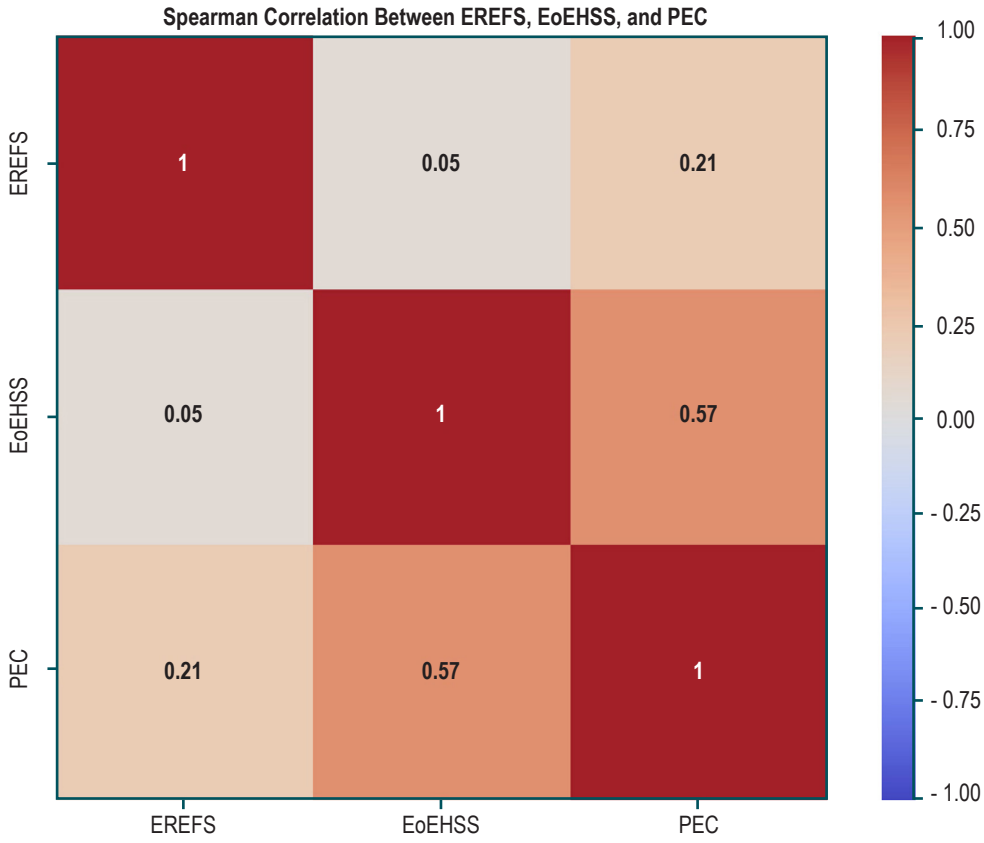


Figure 3. Heat map illustrating Spearman correlation (r; *p-value*) between endoscopic score, histological score, and peak eosinophil count. 0.91–1.00: very high; 0.71–0.90: high; 0.51–0.70: moderate; 0.31–0.50: weak; 0.00–0.30: negligible. Author's file.

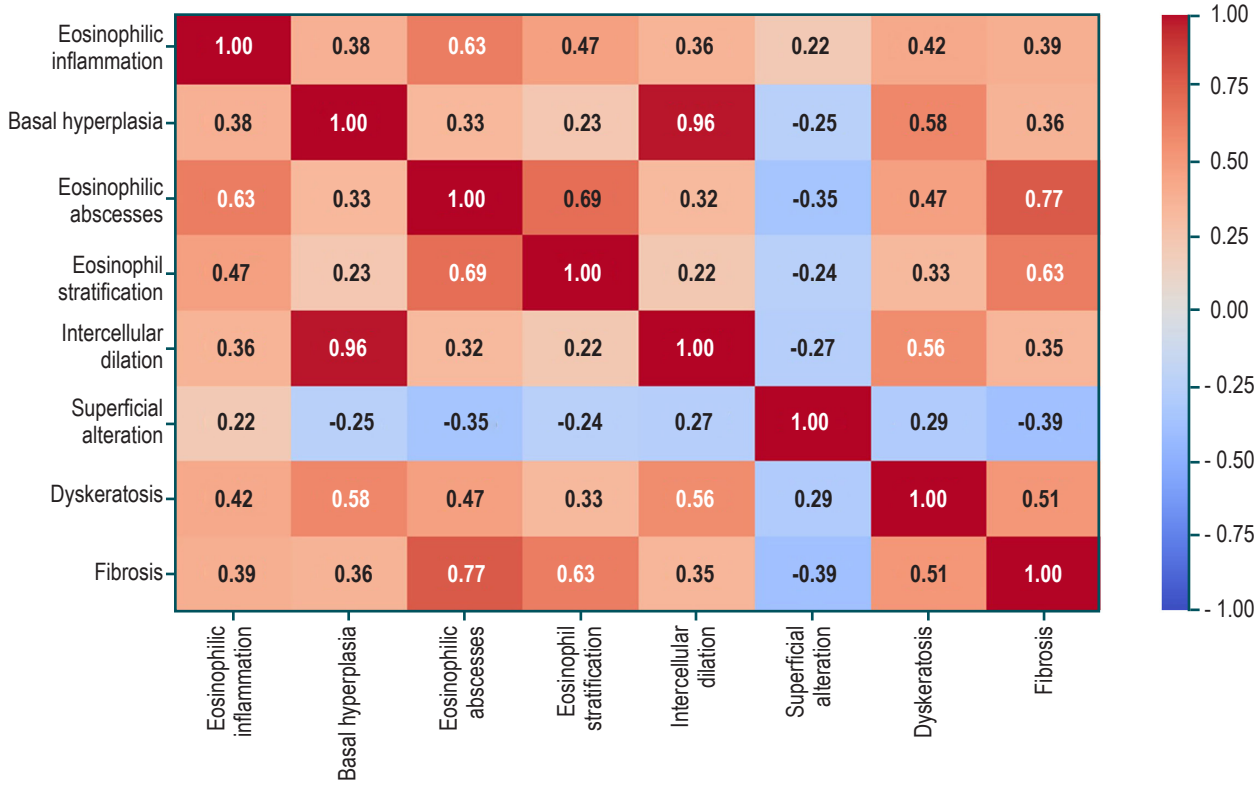


Figure 4. Heat map illustrating Spearman correlation (r; *p-value*) between histological score and peak eosinophil count. Author's file.

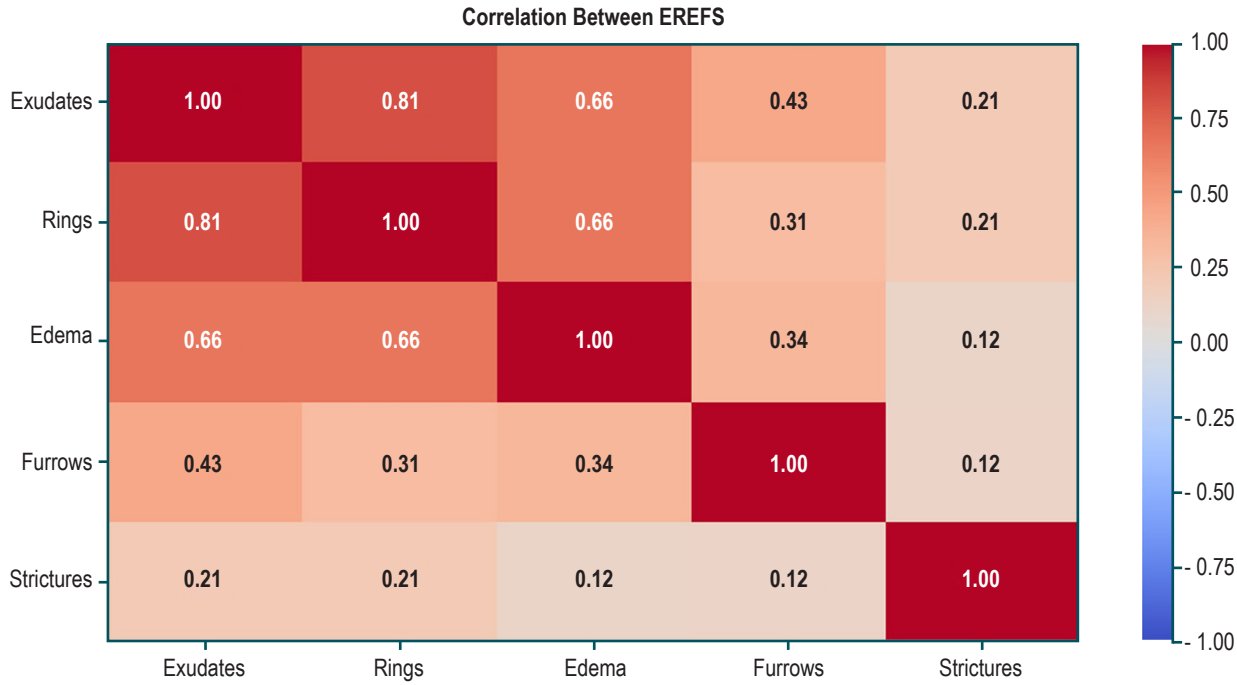


Figure 5. Heat map illustrating Spearman correlation (r; *p-value*) between endoscopic score and peak eosinophil count. Author's file.

Table 4. Diagnostic Metrics (AUC, Sensitivity, Specificity) of the Systems and Combined Model

Variable	Sensitivity (95% CI)	Specificity (95% CI)	Accuracy (95% CI)	AUC	*p*-Value
Eosinophilic inflammation	0.959 (0.898-0.984)	0.956 (0.893-0.982)	0.957 (0.896-0.983)	0.957	**<0.001**
Combined model	0.837 (0.739-0.962)	0.956 (0.792-1.0)	0.929 (0.833-1.0)	0.932	**<0.001**
EoEHSS	0.918 (0.845-0.959)	0.778 (0.684-0.850)	0.851 (0.765-0.909)	0.902	**<0.001**
Furrows	0.939 (0.871-0.972)	0.578 (0.477-0.673)	0.766 (0.671-0.840)	0.758	**<0.001**
Eosinophilic abscesses	0.571 (0.471-0.667)	0.933 (0.864-0.969)	0.745 (0.648-0.822)	0.752	**<0.001**
Eosinophil stratification	0.347 (0.258-0.447)	0.978 (0.924-0.994)	0.649 (0.548-0.738)	0.662	**<0.001**
Dyskeratosis	0.837 (0.749-0.898)	0.467 (0.369-0.567)	0.660 (0.559-0.747)	0.652	**0.003**
Fibrosis	0.510 (0.411-0.609)	0.778 (0.684-0.850)	0.638 (0.538-0.728)	0.644	**0.007**
Superficial alteration	0.327 (0.240-0.427)	0.933 (0.864-0.969)	0.617 (0.516-0.709)	0.630	**0.004**
EREFS	0.694 (0.595-0.778)	0.422 (0.327-0.523)	0.564 (0.463-0.660)	0.624	0.339
Basal hyperplasia	0.918 (0.845-0.959)	0.289 (0.207-0.387)	0.617 (0.516-0.709)	0.604	**0.019**
Intercellular dilation	0.918 (0.845-0.959)	0.267 (0.188-0.364)	0.606 (0.505-0.699)	0.593	**0.035**
Rings	0.500 (0.401-0.599)	0.276 (0.196-0.374)	0.373 (0.282-0.473)	0.589	0.178
Exudates	0.690 (0.590-0.774)	0.414 (0.320-0.515)	0.552 (0.451-0.648)	0.546	0.585
Strictures	0.041 (0.016-0.102)	0.978 (0.924-0.994)	0.489 (0.391-0.589)	0.509	1.000
Edema	0.714 (0.616-0.796)	0.289 (0.207-0.387)	0.511 (0.411-0.609)	0.502	1.000

Eos: eosinophils; CI: confidence interval. Author's own research.

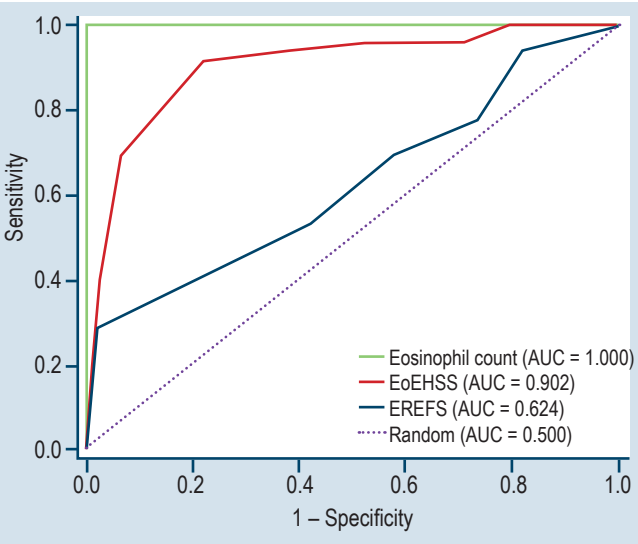


Figure 6. ROC curves for the endoscopic and histological references PEC, EoEHSS, and EREFS. Author's file.

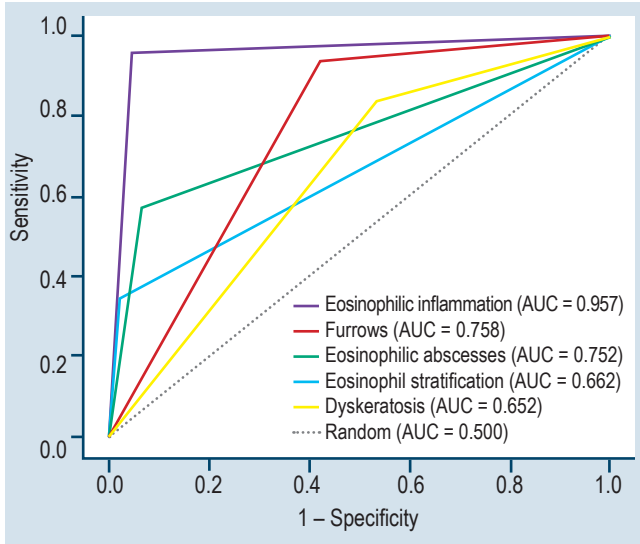


Figure 7. ROC curves for the most relevant individual histological and endoscopic components.

logy. This association was more pronounced in active EoE than in the inactive form. This discrepancy contrasts with reports in the literature describing stronger associations, mainly in pediatric populations[20], whereas in studies involving adults the relationship has also been modest[21], which may be influenced by this cohort being more inflammatory than fibrostenotic.

The demographic characteristics of the cohort (69% male, 53% with atopy) are consistent with the current epidemiology of adult EoE[22]. Twenty-five percent presented with an endoscopically normal esophagus, in agreement with series reporting between 20% and 30% normal endoscopies despite confirmed eosinophilia[23]. The predominant endoscopic phenotypes were inflammatory (furrows 78%, exudates) and, to a lesser extent, fibrostenotic (rings 81%, strictures 3%), which aligns with the current phenotypic classification[24]. Furrows showed the most robust correlation with PEC, replicating findings from Asian and Western cohorts[5,10].

The main innovation of this study was the precise characterization of the relationship between endoscopic and histological scores in EoE. Twenty-five percent of patients had an endoscopically normal esophagus despite detectable histological abnormalities, demonstrating that EoEHSS is more sensitive than PEC for identifying subtle mucosal changes and suggesting a discrepancy between microscopic inflammation and visible endoscopic findings. Furrows correlated significantly with basal hyperplasia and papillary elongation, whereas edema and exudates showed weak correlations. These associations were more pronounced in the active inflammatory phenotype (active EoE), supporting the concept that endoscopic findings mainly reflect advanced inflammation rather than mild submucosal processes. Consistent with recent literature, the correlation between endoscopy and histology in EoE is only moderate[25].

Currently, there are no universally accepted threshold values for endoscopic (EREFS) or histological (EoEHSS) scores that accurately predict EoE activity status. This lack of standardization limits their routine application in clinical practice and underscores the need for thresholds adapted to endoscopic phenotype and degree of tissue remodeling. In recent studies, an EREFS ≥2 demonstrated 79% sensitivity and 86% specificity for the diagnosis of active EoE (AUC = 0.73) in Korean adults[10]. Similarly, another study reported that an EREFS ≤2 was associated with histological remission following treatment, with 80% sensitivity and 83% specificity (AUC = 0.88)[26]. In contrast, histological scores derived from EoEHSS have shown better overall discriminative capacity (AUC ≈ 0.90) and a closer correlation with inflammatory activity[13].

Furthermore, a recent review highlights that the systematic integration of endoscopic and histological assessments is essential for stratifying EoE activity, since each modality captures distinct disease domains and their combination significantly reduces the risk of underdiagnosis[27]. These findings support the concept that isolated assessment using

either EREFS or PEC is insufficient, and that a combined endoscopic-histological approach constitutes a superior strategy for estimating disease activity and predicting therapeutic response.

This study has several limitations. Its retrospective design based on electronic medical record review makes misclassification bias plausible. We predominantly included patients with the inflammatory EoE phenotype; therefore, our findings may not be generalizable to adult patients with a fibrostenotic phenotype. Due to the lack of a biopsy protocol, it was not possible to determine how specific endoscopic changes could affect histological metrics. Only the degree of abnormality (grade score) was used to evaluate relationships; therefore, the extent of pathology (stage score) was not analyzed. Nevertheless, recent studies have demonstrated that grade and stage exhibit a very high correlation (r >0.90) and respond similarly to treatment, validating the use of grade as the primary metric in the histopathological evaluation of EoE[21]. Endoscopic evaluations were performed by different endoscopists and histological assessments by multiple pathologists (multicenter design), without centralized review by an expert pathologist; this increases interobserver variability and limits the applicability of the findings to routine adult and pediatric endoscopy practice.

Despite the above, this study also has several strengths. We included consecutive patients with EoE undergoing endoscopy, thereby minimizing selection bias. All EREFS scores were recorded at the time of endoscopy (EGD), eliminating recall bias or subsequent reassessment based on archived photographs. The sample size was sufficient to detect a 10% Spearman correlation with $\alpha = 0.05$ and a power of 0.80. PEC and EoEHSS scoring were performed simultaneously on biopsy samples, without relying on historical readings or previous reports of correlations between endoscopy and histology.

The main findings of the study are as follows:

- The EoEHSS histological score and PEC are strong markers highly correlated with inflammatory activity in adult EoE, maintaining statistical significance after correction for multiple comparisons ($r = 0.70$; $p < 0.001$).
- The EREFS endoscopic score shows a weak and nonsignificant correlation with histological activity ($r = 0.21$; $p = 0.11$ after Bonferroni correction); therefore, it should not be used as an isolated substitute for histological analysis when assessing active tissue inflammation.
- An integrated predictive model combining eosinophilic inflammation, endoscopic furrows, eosinophilic abscesses, epithelial stratification, and dyskeratosis achieved an AUC of 0.93, with 83% sensitivity and 95% specificity, substantially outperforming EREFS (AUC: 0.62) and EoEHSS (AUC: 0.90) individually.
- Multimodal evaluation (endoscopic plus selective histological assessment) is essential for accurate stratification of EoE activity and should guide therapeutic and follow-up decisions in clinical practice.
- These findings validate a more efficient diagnostic and prognostic approach in adults with EoE, laying the foundation for prospective studies incorporating this combined panel as a composite endpoint in clinical trials and longitudinal management.

CONCLUSIONS

In adults with EoE, isolated endoscopic assessment (EREFS) does not replace histological analysis: its correlation with inflammatory activity is weak and loses significance after statistical adjustments. In contrast, the EoEHSS histological score and peak eosinophil count are strongly correlated with active tissue inflammation. An integrated panel of five markers (eosinophilic inflammation, furrows, eosinophilic abscesses, epithelial stratification, and dyskeratosis) predicts active EoE with an AUC of 0.93, 83% sensitivity, and 95% specificity, outperforming any individual system. This multimodal model redefines EoE assessment, offering a precise, reproducible, and clinically actionable tool to guide treatment and follow-up in daily practice.

Conflict of Interest

The authors declare that they have no conflicts of interest relevant to the content of this article.

Statement on the Use of Artificial Intelligence

The authors declare that artificial intelligence tools were used in a limited manner, exclusively for paraphrasing and linguistic revision of the text. Under no circumstances were they used for data analysis, interpretation, or the formulation of scientific conclusions. The authors assume full responsibility for the content, integrity, and originality of the manuscript.

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Evidence-Based Colombian Consensus for the Management of Intestinal Failure Secondary to Short Bowel Syndrome in Pediatrics

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INTRODUCTION

Short bowel syndrome (SBS) is an anatomical condition characterized by a significant reduction in the length of the small intestine, generally secondary to extensive intestinal resections due to necrotizing enterocolitis, congenital malformations, or ischemic events[1]. When this loss of intestinal surface area results in the inability of the gastrointestinal tract to maintain adequate nutritional and hydration status without prolonged intravenous support, intestinal

Abstract

Introduction: Intestinal failure secondary to short bowel syndrome in pediatric patients leads to malabsorption, metabolic disturbances, and frequent reliance on parenteral nutrition. Clinical variability and therapeutic management require the implementation of a local clinical practice guideline. **Objective:** To provide evidence-based recommendations, with emphasis on early evaluation, appropriate therapeutic selection, and long-term follow-up. **Methods:** A multidisciplinary group of 25 experts formulated 12 questions. Through independent systematic literature review and analysis, recommendations were developed using a modified Delphi methodology to achieve consensus. **Results:** A total of 1,124 references were screened. Thirty-eight were included in the evidence synthesis (20 systematic reviews, 10 guidelines, and 8 primary studies). The expert panel issued 88 recommendations. Management strategies were identified regarding the use of proton pump inhibitors, prokinetics, antibiotics, and the implementation of individualized nutrition. The use of teduglutide is recommended in patients with prolonged dependence on parenteral nutrition, along with the need for multidisciplinary evaluation and follow-up for complication management. **Conclusions:** The management of intestinal failure secondary to short bowel syndrome is complex and requires a multidisciplinary intestinal rehabilitation team. Evaluation strategies, pharmacological and surgical treatment, nutritional support, and complication management should be individualized. This consensus provides evidence-based recommendations and standardized practices to improve clinical outcomes.

Keywords

Intestinal failure; short bowel syndrome; parenteral nutrition; enteral nutrition; teduglutide.

failure develops, a functional condition that in this context is referred to as intestinal failure secondary to short bowel syndrome (IF-SBS)[1,2].

Pediatric IF-SBS represents a major clinical challenge because of its impact on both quality of life and patient prognosis. Its consequences include nutrient malabsorption, electrolyte disturbances, metabolic imbalances, and malnutrition[1].

The management of these patients is particularly complex and requires a multidisciplinary approach integrating specialized nutritional support, pharmacological management, surgical interventions, and close follow-up to prevent complications such as catheter-related infections, metabolic disturbances, and intestinal failure-associated liver disease[3].

Despite advances in pathophysiological knowledge and therapeutic strategies, the available evidence remains limited and heterogeneous, resulting in considerable variability in clinical practice and in the approach to key aspects of the diagnosis, treatment, and follow-up of these patients. In this context, integrating the best available evidence with expert clinical experience is essential to guide decision-making. Therefore, the present evidence-based consensus for the management of intestinal failure secondary to short bowel syndrome in pediatrics was developed, the objective of which is described below.

Objective and Scope of the Consensus

The objective of this consensus is to provide evidence-based recommendations for the optimal management of IF-SBS in pediatric patients, addressing early identification, comprehensive evaluation, appropriate selection of therapeutic options, and long-term follow-up.

Target Population and Scope of Application

This consensus is intended for pediatricians, neonatologists, pediatric gastroenterologists, pediatric surgeons, nurses, nutritionists, and other healthcare professionals involved in the care and management of patients with IF-SBS in hospitals and pediatric and neonatal intensive care units.

Excluded Aspects

This consensus does not address the management of causes of intestinal failure unrelated to SBS.

Context and Limitations

This consensus was developed based on the evidence available up to the date of its preparation. The management of IF-SBS may vary according to local conditions and patient-specific factors, and adaptation of the recommendations to individual circumstances is encouraged.

Review Date and Validity

The need to review and update the consensus five years after its publication is established.

IF-SBS in Pediatrics

SBS is a malabsorptive state resulting from surgical resection or congenital disease affecting a significant portion of the small intestine[1,2]. It is characterized by a residual intestinal length of less than 25% of the expected length

for age[1,2]. SBS is the leading cause of intestinal failure in children and the underlying condition in 50% of patients receiving home parenteral nutrition (PN)[2,3].

The severity of SBS has been classified according to residual intestinal length, measured from the ligament of Treitz. Ultrashort bowel syndrome (USBS) is defined as an intestinal length of less than 10 cm or less than 10% of the expected length for age. Another classification anatomically categorizes SBS into three forms according to the surgical reconstruction performed after intestinal resection: patients with terminal jejunostomy (J-SBS or type I); those with jejunocolic anastomosis (JC-SBS or type II); and patients with jejunoileal anastomosis preserving both the colon and the ileocecal valve (JIC-SBS or type III). This categorization is not limited to an anatomical description, but also has important clinical and prognostic implications, as the type of intestinal configuration determines absorptive capacity, the degree of dependence on parenteral nutrition, and the likelihood of achieving intestinal autonomy over the course of the disease[1,4].

Intestinal failure is defined as a reduction in intestinal function below the minimum necessary for the absorption of macronutrients, water, and electrolytes, requiring intravenous supplementation to maintain health or growth. It is associated with the need for PN for more than 60 days after loss of intestinal function or surgical resection[2,5,6]. Intestinal adaptation is the process by which the remaining gastrointestinal tract adjusts to meet the patient's physiological needs[1,6].

Data regarding the prevalence and incidence of pediatric IF-SBS vary depending on the population and geographic setting. The estimated incidence in neonates is 24.5 per 100,000 live births[7–9]. Its disease burden is substantial and negatively affects the quality of life of both patients and caregivers. Treatments are associated with high costs for both patients and healthcare systems[8,9].

The treatment of IF-SBS focuses on promoting intestinal adaptation through the use of enteral nutrition (EN) and PN. PN should be initiated early within a multidisciplinary approach. EN, including breast milk and specialized formulas, is essential to stimulate intestinal growth and reduce dependence on PN. Pharmacological treatment includes proton pump inhibitors (PPIs), antibiotics for small intestinal bacterial overgrowth, and gastrointestinal hormones such as glucagon-like peptide-2 (GLP-2) analogs to induce intestinal adaptation. Surgical management focuses on preserving the greatest possible amount of functional intestine, restoring intestinal continuity, and, in some cases, intestinal transplantation in patients with severe complications[6,10–13].

Intestinal Failure-Associated Liver Disease

Intestinal failure-associated liver disease (IFALD) is a hepatic disorder resulting from factors intrinsic to IF-SBS and its medical-surgical management, which may progress to end-stage liver failure. Up to 50% of children with IF-SBS may develop IFALD, with a higher prevalence in neonates. Risk factors such as prematurity, prolonged PN, intestinal surgery, and comorbidities including infections and intestinal dysmotility increase the likelihood of its development. Signs and symptoms include cholestatic jaundice, steatosis, hepatomegaly, and growth retardation. Diagnosis is based on biochemical analyses and exclusion of other causes of liver disease. Prevention is essential, and cycling PN, optimizing EN, and implementing pharmacological strategies are recommended. In severe cases, liver transplantation may be required[14–17].

METHODOLOGY

Clinical Questions

The development group, composed of pediatric gastroenterologists and epidemiologists, formulated 12 clinical questions that guided the evidence search used to develop the recommendations discussed by the expert panel. These questions addressed key aspects of the diagnosis, treatment, and follow-up of IF-SBS. The clinical questions were formulated using the PICO structure (population, intervention, comparator, and outcomes).

Evidence Search and Synthesis

A systematic literature search was conducted in electronic databases (Medline, Embase, Lilacs, Cochrane Library, Google Scholar, and Epistemonikos), as well as repositories of organizations involved in the development and compilation of consensus statements and clinical practice guidelines (CPGs). Search strategies were developed from the clinical questions formulated in PICO format, combining controlled vocabulary (MeSH and Emtree terms) and free-text language through the use of Boolean operators (AND, OR), truncation symbols, and proximity operators. Clinical practice guidelines, systematic literature reviews (SLRs), meta-analyses, and network meta-analyses published within the last five years in English and Spanish were included. The methodological quality of the included evidence sources was assessed using validated tools according to the type of document. CPGs were evaluated using the Appraisal of Guidelines for Research and Evaluation (AGREE II) instrument[18], and SLRs were assessed using the Risk of Bias in Systematic Reviews (ROBIS) tool[19]. The process is summarized in the flow diagram presented in **Figure 1**. Evidence synthesis was performed narratively, highlighting the main quantitative findings supporting each recommendation, which are presented in the supplementary material.

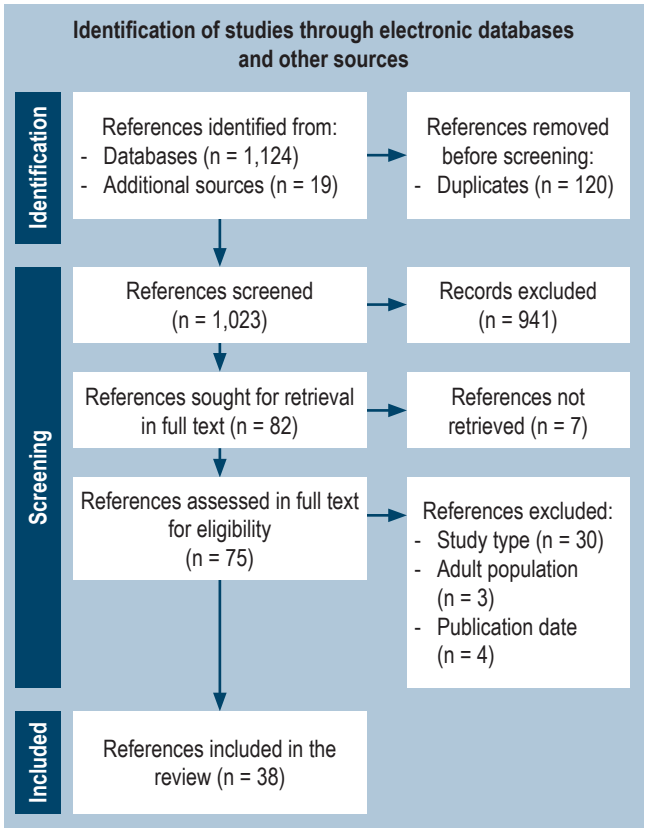


Figure 1. PRISMA flow diagram of the study search and selection process. Author's file. Adapted from: Page MJ and colleagues. BMJ. 2021;372:n71[20].

Composition of the Expert Panel

The preliminary recommendations derived from the evidence synthesis were discussed and subjected to a consensus process using a modified Delphi methodology[21]. The expert panel was composed of specialists with recognized clinical and academic expertise in the management of pediatric intestinal failure from different regions of the country (Barranquilla, Medellín, Cali, and Bogotá), with the aim of ensuring diversity of clinical perspectives and representativeness in the development of the consensus. A panel of 25 experts was convened, including pediatric gastroenterologists, pediatric surgeons, radiologists, nutritionists, and epidemiologists. A first round of anonymous voting was conducted through electronic forms with the following response options: "agree," "agree with modifications," or "disagree." Recommendations that did not reach the 75% agreement threshold were revised according to the modifications proposed by the experts and submitted to a second round of voting. In this second round, the response options were "agree" or "disagree," and the strength of the recommendation was classified according to the percentage of agreement achieved using a quartile-based scale, as shown in **Table 1**.

Table 1. Levels of Consensus

Percentage of Agreement Achieved	Interpretation
75-100	Strong consensus
50-74	Moderate consensus
25-49	Low level of consensus
Less than 25	Lack of consensus

Author's own research.

RESULTS

Search, Reference Screening, and Study Selection

A total of 1,124 records were identified through electronic databases, and 19 additional records were identified through manual searches and other sources. After duplicate removal, the titles and abstracts of the identified studies were screened. Subsequently, potentially relevant articles were reviewed in full text to determine eligibility. Finally, 38 studies that met the inclusion criteria were included and used for the evidence synthesis. The complete selection process is presented in **Figure 1** using a PRISMA flow diagram[22–60].

Risk of Bias Assessment of the Studies

Assessment of the quality of various CPGs using the AGREE II instrument[18] revealed variability. The risk of bias analysis is presented in the supplementary material.

Clinical Questions and Consensus Recommendations

Two rounds of voting were conducted. Overall, 76% (n = 77) achieved strong consensus, with more than 75% agreement. In the second round, 17 recommendations were voted on, and consensus was achieved for all of them. Differences in the denominator across recommendations are explained by minor variations in expert participation during the voting rounds. To ensure methodological accuracy, agreement percentages were always calculated based on the total number of valid responses received for each recommendation.

The recommendations derived from the consensus are presented below.

QUESTION 1. WHAT IS THE MOST EFFECTIVE AND SAFE PHARMACOLOGICAL MANAGEMENT FOR INTESTINAL FAILURE IN PEDIATRIC PATIENTS REGARDING THE USE OF PPIS, PROKINETICS, BILE ACID SEQUESTRANTS, PROBIOTICS, ANTIBIOTICS, AND ANTIDIARRHEAL AGENTS?

R-1: Use of Proton Pump Inhibitors

The use of PPIs, preferably esomeprazole, is recommended to reduce gastric acid secretion in patients with IF-SBS (**Table 2**)[25,26,29].

Strong consensus (final agreement 100% [21/21]), moderate quality of evidence

Table 2. Doses of Proton Pump Inhibitors

Name	Route of Administration	Dose
Esomeprazole[a]	Oral or intravenous	1–2 mg/kg/day, administered every 12 or 24 hours (maximum: 40 mg/day)
Omeprazole[b]	Oral or intravenous	1–4 mg/kg/day, administered every 12 or 24 hours (maximum: 80 mg/day)

a. Preferred option according to availability.
b. Second-line option. It may be used as a compounded formulation if necessary. Author's own research.

Good Clinical Practice Points

The use of PPIs is important during the first three months after surgical resection, with a recommended duration of up to six months, at which point the need for continuation should be reassessed. Patients should be monitored for adverse effects such as recurrent gastrointestinal infections and vitamin B12 and magnesium deficiency.

R-2: Use of Domperidone

The individualized use of domperidone is recommended because of its prokinetic effect. The recommended dose is 0.2–0.4 mg/kg/dose, administered orally every 6–8 hours, with a maximum dose of 30 mg/day. Dose adjustment according to individual needs is essential[26,29].

Strong consensus (final agreement 100% [21/21]), moderate quality of evidence.

R-3: Use of Erythromycin

The individualized use of erythromycin is recommended. As a prokinetic agent, erythromycin is administered at doses of 3–5 mg/kg/dose every six hours. It is used in gastroparesis to improve gastric emptying. Prolonged use may lead to tachyphylaxis. Its use should be avoided in neonates because of the risk of hypertrophic pyloric stenosis[26,29].

Strong consensus (final agreement 100% [21/21]), moderate quality of evidence.

R-4: Use of Ondansetron

The individualized use of ondansetron is recommended. The standard dose is 0.15 mg/kg/dose, administered orally or intravenously every 8–12 hours, with a maximum dose of 16 mg/day. Indication: control of nausea and vomiting in conditions such as SBS[26,29].

Strong consensus (final agreement 100% [21/21]), moderate quality of evidence.

Good Clinical Practice Point

These prokinetic agents may prolong the QT interval. It is recommended to perform an electrocardiogram before and after treatment initiation in at-risk patients and to review potential drug interactions. Their use warrants careful assessment of risks and benefits, avoiding routine administration.

R-5: Use of Cyproheptadine

The individualized use of cyproheptadine is recommended. It is administered at a dose of 0.25 mg/kg/day, divided into 2–3 doses. It is used to stimulate appetite in pediatric patients, particularly those with malnutrition or increased caloric requirements. Precautions: although generally well tolerated, it may cause drowsiness and weight gain[29].

Strong consensus (final agreement 100% [21/21]), moderate quality of evidence.

R-6: Use of Ursodeoxycholic Acid

The use of ursodeoxycholic acid (UDCA) is recommended in pediatric patients with IF-SBS and IFALD. Evidence suggests that UDCA contributes to reducing serum bilirubin levels and improving liver function parameters, which may mitigate progression to advanced liver disease and improve long-term quality of life. Potential drug interactions with other medications, including prokinetics, aluminum-containing compounds, statins, and antibiotics, should be considered[29,32]. Dose: 20–30 mg/kg/day, administered orally and divided into two to three daily doses.

UDCA is generally well tolerated, although potential adverse effects include diarrhea, abdominal pain, and, in exceptional cases, gallbladder calcification. Continuous monitoring of liver function and bilirubin levels is essen-

tial in order to adjust the dose and minimize associated risks[29,32].

Strong consensus (final agreement 100% [21/21]), high quality of evidence.

R-7: Avoidance of Probiotic Administration

The use of probiotics is contraindicated in patients with central venous access, immunosuppression, or critical illness because of the risk of severe complications such as bacteremia or fungemia. In patients with IF-SBS without central venous access, evidence regarding probiotic administration is insufficient and inconclusive; therefore, their use is not recommended[25,27].

Strong consensus (final agreement 85.7% [18/21]), moderate quality of evidence.

R-8: Use of Antibiotics

The use of systemic antibiotics in combination with local antibiotic therapies, such as antibiotic lock therapy, is recommended in pediatric patients with catheter-related infections (CRIs). Antibiotic selection should be guided by antimicrobial susceptibility testing to ensure effectiveness against the specific pathogens involved[26,29].

Strong consensus (final agreement 100% [21/21]), high quality of evidence.

Good Clinical Practice Point

Initial antibiotic management should include coverage for gram-positive and gram-negative organisms, based on local epidemiology and antibiotic availability. Appropriate empiric treatment should be initiated while awaiting antimicrobial susceptibility results in order to adjust therapy accordingly.

R-9: Use of Loperamide and Cholestyramine

The use of loperamide or cholestyramine is recommended for the management of IF-SBS in pediatric patients with high fecal output (greater than 40–50 mL/kg/day). Selection should be based on a comprehensive evaluation, considering both efficacy in reducing fecal output and the safety profile of each medication[27,29].

- Loperamide:
  - Dose: 0.4–0.8 mg/kg/day, administered orally every six hours (maximum dose: 16 mg/day).
- Cholestyramine:
  - Its use is recommended in patients with preserved colon and intestinal continuity when increased fecal output due to bile acid malabsorption or choleretic diarrhea is suspected. It should ideally be administered one hour before other medications or food intake[27,29].
  - Dose: 240 mg/kg/day administered orally every 8 or 12 hours.

Strong consensus (final agreement 100% [21/21]), moderate quality of evidence.

QUESTION 2. WHAT ARE THE EFFECTIVENESS AND SAFETY OF ENTEROHORMONES IN PEDIATRIC PATIENTS WITH INTESTINAL FAILURE SECONDARY TO SHORT BOWEL SYNDROME?

R-10: Use of Teduglutide

Teduglutide is a glucagon-like peptide-2 (GLP-2) analog. This hormone promotes epithelial proliferation through crypt cell growth and inhibits enterocyte apoptosis in the small intestine. Teduglutide is currently indicated for pediatric patients aged one year and older with IF-SBS who are dependent on PN or intravenous fluid support. It is not considered a first-line treatment for patients with IF-SBS. Its use should only be considered when the patient has received optimal treatment at a specialized center and, despite this, remains dependent on PN without achieving intestinal adaptation. The recommended dose is 0.05 mg/kg once daily, administered subcutaneously under the supervision of a specialized intestinal failure team (**Table 3**)[22,25–28,33,34,53].

Mild adverse effects include abdominal pain, nausea, distension, and vomiting. Cases of cholecystitis, pancreatitis, and intestinal obstruction at anastomoses or stoma sites have been reported. Elevation of aminotransferases, as well as increased lipase, phosphorus, and blood urea nitrogen levels, has been observed in approximately 5% of treated patients[22,25–28,33,34,53].

Strong consensus (final agreement 100% [21/21]), moderate quality of evidence.

R-11: Monitoring and Duration of Teduglutide Treatment

During the first four weeks, weekly assessment of weight, height, heart rate, blood pressure, volume of orally ingested fluids, urinary output, and fecal output is recommended. Serum electrolytes, blood glucose, renal function, and liver transaminases should be monitored every two weeks during the initial phase of treatment and subsequently on a monthly basis. Before treatment initiation, endoscopic studies (esophagogastroduodenoscopy and colonoscopy) should be performed to rule out polyps. Endoscopic follow-up with colonoscopy is recommended one year after initiation of teduglutide treatment and subsequently

every three to five years, or earlier if clinically indicated. Appropriate patient selection and follow-up are essential to maximize benefits and mitigate risks.

Treatment duration: a responder is defined as a patient who achieves a 20% reduction in PN requirements. Most patients respond during the first year of treatment; however, some are considered late responders, in whom the multidisciplinary team should evaluate the appropriateness of continuing or discontinuing treatment. Patients who respond to teduglutide treatment should continue therapy even after achieving intestinal adaptation, as no discontinuation protocol currently exists[22,25–28,33,34,53].

Strong consensus (final agreement 100% [21/21]), moderate quality of evidence.

Table 3. Considerations for the Use of Teduglutide

Candidates for Treatment
The patient must meet ALL of the following criteria:
- Patients aged one year and older with SBS.
- Requirement for PN for more than six months.
- Stable parenteral/enteral nutrition without the possibility of reduction >10% during the previous three months.
- PN providing >20% of caloric or fluid/electrolyte requirements.
- Patient without additional medical-surgical treatment options to improve intestinal adaptation.
- Interval >3 months since the last surgical intervention.
- History of complications associated with IF-SBS: hydroelectrolytic imbalance, liver disease, catheter-related infections, or thromboembolic events.
Patients Without Indication for Teduglutide
- Intestinal failure due to an etiology other than SBS.
- Patients showing satisfactory progression with conventional intestinal rehabilitation treatment.
- Patients who have received growth hormone (somatropin) within the previous six months.
- Patients who do not require PN.
- Patients with a history of gastrointestinal neoplasia within the previous five years.
Contraindications
- Allergic reactions to the active substance or excipients.
- Hypersensitivity to tetracyclines.
- Suspected or confirmed active malignant neoplasia.

Author's own research.

QUESTION 3. WHAT ARE THE APPROPRIATE PARENTERAL NUTRITION STRATEGIES IN A PATIENT WITH IF-SBS?

R-12: Fluid Intake

Individualization of PN fluid volume according to the patient's age, weight, clinical status, and insensible losses is recommended, using the Holliday-Segar formula as the basis. Monitoring fluid balance and adjusting doses are essential to avoid complications such as fluid overload or dehydration[23,27,29,30].

Strong consensus (final agreement 100% [22/22]), moderate quality of evidence.

R-13: Macronutrient Requirements

A protein intake according to patient age of 1.5–3.5 g/kg/day is recommended to ensure a positive nitrogen balance. Carbohydrates are recommended to account for 50%–60% of total caloric intake and fats for 30%–40%, preferably using mixed lipid emulsions to minimize the risk of IFALD[23,27,29,30].

Strong consensus (final agreement 100% [22/22]), moderate quality of evidence.

R-14: Micronutrient Requirements

Appropriate supplementation and monitoring of vitamins and minerals are essential and should be adjusted periodically according to laboratory results to prevent deficiencies that may negatively affect growth and development[6,15,23,30].

Strong consensus (final agreement 100% [22/22]), moderate quality of evidence.

R-15: Lipid Intake

Administration of lipid emulsions composed of a mixture of oils (soybean, coconut, olive, and fish oils) is recommended to reduce the risk of hepatic complications in pediatric patients requiring PN. The suggested dose ranges from 1 to 4 g/kg/day, adjusted according to the patient's age, tolerance, and clinical status.

Specific approach: priority should be given to lipid emulsions enriched with omega-3 fatty acids (eicosapentaenoic acid [EPA] and docosahexaenoic acid [DHA]) because of their anti-inflammatory properties and lower negative impact on liver function compared with emulsions based exclusively on soybean oil. However, the exclusive use of omega-3 emulsions should be temporary and reserved for situations of established liver injury because of the risk of

inducing essential fatty acid deficiency. Systematic monitoring of liver function parameters and lipid profile is imperative, as it allows adjustment of PN therapy and prevention of complications such as IFALD[23,27,29,30].

Strong consensus (final agreement 95.2% [20/21]), moderate quality of evidence.

R-16: Electrolyte Balance

Regular monitoring of serum sodium, potassium, calcium, magnesium, and phosphate levels is recommended, with adjustment of PN solutions to maintain optimal balance and prevent severe complications. Gastrointestinal losses should be considered when adjusting sodium and other electrolyte requirements[23,27,29,30].

Strong consensus (final agreement 100% [22/22]), moderate quality of evidence.

R-17: Parenteral Nutrition in the Acute Phase

It is recommended that parenteral nutrition be managed according to phases as outlined in the European Society for Paediatric Gastroenterology, Hepatology and Nutrition guidelines (ESPGHAN 2023): during the early acute phase (0–48 hours), the focus is on restoring normal physiological status through fluid and electrolyte management, including glucose administration (3.5–7 mg/kg/min) to prevent catabolism[23,25,26,29,38].

Strong consensus (final agreement 100% [22/22]), high quality of evidence.

R-18: Parenteral Nutrition in the Subacute Phase

During the intermediate postoperative phase (48 hours–7 days), priority is given to meeting basic metabolic requirements with PN when EN is not feasible, ensuring protein intake (1.3–01.5 g/kg/day) and balanced lipid emulsions, preferably including fish oil during prolonged periods or in the presence of cholestasis. In the subacute phase (from day 7 onward), optimization of nutritional support with a focus on gradual transition to EN is recommended in order to reduce dependence on PN and stimulate intestinal function. Monitoring nutritional parameters (albumin, prealbumin, fat- and water-soluble vitamins, urinary sodium >20 mmol/L) at intervals adapted to patient stability (weekly, biweekly, or monthly) is essential, and the strategy should be adjusted to prevent complications such as cholestasis. Appropriate implementation of PN improves long-term clinical outcomes[23,25,26,29,38].

Strong consensus (final agreement 85.7% [18/21]), high quality of evidence.

R-19: Parenteral Nutrition in the Chronic Phase

During the chronic phase (>30 days), continuous optimization of PN is recommended, adjusting its composition according to biochemical parameters and always under the supervision of a nutritional support team; gradually reducing dependence on PN while promoting intestinal absorption and the progressive introduction of EN[23,25,26,29,38].

Strong consensus (final agreement 100% [22/22]), high quality of evidence.

Good Clinical Practice Point

Cycling of PN should be considered in clinically and metabolically stable patients who have achieved their nutritional goals and who receive some proportion of EN or oral intake.

QUESTION 4. WHAT ARE THE STRATEGIES FOR FLUID AND ELECTROLYTE MANAGEMENT AND MONITORING IN A PATIENT WITH SBS?

R-20: Quantification of Losses

Daily monitoring and quantification of fecal losses, stool consistency, and urine output are recommended. In patients with ostomies, detailed measurement of output volume and consistency should be performed. Fecal losses should be maintained below 50 mL/kg/day to prevent dehydration and electrolyte imbalances[23,26,29,30].

Strong consensus (final agreement 100% [22/22]), moderate quality of evidence.

R-21: Intravenous Replacement

Initiation of intravenous fluid and electrolyte replacement is recommended during the initial phases of treatment or during acute decompensations. Prolonged PN should be adjusted according to the patient's specific needs in order to maintain hydroelectrolytic and nutritional balance. Serum electrolyte levels should also be monitored regularly, initially every two weeks and subsequently monthly according to patient stability[23,26,29,30].

Sodium should be administered to maintain urinary sodium levels between 20 and 60 mmol/L and to ensure a urinary sodium-to-potassium ratio of at least 2:1[23,26,29,30].

Strong consensus (final agreement 100% [22/22]), moderate quality of evidence.

R-22: Monitoring of Clinical Parameters and Adjustments

Weekly body weight measurements are recommended during the first month, every two weeks during the second

month, and subsequently monthly or at alternate intervals depending on clinical evolution. Signs of fluid overload and variations in fecal or ostomy output should be monitored weekly during the first months and then monthly thereafter[23,26,29,30].

Strong consensus (final agreement 100% [22/22]), moderate quality of evidence.

QUESTION 5. WHAT ARE THE APPROPRIATE FEEDING AND ENTERAL NUTRITION STRATEGIES IN PATIENTS WITH INTESTINAL FAILURE?

R-23: Timing of Enteral Nutrition Initiation

Enteral feeding should be initiated as soon as the patient's condition permits, generally once postoperative ileus has resolved and bowel sounds and stool passage are present. This approach takes advantage of the benefits of oral feeding, which is more physiological and promotes intestinal adaptation[36,37,40,41].

Strong consensus (final agreement 77.3% [17/22]), high quality of evidence.

R-24: Use of Breast Milk

Breast milk should be the first option for EN in infants with intestinal failure. It contains immunological and growth factors that support intestinal adaptation and strengthen the immune system.

Dose: initiate with volumes of 10–20 mL/kg/day, administered as assisted feeding or continuous infusion, with progressive increases according to tolerance in order to maintain fecal losses below 50 mL/kg/day[36,37,40,41].

Strong consensus (final agreement 86.4% [19/22]), high quality of evidence.

R-25: Use of Infant Formulas

In the absence of available breast milk, the use of semi-elemental infant formulas is recommended. These formulas contain extensively hydrolyzed protein and medium-chain triglycerides (MCTs) and are lactose-free. In cases of suspected severe food allergy or intolerance to semi-elemental formula, the use of elemental formulas (free amino acids) should be considered. MCTs are useful in patients with intestinal dysfunction because they are more easily absorbed than long-chain triglycerides, as their absorption occurs directly through the portal circulation[36,37,40,41].

Recommended dose: initiate with volumes of 10–20 mL/kg/day, progressively increasing according to patient tolerance until established nutritional requirements are achieved[36,37,40,41].

Strong consensus (final agreement 100% [22/22]), high quality of evidence.

R-26: Key Points for Evaluating Tolerance

Assessment of feeding tolerance through monitoring of fecal output or stool frequency is recommended. These indicators are crucial for adjusting the volume and composition of enteral feeding[36,37,40,41].

Strong consensus (final agreement 81.8% [18/22]), high quality of evidence.

R-27: Transition to Full Enteral Feeding

The transition should be performed carefully, beginning with breast milk or specialized formulas and gradually advancing the volume and diversity of foods according to tolerance and clinical response[36,37,40,41].

Moderate consensus (final agreement 72.7% [16/22]), high quality of evidence.

R-28: Complementary Feeding

Initiation of complementary feeding is recommended between four and six months of chronological age or corrected age in preterm infants, according to the residual anatomy and neurocognitive development of the patient. New foods should be introduced gradually, testing one new food every two to four days in order to evaluate tolerance and minimize potential adverse effects. Administration of complete proteins and restriction of simple carbohydrates are recommended[36,37,40,41].

Specifications according to the type of resection:

- Type I SBS: diet containing 40%–50% complex carbohydrates, high in fat (40%), without the need for oxalate restriction.
- Type II SBS: caution with excessive fat intake, as fats may bind to calcium, increasing the risk of oxalate formation.
- Type III SBS: priority should be given to the use of soluble fiber to promote the production of short-chain fatty acids, which are essential for maintaining the integrity of the colonic mucosa.

Moderate consensus (final agreement 100% [22/22]), high quality of evidence.

R-29: Routes of Enteral Nutrition Administration

Selection of the route of EN administration should be based on the type of intestinal resection and the clinical condition of each patient[36,37,40,41].

Orogastric and Nasogastric Tubes

The orogastric tube is used primarily in neonates. Both tubes are employed for temporary feeding and during the transition to full EN. The use of silicone tubes is recommended because of their greater durability and lower risk of complications.

Nasojejunal and Gastrojejunal Tubes

These are indicated for patients with gastroparesis, motility disorders, and risk of aspiration, allowing direct access to the jejunum. These tubes require continuous monitoring to prevent mucosal erosion, especially during prolonged use. Tube migration, as well as nasal or esophageal complications associated with insertion and prolonged placement, should be monitored and prevented.

Gastrostomy

Recommended for long-term feeding in patients requiring more than 4–8 weeks of nasogastric tube feeding. Careful supervision is essential to prevent insertion-site infections and tube displacement, as well as to ensure appropriate stoma maintenance.

Additional Considerations

Depending on tolerance and the patient's specific needs, both bolus administration and continuous infusion may be used. Selection of the method should be individualized and should consider factors such as the absorptive capacity of the remaining intestine and the comfort of the patient and family.

Moderate consensus (final agreement 100% [22/22]), high quality of evidence.

QUESTION 6. WHAT ARE THE SURGICAL MANAGEMENT STRATEGIES FOR INTESTINAL FAILURE SECONDARY TO SHORT BOWEL SYNDROME AND THEIR INDICATIONS?

R-30: Intestinal Remodeling

Restoration of gastrointestinal tract continuity through intestinal remodeling techniques is recommended, including enteroplasty, ostomy closure, stricturoplasty, or the Bianchi technique, in order to increase the absorptive surface area of the small intestine. The risk of postoperative complications, such as intestinal obstruction and anastomotic leaks, should be considered[25–27].

Strong consensus (final agreement 95% [19/20]), moderate quality of evidence.

R-31: Intestinal Lengthening

Consideration of intestinal lengthening surgery, specifically using the Serial Transverse Enteroplasty Procedure (STEP) technique, is recommended in pediatric patients with IF-SBS. This technique has been shown to be effective in increasing functional intestinal length, improving nutrient absorption, and reducing dependence on PN. The STEP technique may be associated with complications such as sepsis and intestinal obstruction[25–27].

Strong consensus (final agreement 95% [19/20]), moderate quality of evidence.

R-32: Comparison and Selection of Technique

Selection of the surgical technique should be based on a comprehensive evaluation of patient characteristics, the length and functionality of the remaining intestine, and the presence of preexisting complications.

When enteroplasty or the Bianchi technique is used, appropriate monitoring should be implemented, including hemodynamic, nutritional, and radiological surveillance according to each clinical scenario.

STEP procedures should be performed exclusively in specialized centers, with rigorous postoperative follow-up to ensure treatment success and patient safety[25,27,35,42,43].

Strong consensus (final agreement 100% [21/21]), high quality of evidence.

R-33: Gastrostomy and Insertion Technique

Insertion of a percutaneous endoscopic gastrostomy is recommended in pediatric patients with IF-SBS. This technique represents a minimally invasive approach that, in cases of complex anatomy, may be complemented with laparoscopic assistance or, ultimately, by surgical gastrostomy placement. Selection of the insertion technique should be individualized and should take into account the expertise of the treating team[29–31,36,37,40,44].

Strong consensus (final agreement 75% [15/20]), high quality of evidence.

R-34: Effectiveness of Intestinal Transplantation

Intestinal transplantation provides significant improvement in long-term survival and quality of life in patients with severe intestinal failure. Studies report survival rates of approximately 50% at 5 years after transplantation[23,25,27,29].

Strong consensus (final agreement 100% [17/17]), high quality of evidence.

R-35: Indications for Referral to a Transplant Center

Irreversible intestinal failure: patients who are unable to achieve enteral autonomy despite intensive medical and surgical management and whose quality of life under intestinal rehabilitation treatment is poor[23,25,27,29]:

- Progressive IFALD or irreversible liver disease or progression to cirrhosis.
- Multiple vascular thromboses.
- Recurrent episodes of catheter-related sepsis (≥2 per year).
- Severe hydroelectrolytic disorders that cannot be corrected or managed.

Strong consensus (final agreement 100% [18/18]), high quality of evidence.

R-36: Referral to a Specialized Transplant Center

In pediatric patients with severe IF-SBS, referral to a specialized intestinal transplant center should be considered as a viable therapeutic option when conventional interventions have failed to restore adequate intestinal function. Candidate selection should be performed under strict criteria, including irreversibility of intestinal failure and the presence of severe complications related to prolonged PN, such as IFALD or recurrent infections[23,25,27,29].

Decision-making process: the multidisciplinary intestinal failure management team should evaluate each case and determine whether the patient meets the criteria for referral to a transplant center.

Social considerations: evaluation of the social context is essential, as limitations affecting implementation of the recommendation, such as access to a specialized center or family support, may influence the success of post-transplant treatment. Available resources and support systems for the patient and family should be specified and documented before proceeding with referral[23,25,27,29].

Strong consensus (final agreement 100% [18/18]), high quality of evidence.

QUESTION 7. WHAT ARE THE MOST RECOMMENDED TYPES OF VASCULAR ACCESS AND DEVICES, CARE MEASURES, AND PREVENTION AND TREATMENT STRATEGIES FOR COMPLICATIONS IN PEDIATRIC PATIENTS WITH INTESTINAL FAILURE SECONDARY TO SHORT BOWEL SYNDROME?

R-37: Use of Tunneled Catheters

The use of tunneled catheters, preferably silicone rather than polyurethane, single-lumen, and cuffed catheters, is recommended for children with IF-SBS[15,23,53].

Strong consensus (final agreement 100% [18/18]), high quality of evidence.

R-38: Catheter Location

Vascular access in the upper part of the trunk is preferably recommended when these vessels remain patent[23,27,53].

Strong consensus (final agreement 100% [20/20]), high quality of evidence.

R-39: Endovascular Procedures

In patients with difficult vascular access who require alternative access or endovascular procedures, these should be performed by experienced pediatric surgeons or interventional radiologists, preferably in a specialized intestinal rehabilitation or transplant center[23,27,53].

Strong consensus (final agreement 100% [20/20]), high quality of evidence.

R-40: Importance of Technique and Hygiene in Central Venous Catheter Care

Use of appropriate and hygienic techniques in central venous catheter care is recommended to prevent associated complications. It is essential that caregivers receive specific education before patient discharge, with reinforcement sessions as needed to ensure proper understanding and practice[23].

Strong consensus (final agreement 100% [19/19]), high quality of evidence.

R-41: Use of Chlorhexidine-Impregnated Supplies

For coverage of the central catheter insertion site in pediatric patients with IF-SBS, consideration should be given to the use of 2% chlorhexidine-impregnated supplies, such as discs, sponges, or dressings. These products may help reduce the risk of catheter-related infections[23].

Strong consensus (final agreement 100% [18/18]), high quality of evidence.

R-42: Routine Surveillance of Central Venous Access

Routine surveillance of central venous access should be based on clinical assessment, and in cases of suspected abnormalities, ultrasound should be performed to monitor for potential complications. When more detailed delineation of venous access is required, the interventional radiologist from the intestinal rehabilitation team should be consulted regarding the diagnostic approach[23].

Strong consensus (final agreement 100% [17/17]), high quality of evidence.

R-43: Emergency Letter

All children with IF-SBS should have a letter detailing their specific needs in emergency situations[23].

Strong consensus (final agreement 100% [16/16]), high quality of evidence.

R-44: Discussion Regarding Physical Activities

It is important to discuss with families the risks associated with swimming and participation in sports, as well as strategies to protect the catheter insertion site dressing and the central line during these activities[23].

Strong consensus (final agreement 100% [17/17]), high quality of evidence.

R-45: Travel Planning

It is recommended that travel plans be discussed with the intestinal rehabilitation team sufficiently in advance to develop an emergency care plan[23].

Strong consensus (final agreement 100% [18/18]), high quality of evidence.

R-46: Management of Fever in Children with IF-SBS and a Central Venous Catheter

All children with IF-SBS and a central venous catheter who develop fever should be hospitalized and evaluated to rule out bacteremia through central and peripheral blood cultures. They should receive empiric broad-spectrum antibiotics through the central venous catheter for at least 48 hours while awaiting culture results, regardless of the presence of other possible sources of infection[23,27,53].

Strong consensus (final agreement 100% [18/18]), high quality of evidence.

R-47: Consultation Before Catheter Removal in Central Line-Associated Bloodstream Infection (CLABSI)

In a patient with CLABSI who is clinically stable, the intestinal rehabilitation team should be consulted before proceeding with catheter removal[23,27,53].

Strong consensus (final agreement 100% [18/18]), high quality of evidence.

R-48: Prophylactic Lock Therapy

Prophylactic lock therapy with ethanol or other non-antibiotic lock solutions should be strongly considered in all children with IF-SBS from the time of tunneled catheter insertion[23,27,53].

Strong consensus (final agreement 100% [18/18]), high quality of evidence.

R-49: Management of Mechanical Complications

In children with IF-SBS, the central venous catheter should be repaired whenever possible in order to preserve venous access, according to the availability of repair kits in the country[23,27,53].

Strong consensus (final agreement 100% [18/18]), high quality of evidence.

R-50: Treatment of Catheter-Related Thrombosis (CRT)

Children with IF-SBS and newly identified catheter-related thrombosis should be treated with low-molecular-weight heparin for at least six weeks. Those with persistence of at least one chronic thrombus should remain on prophylactic anticoagulation under the supervision of a hematologist[23,27,53].

Strong consensus (final agreement 100% [16/16]), high quality of evidence.

R-51: Evaluation for Intestinal Transplantation

Children who have lost multiple central venous access sites should be considered for referral to an intestinal transplant center for evaluation and management[23,27,53].

Strong consensus (final agreement 100% [19/19]), high quality of evidence.

R-52: Recommendation for the Management of Central Venous Access Programs

All centers caring for children with IF-SBS should record the number of CLABSIs in hospitalized or outpatient patients per 1,000 catheter-days[23,27,53].

Strong consensus (final agreement 100% [18/18]), high quality of evidence.

QUESTION 8. WHAT ARE THE RECOMMENDATIONS FOR THE DIAGNOSIS, PREVENTION, AND TREATMENT OF INTESTINAL FAILURE-ASSOCIATED LIVER DISEASE SECONDARY TO SHORT BOWEL SYNDROME IN PEDIATRICS?

R-53: Monitoring of Liver Biochemistry

Monitoring of hepatic biochemical parameters, such as bilirubin, transaminases, γ-glutamyltransferase, and alkaline phosphatase, is recommended in order to adjust nutritional treatment and detect early signs of hepatic deterioration[27].

Strong consensus (final agreement 100% [18/18]), moderate quality of evidence.

Good Clinical Practice Points

To date, there is no universally accepted diagnostic definition for intestinal failure-associated liver disease; however, in clinical practice, biochemical criteria based on persistent abnormalities in liver profile tests are used. In the pediatric population, elevations of cholestatic enzymes (mainly alkaline phosphatase and γ-glutamyltransferase) above 1.5 times the upper limit of normal persisting for more than six weeks are considered suggestive. Additionally, alanine aminotransferase (ALT) elevations greater than 2–3 times the normal value may be observed, as well as increases in total bilirubin within a similar range.

R-54: Adjustment of Lipid Emulsion Dose and Infusion Rate

Adjustment of the dose or infusion rate of lipid emulsions is recommended while respecting the oxidation rate of fatty acids[27].

Strong consensus (final agreement 100% [19/19]), moderate quality of evidence.

R-55: High Soybean Content Lipid Emulsions

Avoidance of lipid emulsions with a high soybean oil content (first-generation emulsions) is recommended[27].

Strong consensus (final agreement 100% [22/22]), moderate quality of evidence.

R-56: Composite Lipid Emulsions

Use of composite lipid emulsions (soybean oil, olive oil, MCTs, and fish oil) is recommended[27].

Strong consensus (final agreement 100% [20/20]), moderate quality of evidence.

R-57: Prevention and Treatment of CLABSI

Implementation of strict prevention and treatment measures for CLABSI and small intestinal bacterial overgrowth (SIBO) is recommended, as infections may aggravate hepatic involvement[27].

Strong consensus (final agreement 100% [21/21]), moderate quality of evidence.

R-58: Cyclic Administration of Parenteral Nutrition

Cyclic administration of PN is recommended as soon as possible[27].

Strong consensus (final agreement 100% [21/21]), moderate quality of evidence.

R-59: Intestinal Reconstruction

Surgical interventions should be evaluated and considered when necessary, including reconstruction of intestinal continuity and treatment of dilated bowel loops, in order to improve intestinal adaptation and reduce hepatic burden[26,27,29].

Strong consensus (final agreement 100% [21/21]), moderate quality of evidence.

R-60: Clinical Evaluation of IFALD

When IFALD is suspected, clinical evaluation is recommended to identify signs of persistent jaundice, hepatomegaly with an irregular liver edge, and splenomegaly. In advanced stages, the presence of collateral circulation, variceal bleeding secondary to portal hypertension, and ascites should be monitored[26,27,29].

Strong consensus (final agreement 100% [20/20]), high quality of evidence.

R-61: Biochemical Evaluation of IFALD

When IFALD is suspected, monitoring of biochemical parameters (bilirubin, transaminases, γ-glutamyltransferase, and alkaline phosphatase) every one to four weeks is recommended, depending on the degree of hepatic involvement[26,27,29].

Strong consensus (final agreement 100% [17/17]), high quality of evidence.

R-62: Imaging Studies and Pathological Anatomy

Upon diagnosis of IFALD, total abdominal ultrasound and splenoportal Doppler ultrasound are recommended to characterize parenchymal involvement and portal hypertension. Other studies, such as abdominal computed tomography, magnetic resonance imaging, elastography, and endoscopic studies, should be evaluated according to the clinical presentation. Liver biopsy is the reference standard for the diagnosis and classification of fibrosis; however, its indication should be determined by the intestinal failure team[26,27,29].

Strong consensus (final agreement 100% [21/21]), high quality of evidence.

R-63: Temporary Reduction of Lipid Emulsions

Temporary reduction of the dose or suspension for several days of lipid emulsions in PN is recommended according

to the severity of hepatic involvement, while ensuring the provision of essential fatty acids[26,27,29].

When available, the use of lipid emulsions containing 100% fish oil at a dose of 1 g/kg/day should be considered while hepatic involvement persists[26,27,29].

Strong consensus (final agreement 94.4% [17/18]), high quality of evidence.

R-64: Use of Hepatoprotective Medications

Use of UDCA is suggested to improve bile flow and reduce cholestasis in patients with early signs of IFALD[26,27,29].

Strong consensus (final agreement 100% [21/21]), high quality of evidence.

R-65: Liver Transplantation

Early identification and evaluation of patients with advanced liver disease who do not respond to conventional therapies are recommended in order to consider liver transplantation or multivisceral transplantation.

A transplant team should also be involved in patient follow-up and preparation, ensuring that all medical and nutritional needs are addressed[26,27,29].

Strong consensus (final agreement 100% [22/22]), high quality of evidence.

QUESTION 9. WHAT ARE THE RECOMMENDATIONS FOR DIAGNOSIS AND TREATMENT, IN TERMS OF EFFECTIVENESS AND SAFETY, FOR THE MANAGEMENT OF OTHER MEDICAL COMPLICATIONS INHERENT TO INTESTINAL FAILURE?

R-66: Lactulose or Glucose Breath Test for the Diagnosis of SIBO

Use of the lactulose or glucose breath test is recommended as a noninvasive diagnostic method for SIBO, based on its availability and diagnostic accuracy. Jejunal aspirate with culture is recommended only in complex or refractory cases because of its greater diagnostic accuracy[45].

Strong consensus (final agreement 95.2% [20/21]), moderate quality of evidence.

R-67: Use of Rotating Cycles of Antibiotics for the Treatment of SIBO

Use of rotating cycles of antibiotics such as rifaximin and metronidazole is suggested for the treatment of SIBO, as this strategy has demonstrated effectiveness in reducing symptoms of malabsorption and abdominal distension, with a favorable safety profile[48].

Strong consensus (final agreement 100% [20/20]), moderate quality of evidence.

Good Clinical Practice Point

In patients with neurological involvement and high anion gap metabolic acidosis with normal lactate levels, the presence of D-lactic acidosis should be considered. This can be confirmed through D-lactate measurements according to their availability.

R-68: Dietary Modification

Dietary modification, including restriction of simple carbohydrates and increased fat intake, is recommended in patients with recurrent D-lactic acidosis, as this approach has been shown to reduce bacterial fermentation and D-lactate production[27].

Strong consensus (final agreement 100% [20/20]), moderate quality of evidence.

R-69: Use of Preventive Antibiotics

Use of antibiotics (metronidazole or vancomycin) is suggested in severe cases of D-lactic acidosis associated with bacterial overgrowth[27].

Strong consensus (final agreement 95% [19/20]), moderate quality of evidence.

R-70: Bone Metabolism

Monitoring of biochemical markers of bone metabolism is recommended, including serum levels of 25-OH-vitamin D3, alkaline phosphatase, phosphate, and calcium every three months, as well as urinary calcium and parathyroid hormone once yearly[27].

Strong consensus (final agreement 85% [17/20]), moderate quality of evidence.

R-71: Vitamin D Supplementation

Supplementation with vitamin D (800-1,000 IU/day) and calcium (1-1.5 grams/day) is recommended in patients with IF-SBS, as deficiency is associated with an increased risk of metabolic bone disease. Supplementation should be individualized and determined by the intestinal failure team[27].

Strong consensus (final agreement 100% [21/21]), moderate quality of evidence.

Good Clinical Practice Point

Recommendation or indication for the use of therapies such as bisphosphonates in patients with diagnosed osteoporosis should be discussed with a pediatric endocrinologist.

R-72: Endoscopic Studies in Recurrent Gastrointestinal Bleeding

In patients with recurrent gastrointestinal bleeding without a clear etiology, endoscopic studies with biopsy sampling are recommended to differentiate eosinophilic gastrointestinal disorders from other etiologies[27].

Strong consensus (final agreement 100% [21/21]), moderate quality of evidence.

R-73: Diet in Eosinophilic Intestinal Disorders

In patients with confirmed eosinophilic intestinal disorders, an individualized allergen elimination diet is recommended, aiming to be as minimally restrictive as possible: milk, egg, wheat, soy, peanuts, fish, shellfish, tree nuts, and sesame[27].

Strong consensus (final agreement 78.9% [15/19]), moderate quality of evidence.

QUESTION 10. WHAT ADDITIONAL DIAGNOSTIC STUDIES SHOULD BE REQUESTED FOR THE DIAGNOSIS AND FOLLOW-UP OF PEDIATRIC PATIENTS WITH INTESTINAL FAILURE?

R-74: Frequency of Biochemical Monitoring

The frequency of biochemical monitoring should be individualized and determined by the multidisciplinary intestinal rehabilitation team[27,29,56,57].

Strong consensus (final agreement 100% [22/22]), moderate quality of evidence.

R-75: Recommendation Regarding Densitometry

Dual-energy X-ray absorptiometry (DXA) is considered the gold standard for the diagnosis and monitoring of bone health in pediatric patients with IF-SBS from five years of age onward. DXA is recommended every 1–3 years, adjusting the frequency according to previous Z-score results, clinical presentation, and occurrence of fractures[27,29,56,57].

Strong consensus (final agreement 100% [22/22]), moderate quality of evidence.

R-76: Use of Diagnostic Imaging

The role of imaging is to:

- Assess preoperative and postoperative intestinal anatomy.
- Identify stenoses, fistulas, collections, or other complications.
- Exclude congenital malformations.

Close communication between clinicians and radiologists is recommended in order to select the most appropriate diagnostic modality and avoid unnecessary exposure to ionizing radiation[25,27,38,58,59].

Strong consensus (final agreement 100% [22/22]), high quality of evidence.

R-77: Gastrointestinal Fluoroscopy Studies

Fluoroscopy studies are recommended to evaluate preoperative and postoperative intestinal anatomy. These studies allow measurement of intestinal length and assessment of anatomical integrity[25,27,38,58,59].

Strong consensus (final agreement 100% [22/22]), high quality of evidence.

Good Clinical Practice Point

Iso-osmolar water-soluble contrast should be used, avoiding barium because of the risk of chemical peritonitis in cases of leakage, especially during the immediate postoperative period. Other studies, such as CT enterography or magnetic resonance enterography, should be considered according to each patient's needs.

R-78: Abdominal Ultrasound and Hepatic Doppler

Use of ultrasonography is suggested for follow-up of the hepatic parenchyma and biliary tract, hepatic steatosis in patients dependent on parenteral nutrition, associated malformations, and complications (latest-generation ultrasound equipment can quantitatively measure fat infiltration and fibrosis by elastography). The frequency of use should be individualized for each case according to the indications of the intestinal rehabilitation team[27,35,39,51,60].

Strong consensus (final agreement 100% [22/22]), moderate quality of evidence.

Good Clinical Practice Point

Complementary hepatic Doppler evaluation is advised to assess portal blood flow, especially in patients with suspected IFALD-related portal hypertension.

R-79: Liver Elastography and Magnetic Resonance Imaging

Liver elastography and magnetic resonance imaging may be considered according to availability, on an individualized basis and according to the indications of the intestinal rehabilitation team. If these technologies are used, the patient should be considered his or her own control[27,35,39,51,60].

Strong consensus (final agreement 100% [22/22]), moderate quality of evidence.

R-80: Gastrointestinal Endoscopy

Endoscopic studies, including esophagogastroduodenoscopy (EGD) and colonoscopy, are suggested in patients with anemia refractory to treatment, suspected or documented gastrointestinal bleeding, suspected enteropathies and eosinophilic gastrointestinal disorders, as a baseline study before initiation and follow-up of enterohormone treatment to rule out polyps, and as a route for nasojejunal tube placement[25–27].

Strong consensus (final agreement 100% [22/22]), moderate quality of evidence.

QUESTION 11. WHAT ARE THE INDICATIONS FOR REFERRAL AND THE REQUIREMENTS THAT A MULTIDISCIPLINARY INTESTINAL REHABILITATION CENTER SHOULD FULFILL?

R-81: Indications for Referral to an Intestinal Rehabilitation Center

Referral to an intestinal rehabilitation program is recommended for all pediatric patients with the following indications[25–27]:

- Progressive associated liver disease.
- Recurrent catheter-associated sepsis: two or more catheter-related sepsis episodes within one year.
- Recurrent loss of vascular access.
- Central venous access thrombosis.
- Epithelial enteropathies complicating management.
- Ultrashort bowel.
- Lack of a trained team or infrastructure.
- Lack of diagnostic certainty to guide management.
- Prolonged parenteral nutrition for more than three months.
- Severe hydroelectrolytic disorders.

Strong consensus (final agreement 100% [22/22]), low quality of evidence.

R-82: Requirements That an Intestinal Rehabilitation Center Should Fulfill[25–27]

Multidisciplinary Team

- Pediatric gastroenterologist with experience in intestinal failure and nutrition.
- Pediatric surgeon with experience in complex procedures and vascular access management.
- Specialists in pediatric nutrition (dietitian or pediatric nutrition specialist): pediatric metabolic and nutritional support team.
- Pediatric infectious disease specialist: management of recurrent sepsis and infection prevention.
- Pediatric psychologist or psychiatrist.
- Clinical pharmacist: optimization of nutritional therapy and medications.
- Specialized nursing staff: management of central venous access and administration of parenteral nutrition.
- Comprehensive physical therapy services: speech therapy, occupational therapy, and physiotherapy.

Infrastructure and Services

- Pediatric intensive care unit (PICU).
- Specialized clinical laboratory.
- Advanced imaging services.
- Operating rooms equipped for highly complex procedures.
- Gastroenterology unit with availability of endoscopic equipment for diagnostic studies, follow-up, and interventions such as gastrostomy.
- Advanced nutritional therapies: home parenteral and enteral nutrition and transition to home care.
- Continuing education program for healthcare staff and families focused on home management of parenteral nutrition and catheter care.

Strong consensus (final agreement 100% [22/22]), low quality of evidence.

QUESTION 12. WHAT ARE THE INDICATIONS AND REQUIREMENTS FOR HOME PARENTERAL NUTRITION?

R-83: Indications for Home Parenteral Nutrition[25–27]

- Family members/caregivers of legal age who accept and assume responsibility for treatment and are trained in PN replacement, PN cycling, and emergency situations.
- Home with adequate socioenvironmental conditions for PN administration: hygiene, potable water, electricity, and refrigeration.
- Clinical stability of the patient: underlying disease stability, control of losses, metabolic and hemodynamic stability.
- Expected weight gain.
- Patient requiring prolonged PN and beyond the neonatal period.
- Multidisciplinary team with experience in nutritional support.
- Long-term venous catheter (free of infection and in good condition).
- Contact and accessibility to a nearby healthcare center.
- Payer ensuring coverage.

- Availability of home supplies.
- Appropriate legal framework.

Strong consensus (final agreement 100% [22/22]), low quality of evidence.

R-84: Multidisciplinary Follow-Up

Children discharged with home PN should be monitored by a multidisciplinary intestinal rehabilitation team[25–27].

Strong consensus (final agreement 100% [22/22]), low quality of evidence.

R-85: Family Training and Support

Before discharge, it should be ensured that parents are adequately trained in the administration of PN and EN, as well as in the recognition of warning signs[25–27].

Strong consensus (final agreement 100% [22/22]), low quality of evidence.

R-86: Central Venous Access Team

To prevent loss of vascular access, a specialized team for central venous access management is recommended(25–27).

Strong consensus (final agreement 100% [22/22]), low quality of evidence.

R-87: Psychological Care and Social Workers

Mental health professionals and social workers should address the impact on quality of life and the emotional well-being of patients and families[25–27].

Strong consensus (final agreement 100% [22/22]), low quality of evidence.

R-88: Telemedicine

Telemedicine is a valuable option for reducing the frequency of visits and monitoring patients in remote areas[25,26].

Strong consensus (final agreement 90.9% [20/22]), low quality of evidence.

CONCLUSION

Intestinal failure secondary to short bowel syndrome in pediatrics represents one of the most complex challenges in contemporary pediatric medicine, requiring a comprehensive, multidisciplinary, and highly specialized approach. This consensus, developed through a rigorous Delphi method with participation of 25 multidisciplinary experts, provides 88 recommendations based on the best available evidence, adapted to the context and resources of the Colombian healthcare system.

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Conflict of Interest

The development of this analysis, as well as its conclusions, was conducted independently, transparently, and impartially by the authors.

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Case report

Endoscopic Management of Hepatic Cyst Secondary to Caroli Disease: A New Era—A Case Report

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Abstract

Introduction: Caroli disease is a rare condition characterized by segmental saccular dilatations of the intrahepatic biliary tree, which generally involve the entire hepatic parenchyma. One of its main features is the presence of multiple hepatic cysts throughout the liver parenchyma, although extrahepatic biliary involvement is uncommon. **Case report:** We present the case of a woman with a history of a hepatic cyst in the left lobe. Given her history of Caroli disease, she was admitted with a 10-day clinical course consisting of cholestatic jaundice, weight loss, and pruritus. Magnetic resonance cholangiography revealed multiple saccular dilatations in the intrahepatic bile ducts and a hepatic cyst arising from the biliary tree. **Discussion:** The diagnosis of Caroli disease was primarily established through endoscopic procedures, which demonstrated multiple hepatic cysts and a giant hepatic cyst. In this case, endoscopic methods were employed, resulting in successful treatment with lower morbidity. **Conclusions:** This case report highlights that Caroli disease, being a rare and highly complex condition, has seen limited advances in its treatment. We therefore report on a new era of endoscopic management that enables disease resolution with reduced morbidity and mortality.

Keywords

Caroli disease; intrahepatic bile ducts; cholestasis; jaundice; natural orifice endoscopic surgery.

INTRODUCTION

Jacques Caroli first described Caroli Disease in 1958. This disease is a congenital malformation of the intrahepatic bile ducts characterized by ectasia and dilation of the intrahepatic ducts, which may involve the biliary tract in either a focal or multifocal manner[(1)]. It is a low-prevalence condition, occurring in approximately fewer than one case per 1,000,000 inhabitants[(2)]. The clinical presentation of this disease varies, but it is mainly characterized by right upper quadrant abdominal pain, jaundice, fever, pruritus, and the development of multiple hepatic cysts, which are managed through interventional radiology; however, they carry a high risk of superinfection due to repeated punctures[(2–9)]. Management of complications associated with Caroli disease is primarily performed through percutaneous drainage to resolve the collections that form within the liver. Patients often require multiple punctures performed at different stages to complete drainage and achieve resolution of the septic process[(8,9)]. Consequently, endoscopic surgical techniques have been described in which collection drainage can be achieved through the placement of stents, resulting in lower morbidity.

In caroli Disease, hepatic damage or liver failure is characterized by the presence of hepatic cysts mainly associated with primary hepatic fibrosis, and in rare cases these hepatic

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cysts contain tissues dependent on the intrahepatic biliary tree[3]. Therefore, the present case describes the management of a giant hepatic cyst communicating with the intrahepatic biliary tree, treated through endoscopic surgery.

CLINICAL CASE

A 51-year-old female patient was admitted to the emergency department with a one-week history of generalized jaundice associated with headache, nausea, choluria, and acholia, which had intensified over the previous three days. The patient had a history of a hepatic cyst diagnosed in 2013, which was resected laparoscopically in 2022, with immunohistochemical findings consistent with a simple hepatic cyst. On physical examination, the following vital signs were recorded: blood pressure, 132/77 mm Hg; heart rate, 78 beats per minute (bpm); oxygen saturation (SpO_2), 98%; and temperature, 36.5 °C. Generalized jaundice and tenderness on palpation of the right upper quadrant without signs of peritoneal irritation were noted. A biliopancreatic profile was requested, yielding the following results: total bilirubin, 8.2 mg/dL; direct bilirubin, 7.2 mg/dL; indirect bilirubin, 1.2 mg/dL; lipase, 9 mg/dL; amylase, 25 mg/dL; alkaline phosphatase, 245 mg/dL; aspartate aminotransferase (AST), 52 IU/L; and alanine aminotransferase (ALT), 99 IU/L. Based on these findings, an intermediate risk of choledocholithiasis was established according to the 2019 ASGE criteria, and magnetic resonance cholangiography was requested (**Figure 1**), which identified a giant complex hepatic cyst in the left hepatic lobe measuring 57 × 66 mm in diameter.

Given the obstructive etiology of the jaundice syndrome, an endoscopic retrograde cholangiopancreatography (ERCP) was performed, revealing an angulated and stenotic common bile duct in its middle third, with dilation of the hepatic and intrahepatic ducts. Contrast imaging additionally demonstrated a large hepatic cyst measuring greater than 12 cm, communicating with the left hepatic ducts, with evidence of uncontrollable biliary, hemorrhagic, and purulent drainage through the papilla. During the procedure, a 10 French (Fr) × 12 cm biliary stent was placed.

Subsequently, an endoscopic ultrasound (**Figure 2**) was performed, revealing a complex left hepatic cyst with thick walls, irregular contours, and dense internal fluid. An endoscopic cystogastrostomy was performed with placement of a 10 × 15 mm Hot Axios stent, followed by drainage of the cyst. An *in situ* biliary stent was also observed. A second endoscopic ultrasound was then performed, during which a cystogastrostomy was carried out with placement of a 10 mm × 15 mm Hot Axios stent (**Figure 3**), inserted through a subcardial approach (**Figure 4**), resulting in drainage of 350 mL of hematopurulent content. Findings suggested monolobar left-sided hepatic Caroli disease and severe acute cholangitis.

DISCUSSION

Caroli disease belongs to a family of fibrocystic ductal plate disorders, which also includes Autosomal Recessive Polycystic Kidney Disease, Congenital Hepatic Fibrosis, Autosomal Dominant Polycystic Kidney Disease, biliary hamartomas, and mesenchymal hamartomas[1]. Its etiology remains unknown; however, it appears to be associated with an autosomal recessive inheritance pattern[2].

When symptomatic, Caroli disease usually manifests with recurrent episodes of right upper quadrant abdominal

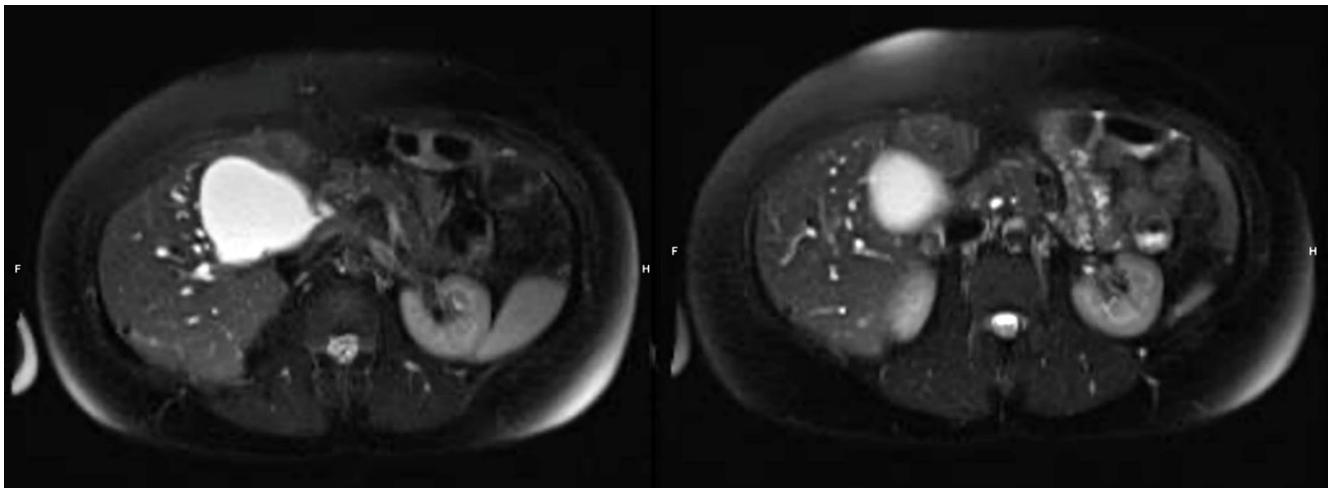


Figure 1. Magnetic resonance cholangiography showing evidence of a giant hepatic cyst with multiple hepatic cysts and collections. Author's file.

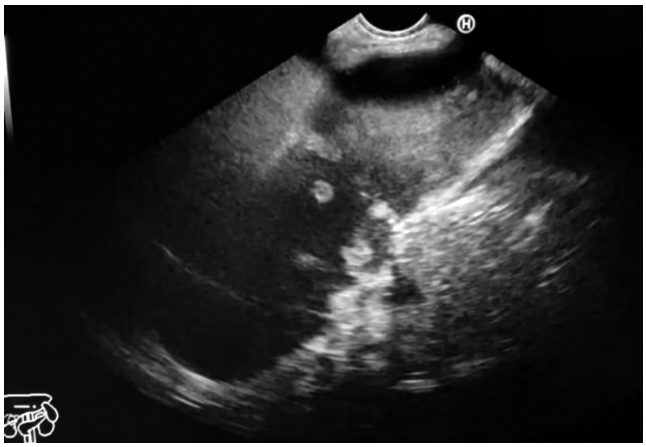


Figure 2. Giant hepatic cyst and multiple cysts identified by endoscopic ultrasound. Author's file.

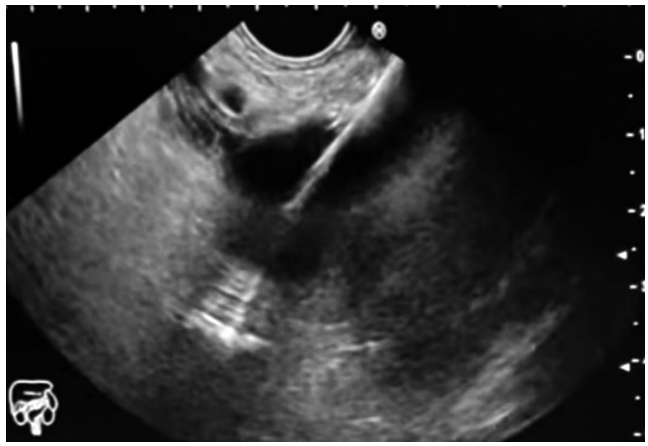


Figure 3. Endoscopic cystogastrostomy with placement of a Hot Axios stent. Author's file.

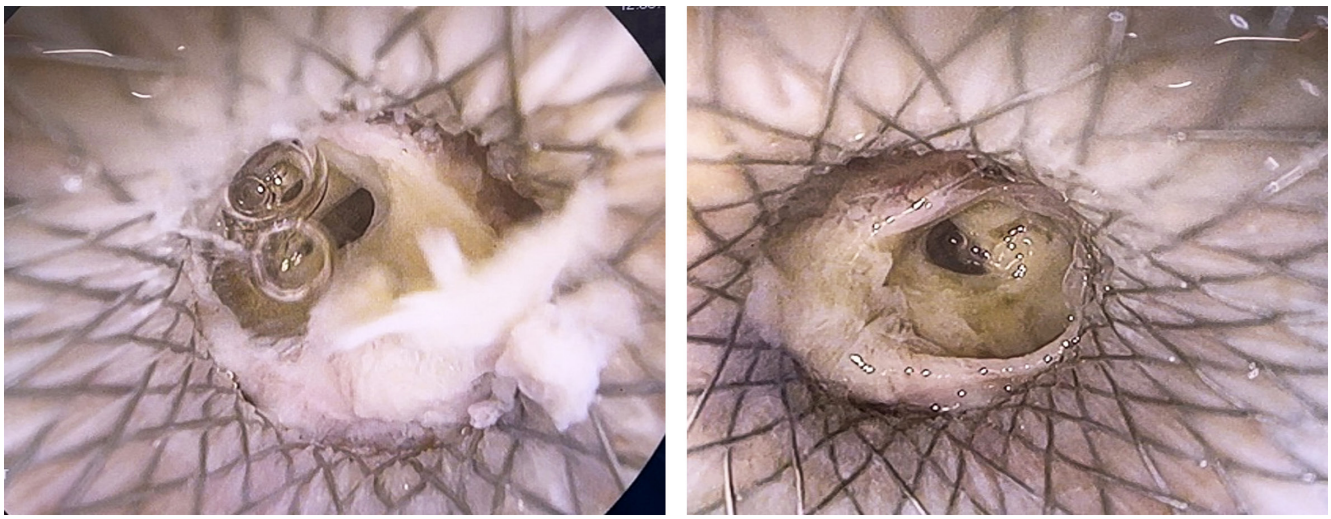


Figure 4. Subcardial endoscopic cystogastrostomy with placement of a 10 × 15 mm Hot Axios stent, showing evidence of intrahepatic ducts. The patient was transferred to the intermediate care unit for management of Tokyo III acute cholangitis. She showed favorable clinical progression and was transferred to the general ward 72 hours after admission to the unit. The patient continued to respond adequately to endoscopic management with the Hot Axios stent, with no evidence of purulent secretion drainage, resolution of acute cholangitis, and subsequent satisfactory recovery. Author's file.

pain, which may be accompanied by jaundice and pruritus. Recurrent bacterial cholangitis is the most common form of presentation and may occur with abdominal pain, fever, and chills[2]. In light of the above, the present case had a relatively typical presentation, with manifestations including abdominal pain, jaundice, choluria, and acholia.

The diagnosis of Caroli disease is based primarily on imaging findings demonstrating distal dilatations dependent on the intrahepatic biliary ducts through ultrasonography, computed tomography, or, as in this case, magnetic resonance cholangiography. Imaging characteristics include cystic dilation of the bile duct, and the presence of adjacent intrahepatic calculi secondary to biliary stasis is also a typical finding[1]. Differential diagnoses include conditions causing severe biliary dilation, as well as polycystic liver disease and congenital hepatic fibrosis[1]. Demonstration of communication between the cysts and the biliary tree is essential for establishing the diagnosis of Caroli disease[4].

Considering that there are currently no management guidelines for Caroli disease[2], treatment is individualized and based on associated comorbidities or complications, such as cholangitis, hepatic abscesses, hepatolithiasis[4], and the development of neoplasms such as cholangiocarcinoma, among others. Consequently, management involves multi-

disciplinary interventions including endoscopy, interventional radiology, and surgery[4]. On the one hand, medical therapy with ursodeoxycholic acid is implemented in some cases, such as cholestatic jaundice syndromes[2]; on the other hand, analgesics and antibiotic therapy are used in cases requiring these medications[3]. Surgical management appears to provide better outcomes in the presence of complications, risk of malignancy, or extensive disease, which may justify surgical intervention, potentially extending to hepatectomy[2]. Surgical management includes segmental or lobar hepatectomies and, in cases such as the diffuse form of Caroli disease, may ultimately require liver transplantation[1,3,4].

Among minimally invasive therapeutic options, transhepatic access or percutaneous drainage performed by the interventional radiology service has been described, as well as hepatogastric drainage guided by endoscopic ultrasonography using lumen-apposing metal stents such as the Hot Axios[6]. The latter option is particularly useful in patients with proximal biliary obstruction and altered surgical anatomy, for example[5].

Complications associated with the use of metal stents include migration rates of up to 21.2%, which are directly proportional to the duration of use; bleeding rates ranging from 0% to 10% of patients have also been reported[6].

Considering the overall incidence of malignant transformation in Caroli disease of 7% and the persistent risk of recurrence, annual follow-up with imaging studies and serial blood testing is maintained[2,3].

CONCLUSIONS

Caroli disease is a rare condition with low incidence. It usually presents with nonspecific symptoms, although one of the main findings is the presence of multiple hepatic cysts, which may be incidental findings. However, when symptomatic, patients present with an obstructive biliary syndrome leading to a clinical picture of acute cholangitis. Initial management has traditionally been performed through percutaneous drainage by interventional radiology; however, the new era has begun to adopt endoscopic drainage management, resulting in lower mortality and morbidity among patients.

Informed Consent

The patients completed informed consent forms in which they authorized the use of their medical records and diagnostic images for research purposes and case reporting. The case reports and methodology were approved by the institutional scientific ethics and research committee under Approval Record No. 023/22 dated May 17, 2021, in compliance with Resolutions No. 8430 of 1993 (risk-free study) and No. 2378 of 2007 issued by the Ministry of Social Protection, as well as in accordance with the provisions of the UNESCO Universal Declaration on Bioethics and Human Rights.

Conflict of Interest

The researchers declared that there were no conflicts of interest of any kind.

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Case report

Weil Disease as a Differential Diagnosis of Febrile Icteric Syndrome: A Case Report

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Abstract

The clinical case of a 56-year-old woman with febrile icteric syndrome is described, whose clinical course led to the diagnosis of severe leptospirosis, known as Weil disease. Leptospirosis is a re-emerging zoonosis primarily transmitted through contact with urine from infected rodents. It presents in two phases: a septicemic phase and an immune phase, which may progress to multiorgan failure. The patient developed jaundice, severe thrombocytopenia, elevated bilirubin levels, and respiratory deterioration. The diagnosis was confirmed by a positive automated immunoassay (AIA) for *Leptospira*. Due to penicillin allergy, treatment with ceftriaxone was initiated. The patient required management in the intensive care unit (ICU) because of pulmonary involvement, evidenced by pneumonitis and acute respiratory distress syndrome (ARDS). Clinical evolution was favorable, with resolution of symptoms and normalization of clinical parameters. This case underscores the importance of early assessment, accurate diagnosis, and multidisciplinary management. It highlights the need to consider this infection in patients exposed to risk factors such as stagnant water or rodents. In addition, it emphasizes the usefulness of the national protocol issued by the National Institute of Health (INS) for diagnosis and treatment. This report provides valuable information for clinical management and epidemiological surveillance.

Keywords

Leptospirosis; icterohemorrhagic leptospirosis; Weil disease; spirochetes; fever; jaundice.

INTRODUCTION

Definition

Leptospirosis is a reemerging zoonotic disease caused by pathogenic spirochetes of the genus *Leptospira*. These are gram-negative, obligate aerobic bacteria that are highly motile, measuring only 0.1 µm in diameter and 6 to 20 µm in length; their posterior end may exhibit a characteristic hook shape. The genus *Leptospira* includes both saprophytic species, which inhabit aquatic environments, and pathogenic species that cause leptospirosis[1,2].

Epidemiology

Leptospirosis has a worldwide distribution, with higher prevalence in tropical regions. Costa colleagues estimated that there are 1,030,000 cases worldwide (95% confidence

interval [95% CI]: 434,000–1,750,000) and 58,900 deaths (95% CI: 23,800–95,900) due to leptospirosis annually; the highest estimates of morbidity and mortality have been observed in South Asia and Southeast Asia, Oceania, the Caribbean, Andean, Central, and Tropical Latin America, and Eastern Sub-Saharan Africa[3].

According to the National Surveillance Information System for epidemiological period VI of 2024, the incidence of confirmed leptospirosis cases in Colombia was approximately 0.06 per 100,000 inhabitants, with a higher number of cases in men (1,999 [57.8%]) than in women (1,459 [42.2%])[4].

Natural History and Transmission

Leptospirosis persists in nature through chronic infection of the renal tubules in carrier animals (wild and domestic mammals), with rodents serving as the principal reservoir. Humans become infected through direct contact with infected animals or indirectly through contact of injured skin or mucous membranes with water and soil contaminated by their urine (the latter being the main mode of transmission). Consequently, the populations most susceptible to infection include individuals who work with animals (veterinarians and butchers), farmers, as well as those engaged in outdoor sports activities and military operations. Transmission increases particularly during periods of heavy rainfall and natural disasters, which may resuspend the bacteria in water and soil, thereby increasing the risk of exposure[5].

OBJECTIVES

The primary objective is to provide relevant public health information regarding the diagnostic and therapeutic approach to an uncommon condition caused by an emerging zoonotic disease involving multisystem involvement. In addition, the study aims to review the existing literature on the severe form caused by the genus *Leptospira*.

PATHOPHYSIOLOGY

After entering the body, hematogenous dissemination occurs, reaching levels of up to 10^6 leptospires per milliliter of blood. The microorganisms rapidly cross tissue membranes, and their transendothelial migration is facilitated by the phenomenon known as systemic vasculitis, which may produce severe injury leading to pulmonary hemorrhage, renal cortical ischemia, and necrosis of tubular epithelial cells, in addition to destruction of hepatic architecture, resulting in jaundice and hepatocellular injury. Possible virulence factors include immune-mediated mechanisms, adhesins, and the production of hemolytic toxins that may act as sphingomyelinases, pore-forming proteins, and collagenases[1].

The genus *Leptospira* directly activates the conversion of plasminogen into plasmin, the principal enzyme of the fibrinolytic system, thereby promoting hemorrhage[6].

Clinical Diagnosis

The clinical presentation of Leptospirosis includes two phases: a septicemic phase characterized by nonspecific febrile illness followed by an immune phase with generally reversible localized organ dysfunction, in which the kidneys and liver are the most frequent targets.

Weil disease is a severe form of leptospirosis associated with fulminant renal and hepatic dysfunction manifested by a triad of jaundice, acute kidney injury, and hemorrhagic manifestations. In addition, the genus *Leptospira* is an emerging cause of acute respiratory distress syndrome, producing dyspnea and hemoptysis; this form of the disease has increased in frequency in recent years[5].

Laboratory Diagnosis

Leptospirosis can be diagnosed through the isolation of *Leptospira* by culture, detection of antibodies by serologic testing, or identification of DNA by molecular techniques. The National Institute of Health of Colombia (INS) defines laboratory-confirmed leptospirosis as a patient with compatible clinical symptoms and any of the following: seroconversion by microscopic agglutination test (MAT) in paired samples, MAT titers equal to or greater than 1:400 in a single sample for fatal cases, a positive culture, or a positive molecular DNA test such as polymerase chain reaction (PCR)[5,7].

The following case describes a febrile icteric syndrome notable for hepatic and pulmonary organ dysfunction due to marked acute direct hyperbilirubinemia and adult respiratory distress syndrome secondary to leptospiral pneumonitis, with a final diagnosis of Weil disease.

CASE PRESENTATION

This is the case of a 56-year-old female patient with no significant past medical history. She reported a history of penicillin allergy and frequent exposure to rodents, as she lives near a landfill where the presence of these animals and their physiologic waste is evident. She presented to the emergency department with a three-day history of intermittent unquantified fever, malaise, five episodes of watery diarrhea, myalgias, arthralgias, retro-orbital pain, and holocranial headache rated 7/10 on the visual analog pain scale.

Initial physical examination revealed only a facial rash, with no other significant findings.

Initial laboratory testing demonstrated mild thrombocytopenia with normal liver function, renal function, and coagulation studies (**Table 1**). Given her symptom profile and the high prevalence of dengue, serologic tests were requested (nonstructural protein 1 antigen [NS1], immunoglobulin M [IgM], and immunoglobulin G [IgG]), all of which were negative. During her in-hospital course, the patient developed scleral icterus, and follow-up laboratory studies showed progressive elevation of transaminases (aspartate aminotransferase [AST] greater than alanine aminotransferase [ALT], without exceeding three times the upper limit of normal), predominantly direct hyperbilirubinemia, and severe thrombocytopenia, raising suspicion for severe leptospirosis or Weil Disease (**Figures 1–3**).

Given the history of penicillin allergy, antibiotic therapy with a third-generation cephalosporin (ceftriaxone) was initiated, together with intravenous hydration and confirmatory testing. Due to the risk of hemodynamic deterioration, transfer to a higher-complexity center with availability of an intensive care unit (ICU) was indicated. In the ICU, the patient experienced unfavorable clinical progression with persistent elevation of liver function markers and hyperbilirubinemia predominantly involving the direct fraction, in addition to persistent thrombocytopenia with slight improvement. Other infectious causes were ruled out through negative serologic testing for hepatitis A, B, and C, and confirmatory testing for *Leptospira* by automated immunoassay was positive, confirming the diagnosis of severe Leptospirosis. Subsequently, the patient developed progressive respiratory deterioration with clinical findings of bilateral basal crackles and a requirement for supplemental oxygen via a 50% Venturi mask. Chest computed tomography demonstrated bilateral interstitial opacities with multisegmental distribution, involvement of the upper and lower lobes and the right middle lobe, as well as bilateral pleural effusion with left-sided predominance. Given the suspicion of concomitant pneumonia, a respiratory viral panel was requested, and the established management was continued.

With medical support, the patient showed progressive improvement, and the pulmonary involvement resolved

Table 1. Laboratory Findings During Hospital Stay and Their Clinical Course

Measurement	Platelets (x 10^3/µL)	Total Bilirubin (mg/dL)	Direct Bilirubin (mg/dL)	ALT (U/L)	AST (U/L)
1	152	8.78	6.92	144	69
2	90	10.28	8.58	138	71
3	90	13.43	10.39	136	70
4	50	10.74	8.97	116	71
5	48	9.08	7.10	98	66
6	38	7.50	6.06	87	67
7	51	6.57	5.30	76	62
8	51	5.45	4.66	66	73
9	83	5.13	4.42	69	67
10	93	4.37	3.56	48	90
11	143	4.18	3.39	55	97
12	217	—	—	51	20
13	289	—	—	22	12
14	385	—	—	—	—
15	402	—	—	—	—
16	522	—	—	—	—

Author's own research.

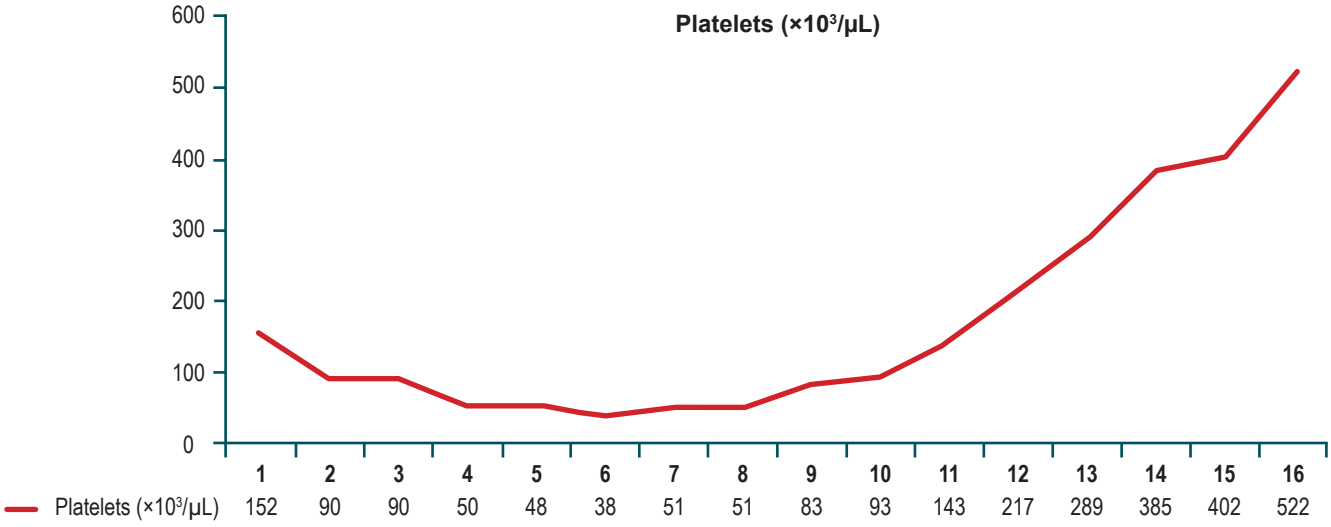


Figure 1. Platelet Trends During Hospital Stay Author's file.

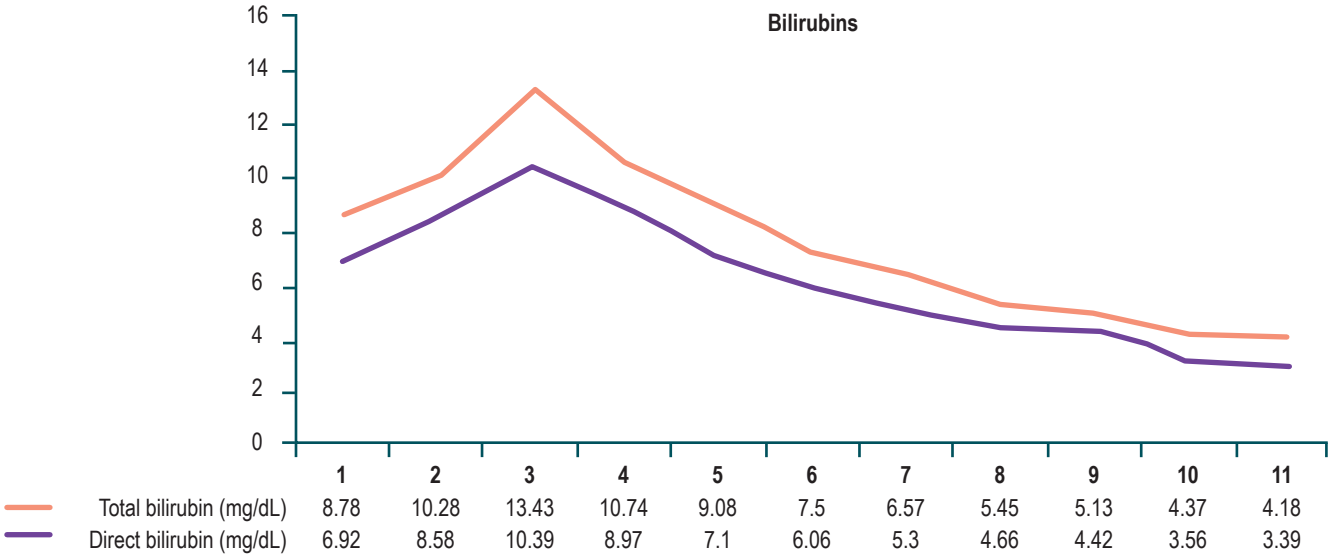


Figure 2. Bilirubin Level Trends During Hospital Stay Author's file.

following oxygen therapy, with gradual reduction in bilirubin levels and persistence of mild transaminase elevation during the first days. Renal function remained preserved, and the complete blood count demonstrated grade II normocytic normochromic anemia according to the World Health Organization (WHO) classification, without transfusion criteria. The antibiotic regimen with a third-generation cephalosporin was completed as a therapeutic alternative, and follow-up laboratory tests demonstrated normalization of the liver profile, resolution of thrombocytopenia, and complete clinical recovery. Finally, the patient was discharged on day 16 after symptom onset, completely asymptomatic and without associated complications.

The final diagnosis was severe Leptospirosis (Weil disease) with hepatic and pulmonary involvement.

DISCUSSION

Leptospirosis, although mild in most cases, may progress to severe forms with multiorgan involvement. Weil Disease and severe pulmonary hemorrhagic syndrome (SPHS) are the most lethal presentations, with mortality rates that may

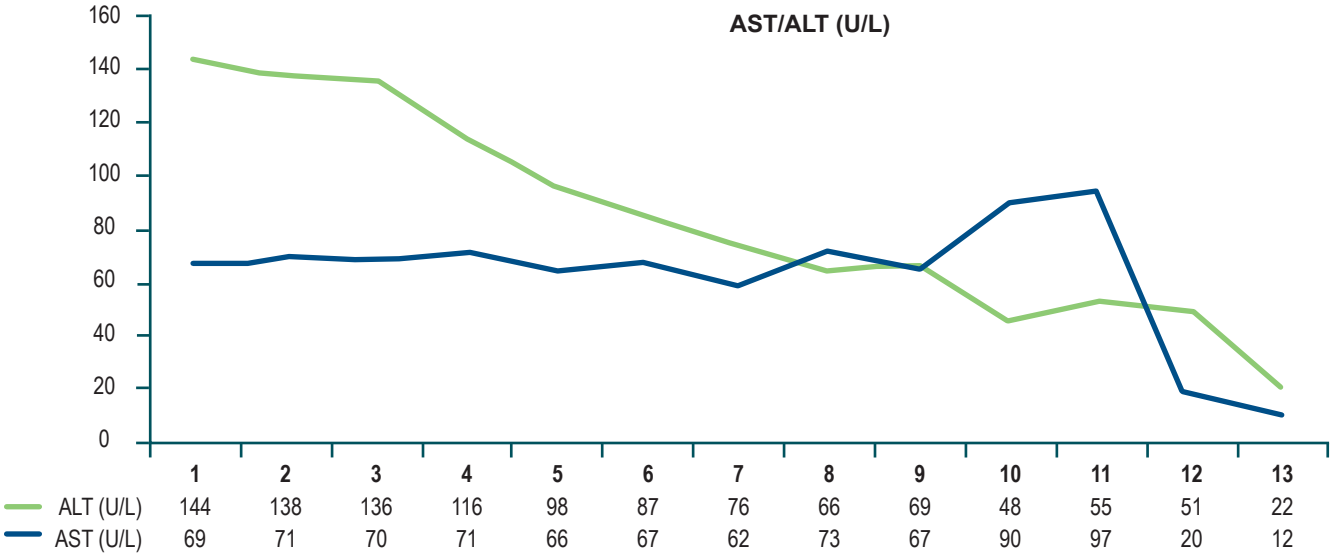


Figure 3. AST/ALT Level Trends During Hospital Stay Author's file.

exceed 50%[8,9]. In these severe forms, phenomena such as the "cytokine storm" and immune dysregulation play a key role in pathogenesis and explain the rapid clinical progression observed in some patients[8,10]. From an immunopathological perspective, the genus *Leptospira* has developed sophisticated immune evasion mechanisms, including the ability to avoid efficient activation of human TLR4 due to structural particularities of its lipopolysaccharide (LPS), thereby promoting a weak initial inflammatory response and systemic dissemination[8,10,11]. In addition, the action of outer membrane proteins, hemolysins, and phospholipases facilitates tissue invasion and hepatocellular injury, which constitutes a central mechanism underlying the jaundice observed in Weil disease[10,11].

In this context, the differential diagnosis of febrile icteric syndrome is essential. Conditions such as severe dengue, viral hepatitis, Malaria caused by *Plasmodium falciparum*, and Yellow Fever must be considered in endemic regions because they share similar initial clinical manifestations. The integration of epidemiological history, such as exposure to stagnant water or contact with animals, is decisive in directing clinical suspicion toward leptospirosis and guiding timely decision-making[12,13]. The recommended diagnostic approach is stepwise. During the leptospiremic phase (the first seven days), polymerase chain reaction (PCR) testing in whole blood with ethylenediaminetetraacetic acid (EDTA) is prioritized, whereas in later phases, serologic tests (enzyme-linked immunosorbent assay for immunoglobulin M detection [IgM ELISA] and microscopic agglutination test [MAT]) are the most useful methods for confirming the diagnosis[7].

Early initiation of antibiotic therapy is critical and should not be delayed while awaiting confirmatory results. In mild cases, doxycycline or amoxicillin are the treatments of choice, whereas in severe cases, sodium penicillin G or ceftriaxone are recommended, the latter as second-line therapy in penicillin-allergic patients[7]. In the present case, the early initiation of ceftriaxone as empirical treatment was consistent with national recommendations and allowed control of infection progression, although the patient developed severe pulmonary and hepatic complications before recovery.

This report emphasizes that unfavorable progression with hepatic and respiratory involvement highlights the value of comprehensive multidisciplinary management combining epidemiological surveillance, stepwise microbiological diagnosis, and immediate antibiotic treatment. Such an approach, in accordance with the provisions established in the Public Health Surveillance Protocol for Leptospirosis, version 6 of the National Institute of Health of Colombia (2024), constitutes a determining factor in the survival of patients with severe leptospirosis.

CONCLUSION

The presented case corresponds to a patient with febrile icteric syndrome and a history of rodent exposure, an epidemiologically relevant sociodemographic factor. The clinical course included acute hepatic dysfunction, evidenced by marked direct hyperbilirubinemia, and severe pulmonary involvement in the form of acute respiratory distress syndrome secondary to leptospiral pneumonitis. The final confirmed diagnosis was Weil disease. This report unders-

cores the importance of considering this etiology in the diagnostic approach to febrile icteric syndromes, particularly in high-risk situations such as slaughterhouse workers, farmers, freshwater swimming, flooding, residence in areas with open sewage systems or inadequate waste management, among others, in order to facilitate timely and appropriate intervention.

Ethical Considerations

This case report was conducted in accordance with the principles of the World Medical Association Declaration of Helsinki and the guidelines of the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use Good Clinical Practice standards for research.

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Case report

Dorsal Pancreatic Agenesis: Case Presentation and Literature Review

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Abstract

Dorsal pancreatic agenesis (DPA) is an exceptionally rare congenital malformation resulting from the partial or complete absence of the dorsal pancreatic bud and accounts for fewer than 200 cases reported worldwide. We present the case of a 62-year-old man with insulin-requiring type 2 diabetes mellitus who presented with postprandial abdominal pain and obstructive jaundice. Initial tests showed a distended gallbladder without lithiasis and biochemical cholestasis. Magnetic resonance cholangiopancreatography (MRCP) revealed absence of the pancreatic neck, body, and tail, confirming DPA and ruling out surgically amenable biliary obstruction. Management was conservative, including hydration, analgesia, optimization of insulin therapy, and close monitoring. The patient showed clinical improvement, normalization of liver enzymes, and acceptable glycemic control, and was discharged with multidisciplinary follow-up to monitor long-term metabolic and pancreatic complications. This case highlights the importance of including DPA in the diagnostic algorithm of non-lithiasic obstructive jaundice, as well as the pivotal role of MRCP and endoscopic ultrasound in delineating ductal anatomy and preventing unnecessary interventions. It also underscores the need for a comprehensive approach that considers the increased risk of chronic pancreatitis, exocrine insufficiency, and potential neoplastic transformation of the ventral remnant.

Keywords

Pancreas; congenital abnormalities; magnetic resonance cholangiopancreatography; type 2 diabetes mellitus; obstructive jaundice.

INTRODUCTION

Dorsal pancreatic agenesis (DPA) is a very rare congenital malformation characterized by the complete or partial absence of the portions derived from the dorsal pancreatic bud, namely the neck, body, tail, minor papilla, and accessory duct of Santorini, resulting from a developmental error occurring between the fourth and seventh weeks of gestation, when the dorsal bud either fails to form or does not fuse adequately with the ventral bud[(1)]. This embryological defect is usually attributed to alterations in Hedgehog signaling, the retinoid gradient, and, more recently, to pathogenic variants in genes regulating pancreatic organogenesis, such as GATA6, HNF1B, PDX1, and PTF1A, among others[(2,3)].

Since the first anatomical description made by Daly and colleagues in 1911, the number of confirmed cases has increased from 53 in 2008 to approximately 134 in 2021,

and continues to rise thanks to the dissemination of magnetic resonance cholangiopancreatography and the greater availability of endoscopic ultrasound (EUS); the most recent series estimate that more than 160 cases had been published by 2025[2,4].

DPA may coexist with other midline malformations, including polysplenia, intestinal malrotation, biliary and renal anomalies, as well as various mucinous and solid-cystic pancreatic neoplasms, suggesting a shared genetic and embryological background(2,4–6).

Initial suspicion may arise from the absence of retrogastric pancreatic tissue on different diagnostic imaging studies (computed tomography or ultrasonography); however, definitive ductal characterization is obtained through secretin-stimulated magnetic resonance cholangiopancreatography (MRCP) or endoscopic retrograde cholangiopancreatography (ERCP). EUS provides high-resolution imaging to rule out associated masses and evaluate glandular reserve[1,3–5].

The case of a patient with DPA is presented as a starting point for a narrative review focused on its clinical presentation and its inclusion within the differential diagnosis of abdominal pain and obstructive jaundice, with emphasis on embryogenetic advances, high-precision imaging modalities, and endocrine-metabolic follow-up strategies.

CLINICAL CASE

A 62-year-old male patient with a 10-year history of insulin-requiring type 2 diabetes *mellitus* and well-controlled arterial hypertension presented to the emergency department with an eight-day history of postprandial abdominal pain in the upper abdomen, maximal in the right hypochondrium, colicky in nature, radiating from the flank to the ipsilateral upper lumbar region, with no relief from rest or antispasmodic agents. The pain was accompanied by multiple episodes of vomiting, initially consisting of food contents and later becoming bilious. The symptoms worsened on the day prior to presentation. The patient denied fever, malaise, acholic stools, choluria, or self-reported weight loss.

Physical examination revealed pain on deep palpation of the right hypochondrium, without signs of peritoneal irritation, masses, or organomegaly; renal percussion tenderness was negative. Of note, jaundice of the skin and mucous membranes was observed upon admission, which had not been previously perceived by the patient. Hemodynamic parameters were within normal limits. Admission laboratory tests showed leukocytosis with neutrophilia, hyperbilirubinemia predominantly involving the direct fraction, and a cholestatic pattern with marked elevation of alkaline phosphatase and γ-glutamyl transferase, in addition to glycemic decompensation and mild renal dysfunction (**Table 1**). Initial abdominal ultrasonography reported a distended gallbladder (105 × 40 mm) with a 4-mm wall thickness and no visible gallstones despite an adequate acoustic window.

With these findings, the condition was initially interpreted as a cholestatic jaundice syndrome under investigation. Although the presence of a distended gallbladder without gallstones transiently raised the possibility of acalculous cholecystitis or functional gallbladder distension, the severity of the cholestatic pattern and the presence of overt jaundice primarily suggested obstructive jaundice syndrome. Consequently, conservative management was initiated with hydration, analgesia, metabolic optimization, and broad-spectrum antibiotics while an infectious etiology was being ruled out. Serologic testing for hepatotropic viruses and leptospira, as well as other infectious and immunologic etiologic studies, yielded negative results.

During hospitalization, the pain progressively subsided; however, glycemic lability was documented, with blood glucose levels >300 mg/dL despite adjustments to the insulin regimen every 48 hours, along with persistence of clinical jaundice and cholestatic abnormalities on serial follow-up tests, without complete normalization of bilirubin levels during the hospital stay. Given the combination of jaundice, a distended gallbladder, and biochemical abnormalities, the general surgery service considered the possibility of obstructive jaundice syndrome of probable periampullary origin, raising the hypothesis of a neoplastic proliferative process (Courvoisier-Terrier sign). Upper gastrointestinal endoscopy revealed no lesions in the duodenal bulb or second portion of the duodenum, nor any signs of a periampullary tumor.

Magnetic resonance cholangiopancreatography (MRCP) was requested as the imaging modality of choice for characterization of the biliary tract and pancreas. This examination confirmed gallbladder distension without gallstones or dilation of the main biliary tract, mild hepatomegaly, a small volume of free fluid, and absence of the pancreatic body and tail, findings consistent with congenital dorsal pancreatic agenesis (**Figure 1**). Surgical obstructive pathology was therefore ruled out, and the hypothesis of periampullary neoplasia initially suggested by the surgical team was reconsidered. Endoscopic retrograde cholangiopancreatography (ERCP) was evaluated as a complementary diagnostic procedure; however, it was deferred because of the absence of evidence of mechanical obstruction on MRCP, the patient's clinical stability, and the non-negligible risk of post-procedural pancreatitis. The treating center does not have access to secretin-enhanced magnetic resonance imaging or pancreatobiliary endoscopic ultrasonography. Due to limitations in availability and insurance coverage, these studies could not be performed,

Table 1. Follow-up Laboratory Findings of the Patient

Laboratory Test	Patient Value	Reference Range
Hemoglobin	14 g/dL	Men: 13,5-17.5 g/dL Women: 12,0-15.5 g/dL
Hematocrit	42%	Men: 41%-53% Women: 36%-46%
Leukocytes	13,470 × 10^3/mm^3	4.5-11 × 10^3/mm^3
Neutrophils	12,160 × 10^3/mm^3	1.5-8.0 × 10^3/mm^3
Lymphocytes	610 × 10^3/mm^3	1.0-4.0 × 10^3/mm^3
Platelets	329,000 × 10^3/mm^3	150-400 × 10^3/mm^3
Sodium	131 mmol/L	136-145 mmol/L
Potassium	4.73 mmol/L	3.6-5.5 mmol/L
Chloride	96 mmol/L	95-108 mmol/L
Amylase	44 U/L	25-115 U/L
Lipase	118 U/L	73-393 U/L
Alkaline phosphatase	766 U/L	46-116 U/L
AST (SGOT)	184 U/L	15-37 U/L
ALT (SGPT)	253 U/L	16-63 U/L
γ-glutamyl transferase	1,878 U/L	15-85 U/L
LDH	178 U/L	85-227 U/L
Creatinine	1.70 mg/dL	0.70-1.30 mg/dL
BUN	24 mg/dL	7-18 mg/dL
Glucose	452 mg/dL	74-106 mg/dL
Total bilirubin	5.7 mg/dL	0.2-1.0 mg/dL
Direct bilirubin	5.5 mg/dL	0.0-0.2 mg/dL
Indirect bilirubin	0.2 mg/dL	≤0.76 mg/dL
C-reactive protein	31.4 mg/dL	<0.3 mg/dL
HbA_{1c}	11.3 %	Diabetes ≥6.5 %
Anti-hepatitis C	Negative	Negative
Leptospira IgG/IgM	Negative	Negative
Hepatitis A IgG	>100 mIU/mL	Reactive >20 mIU/mL
Hepatitis A IgM	0.25 UI	Reactive >1.2 UI
HBsAg	Negative	Negative
HIV	Negative	Negative
CMV IgM	0.27 (UI)	Negative <0.90
CMV IgG	9.55 (UI)	Positive >1.1
Free T_4	1.27 ng/dL	0.8-2.2 ng/dL
Total T_3	3.81 ng/mL	0.8-2.0 ng/mL
TSH	2.47 µIU/mL	0.4-4.0 µIU/mL
ANA	Negative	Negative
Total IgG	1,116 mg/dL	650-1,600 mg/dL
PT (patient/control)	9.5 s/11.4 s	11-13.5 s
INR	0.9	0.8-1.2
aPTT (patient/control)	26.6 s/27.3 s	25-35 s
Urine pH	6.0	4.6-8.0
Urine specific gravity	1.015	1.005-1.030
Glycosuria	1,000 mg/dL	Negative
Proteinuria	30 mg/dL	Negative
Urinary leukocyte sediment	0-2 × field	≤5 × field
Urinary red blood cell sediment	0-2 × field	≤3 × field
Bacterias en orina	Positive (+)	Negative

ALT (SGPT): alanine aminotransferase; ANA: antinuclear antibodies; aPTT: activated partial thromboplastin time; AST (SGOT): aspartate aminotransferase; BUN: blood urea nitrogen; CMV: cytomegalovirus; HBsAg: hepatitis B surface antigen; HbA_{1c}: glycated hemoglobin; HIV: human immunodeficiency virus; IgG: immunoglobulin G; IgM: immunoglobulin M; INR: international normalized ratio; LDH: lactate dehydrogenase; PT: prothrombin time; TSH: thyroid-stimulating hormone. Author's own research.

although they were recommended as complementary evaluations during outpatient follow-up, in accordance with the literature regarding detailed functional and anatomical assessment of the pancreatic duct in dorsal agenesis.

The endocrinology service documented a glycated hemoglobin level of 11.3% and adjusted the insulin regimen in conjunction with intensive education on self-monitoring and home glucose monitoring. No specific genetic studies were performed to rule out variants associated with congenital pancreatic malformations, and consideration of such testing was deferred to referral centers for long-term follow-up. The patient evolved with complete resolution of pain, progressive decline in liver enzyme levels, and improvement in glycemic control following optimization

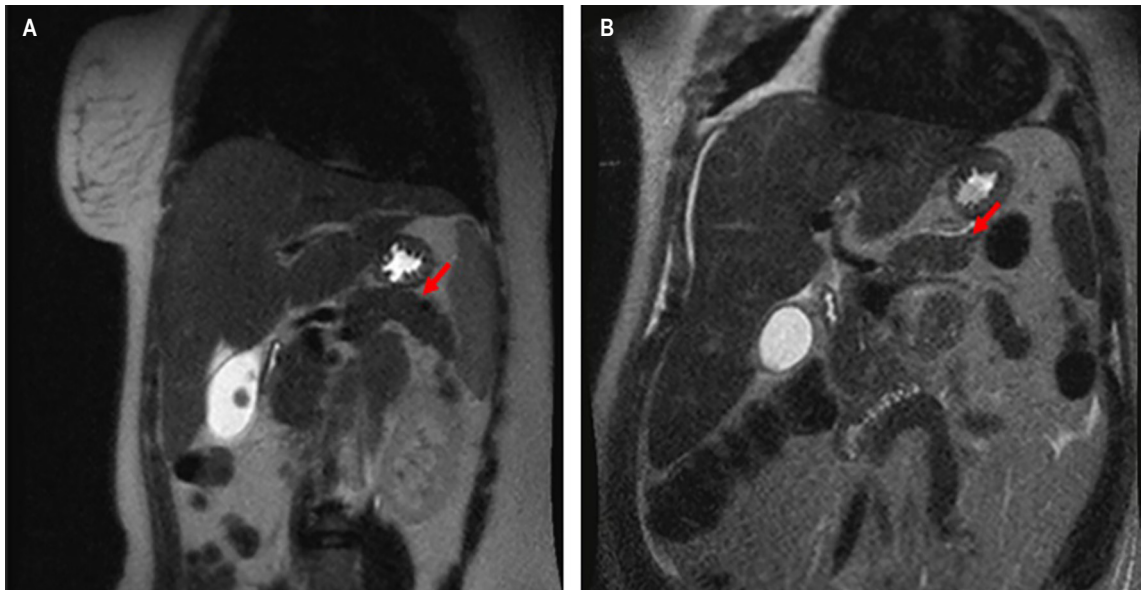


Figure 1. ERCP examination from the clinical case. **A.** Coronal T2-weighted magnetic resonance cholangiography image demonstrating normal pancreatic anatomy (arrow). **B.** Axial T2-weighted magnetic resonance cholangiography image from the patient showing evidence of pancreatic tail agenesis (arrow). Author's file.

of treatment. He was discharged on hospital day 12 with combined follow-up by gastroenterology, endocrinology, and surgery, aimed at monitoring pancreatic exocrine and endocrine function, as well as excluding long-term biliary or pancreatic complications.

DISCUSSION

Definition and Classification

Dorsal pancreatic agenesis (DPA) is an extremely rare congenital anomaly in which the dorsal pancreatic bud fails to develop or undergoes partial or complete involution[1,4]. Two morphological phenotypes are distinguished: complete DPA, characterized by absence of the neck, body, tail, minor papilla, and accessory duct of Santorini; and partial DPA, in which variable portions of the body, minor papilla, or duct of Santorini persist[1,4,6].

The terms *short pancreas* and *pancreatic hypoplasia* have also been described in the literature and correspond to incomplete expressions of the same embryological alteration[1].

Epidemiology

Since the first case identified at autopsy in 1911, reports have increased with the dissemination of MRCP and EUS[2–4]. The most recent systematic reviews include between 68 and 106 published cases from 1913 to 2021, although case series and isolated reports raise the number to approximately 150–160 patients by 2025[7]. The true population prevalence remains uncertain; data from radiologic series place it at 1–2 per 10,000 abdominal examinations[2,4,7].

Embryogenesis and Etiopathogenesis

Pancreatic organogenesis occurs between the fourth and seventh weeks of gestation with the formation of two endodermal buds: the ventral bud, which gives rise to the future uncinate process and the caudal half of the pancreatic head, and the dorsal bud, which corresponds to the cranial half of the head, neck, body, and tail. Between weeks 6 and 7, the duodenum rotates and both buds fuse, giving rise to the main duct of Wirsung and, secondarily, the accessory duct of Santorini (**Figure 2**)[1,4].

Alterations in the Hedgehog pathway, the retinoid gradient, and, most notably, pathogenic variants in genes regulating pancreatic organogenesis listed in **Table 2** have been implicated[2,9–11].

Most cases continue to be considered sporadic; however, autosomal dominant patterns and X-linked inheritance have been described in families with heterotaxy and polysplenia[1].

Clinical Manifestations

Sixty percent of patients with DPA remain asymptomatic, and the diagnosis is made incidentally. In symptomatic patients, the predominant manifestations are chronic or recurrent epigastric pain (approximately 90%), proba-

bly secondary to sphincter of Oddi dysfunction or ductal hypertension of the ventral remnant. Diabetes *mellitus* may also occur (40%–60%), usually requiring insulin therapy, and is attributed to the loss of β-islet cells in the body and tail. Acute or chronic pancreatitis, steatorrhea, and weight loss have been reported in a small percentage of cases associated with overt exocrine insufficiency in <10%[1,4,12]. Other findings include obstructive jaundice syndrome, biliary complications, and associated cystic nephropathy.

Imaging Diagnosis

Contrast-enhanced computed tomography suggests the anomaly by demonstrating absence of pancreatic parenchyma anterior to the splenic vein; gastric or jejunal interposition produces the "dependent stomach/intestine sign"[4,7,12].

Abdominal magnetic resonance imaging with T2-weighted sequences and secretin-stimulated MRCP constitute the diagnostic modalities of choice because they delineate the ductal tree, confirm the absence of the dorsal duct, and rule out pseudoagenesis or atrophy secondary to pancreatitis. Three-dimensional reconstruction increases sensitivity without generating radiation exposure or risk of procedure-induced pancreatitis[1,3,4].

EUS provides the best parenchymal resolution and allows characterization and sampling of incidental space-occupying lesions. ERCP is reserved for cases in which therapeutic intervention with sphincterotomy or stent placement is being considered[13].

Associated Diseases and Malformations

DPA is associated with midline anomalies such as polysplenia, heterotaxy, wandering spleen, and intestinal malrotation; urologic abnormalities such as horseshoe kidney and renal dysplasia; cardiac abnormalities such as tetralogy of Fallot and coarctation; and gynecologic abnormalities such as uterus didelphys[9–12].

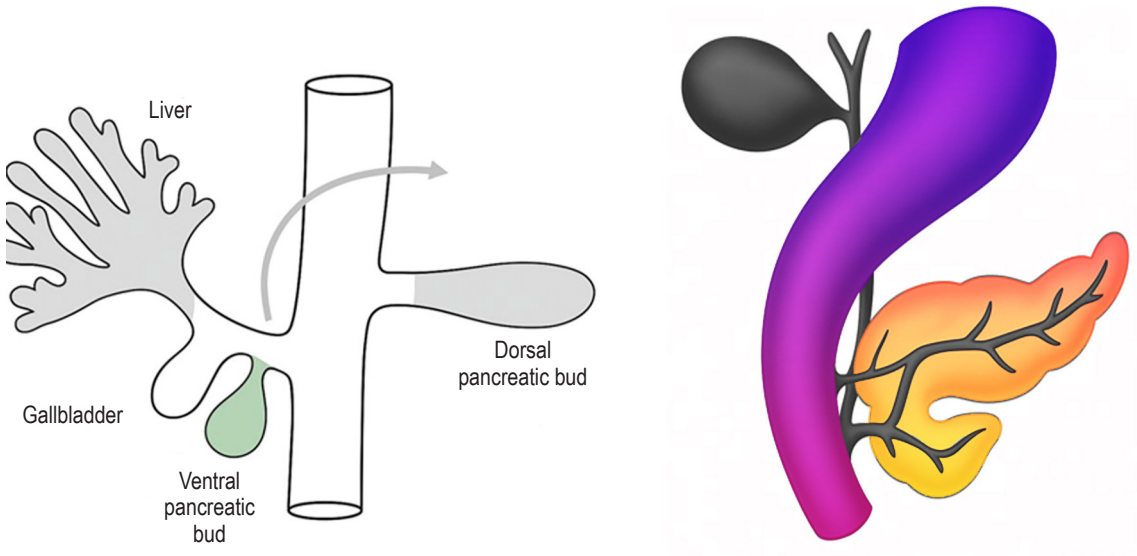


Figure 2. Embryologic development of the pancreas. Adapted from: Suckale J and colleagues. Front Biosci. 2008;13:7156-71[8].

Table 2. Genes Implicated in Dorsal Pancreatic Agenesis

Gene	Proposed Mechanism	Clinical Evidence
HNF1B	Early regulation of dorsal progenitor cells	Heterozygous mutations associated with DPA, diabetes, and cystic nephropathy
GATA6	Essential for proliferation and branching of pancreatic endoderm	Haploinsufficiency associated with agenesis and neonatal diabetes
PDX1 (MODY-4)	Transcription of islet-cell genes	Partial DPA associated with juvenile-onset diabetes

Author's own research.

Over the last 15 years, multiple pancreatic neoplasms associated with DPA have been described, including neuroendocrine tumors, mucinous tumors, and adenocarcinomas. Although causality has not been established, underlying chronic pancreatitis and regenerative stimulation of the ventral remnant could constitute a risk setting because of the unregulated inflammatory response[1–3].

Differential Diagnosis

Differential diagnoses that should be considered include pseudoagenesis secondary to pancreatic atrophy following chronic pancreatitis; distal pancreatic lipomatosis, in which the parenchyma is replaced by fat while the dorsal duct remains intact; pancreas divisum, in which the body and tail are normal and dual Wirsung-Santorini drainage is preserved; and finally, carcinoma of the pancreatic head with retrograde atrophy and cystic tumors of the body and tail[6,7,12].

Treatment and Follow-up

Given its rarity, there is no established treatment for DPA[1]. Patients with DPA are commonly treated according to their symptoms. Based on the clinical manifestations reported in DPA cases, recommendations are focused on low-fat dietary modifications and diabetes control as the primary treatment measures[3,4]. The use of analgesics is recommended for pain management, as well as pancreatic enzymes, which decrease pancreatic secretion and relieve pain. Patients with DPA associated with pancreatitis and pancreatic duct abnormalities may benefit from sphincterotomy. Endoscopic treatment is presented as an alternative to overcome ductal resistance to pancreatic flow[4,6,13].

Prognosis

The prognosis is generally favorable if pain and metabolic complications are adequately controlled. Nevertheless, the coexistence of chronic pancreatitis or neoplasia requires prolonged multidisciplinary follow-up.

CONCLUSIONS

Dorsal pancreatic agenesis, although exceptional, should be systematically incorporated into the differential diagnosis of recurrent abdominal pain and obstructive jaundice, especially when initial studies rule out evident lithiasic or neoplastic causes. This case highlights three cardinal points. First, the importance of considering congenital pancreatic malformations when initial diagnostic imaging is inconclusive; MRCP and EUS have become indispensable techniques for delineating ductal anatomy and avoiding unnecessary surgical interventions. Second, the relevance of a multidisciplinary approach: close collaboration among gastroenterology, surgery, radiology, and endocrinology enables timely diagnosis, optimizes glycemic control, and identifies associated complications such as pancreatitis or exocrine insufficiency. Third, the need for long-term follow-up because of the increasing risk of chronic pancreatitis and possible neoplastic transformation in the ventral remnant. In summary, DPA, although uncommon, should be considered in the diagnostic algorithm for abdominal pain and jaundice; early detection and a structured surveillance plan are essential to improve clinical outcomes and patient quality of life.

Conflict of Interest

The authors declare no conflicts of interest regarding this clinical case.

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Case report

Bacteremia Due to *Bacillus clausii* (*Alkalihalobacillus clausii*): An Emerging Concern—Report of Two Cases

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Abstract

Background: The impact of probiotics on the control and management of diarrheal disease, both acute and chronic, has been significant in recent years. One example is the frequent use of *Bacillus clausii*, currently known as *Alkalihalobacillus clausii*, which is widely administered across diverse populations, from children to older adults. However, an emerging concern has arisen for which high-impact epidemiological data are lacking; few descriptive studies exist, and most reports consist of case reports, such as bacteremia caused by *B. clausii*. This bacterium exhibits a broad intrinsic resistance profile, complicating eradication and requiring prolonged antimicrobial regimens. **Case summary:** This report presents two cases, each with immunosuppressive conditions (invasive lung carcinoma and myelodysplastic neoplasm), who received treatment with *B. clausii* during medical care. Both developed systemic inflammatory response requiring vasoactive support, mechanical ventilation, and broad-spectrum antibiotics, with *B. clausii* isolated from peripheral blood cultures and identified by spectrophotometry. Despite treatment, both patients had unfavorable clinical outcomes, ultimately resulting in death. **Conclusion:** Mortality in these patients is extremely high, particularly among immunocompromised individuals, underscoring the need for prudent use of probiotics to prevent this complication.

Keywords

Bacillus clausii; bacteremia; infectious diarrheal disease; immunocompromised host.

INTRODUCTION

Probiotics are live microorganisms that, when administered in adequate amounts, confer a health benefit on the host[(1)], according to the definition established by the International Scientific Association for Probiotics and Prebiotics. Among the most widely consumed worldwide are *Lactobacillus spp., Bifidobacterium spp., Saccharomyces spp., Bacillus spp., Enterococcus spp.,* and *Streptococcus spp*[(2)].

In particular, the genus *Bacillus* is known for its ability to produce spores, allowing it to survive in diverse environments (water, air, food, and soil) under extreme conditions, such as pH variations, although it cannot reproduce until environmental conditions become favorable[(2,3)]. Within this group, *Bacillus clausii*, currently known as *Alkalihalobacillus clausii*, stands out. It has been identified in the gastrointestinal microbiota and is capable of surviving in this environment, as well as exhibiting intrinsic resistance to several antimicrobials, including macrolides, aminoglycosides, and beta-lactams[(4,5)].

The use of probiotics has been evaluated in various gastrointestinal disorders, such as acute gastroenteritis, antibiotic-associated diarrhea, inflammatory bowel disease, and infections caused by *Clostridioides difficile* and

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Helicobacter pylori. Their mechanisms of action include restoration of intestinal microbiome balance, production of antimicrobial substances, strengthening of the mucosal barrier, generation of short-chain fatty acids, and modulation of the immune system and the gut-brain axis[6].

Systematic reviews have reported that probiotics generally exhibit a favorable safety profile; however, rare adverse events have been described, including bacteremia and bloodstream infection, in both immunocompetent and immunocompromised patients[7]. In the specific case of *B. clausii*, toxicological and clinical studies have demonstrated a low rate of adverse events and the absence of toxin-producing genes or transferable resistance mechanisms, supporting its classification as a generally safe probiotic[8].

Nevertheless, although these events are uncommon, cases of bacteremia associated with the use of probiotics such as *A. clausii* have been reported, particularly in immunocompromised patients, raising concern because of the difficulty in controlling and eradicating these infections and the potential risk of fatal outcomes. These complications may require prolonged antimicrobial therapy and, in some cases, multiple therapeutic rotations[7,8].

In this context, clinical evidence supports the usefulness of *A. clausii* in acute colitis, acute gastroenteritis, antimicrobial-associated diarrhea, irritable bowel syndrome, and as an adjunctive therapy in *Helicobacter pylori* infection[6], as well as its efficacy in acute diarrhea demonstrated in controlled clinical trials[9]. However, its use should be carefully evaluated in high-risk populations.

The following report presents two isolated cases of bloodstream infection in which *A. clausii* was isolated in immunocompromised patients, both with fatal outcomes.

CASE DESCRIPTION

Case 1

This was a 41-year-old male patient with a history of hospitalization for two months at a medium-complexity healthcare center due to respiratory symptoms, chest pain, and deterioration in functional class. He was diagnosed with septic shock of pulmonary origin, requiring invasive ventilatory support, antimicrobial therapy with linezolid and meropenem for 14 days, vasoactive support, and multiple procedures, including video-assisted thoracoscopy, thoracostomy, decortication, and biopsy collection. Vasoactive support was de-escalated on day 5, the patient was extubated on day 10, and, 20 days after the biopsy, a result suggestive of early invasive lung carcinoma was obtained, prompting transfer to a higher-complexity center for evaluation by clinical oncology.

Upon admission to the new hospital center, the patient presented signs of systemic inflammatory response with fever spikes above 38 °C, chills, and dyspnea. Chest radiography (**Figure 1**) and paraclinical findings suggested pulmonary empyema; therefore, he was transferred to the intensive care unit (ICU) due to hemodynamic instability with tachycardia, tachypnea, peripheral desaturation, and hypotension. Management was initiated with vasoactive support, antimicrobial therapy with a carbapenem and an oxazolidinone, and collection of two peripheral blood cultures.

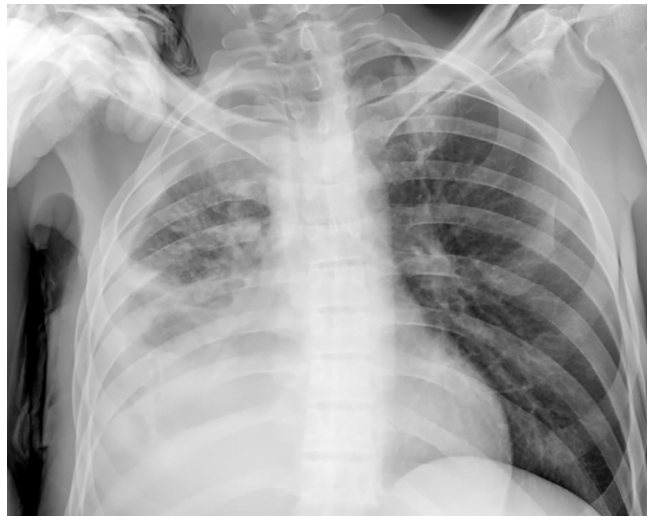


Figure 1. Chest radiograph showing blunting of the right costophrenic angle with decreased pulmonary parenchyma and right pleural effusion with interlobar effusion. Author's file.

On the second day in the ICU, the thoracic surgery service evaluated the patient and proposed abscessed lung carcinoma as the main diagnosis, requesting contrast-enhanced computed tomography (CT) of the chest (**Figure 2**). At 25 hours, blood cultures reported gram-positive bacilli identified as *B. clausii* by spectrophotometry. During rounds on the third day, questioning of both the patient and family members revealed that, during his stay at the referring institution, he had experienced high-output diarrheal stools treated with loperamide and *B. clausii*-type probiotics, with subsequent improvement.

The infectious diseases service evaluated the patient on the fourth day of hospitalization, considering the finding to be probable contamination; therefore, repeat blood cultures were ordered for follow-up and evaluation of antimicrobial rotation. On the fifth day, vasoactive support was successfully de-escalated, maintaining a mean arterial pressure above 65 mm Hg for 48 hours, and the patient was transferred to the general ward on the seventh day.

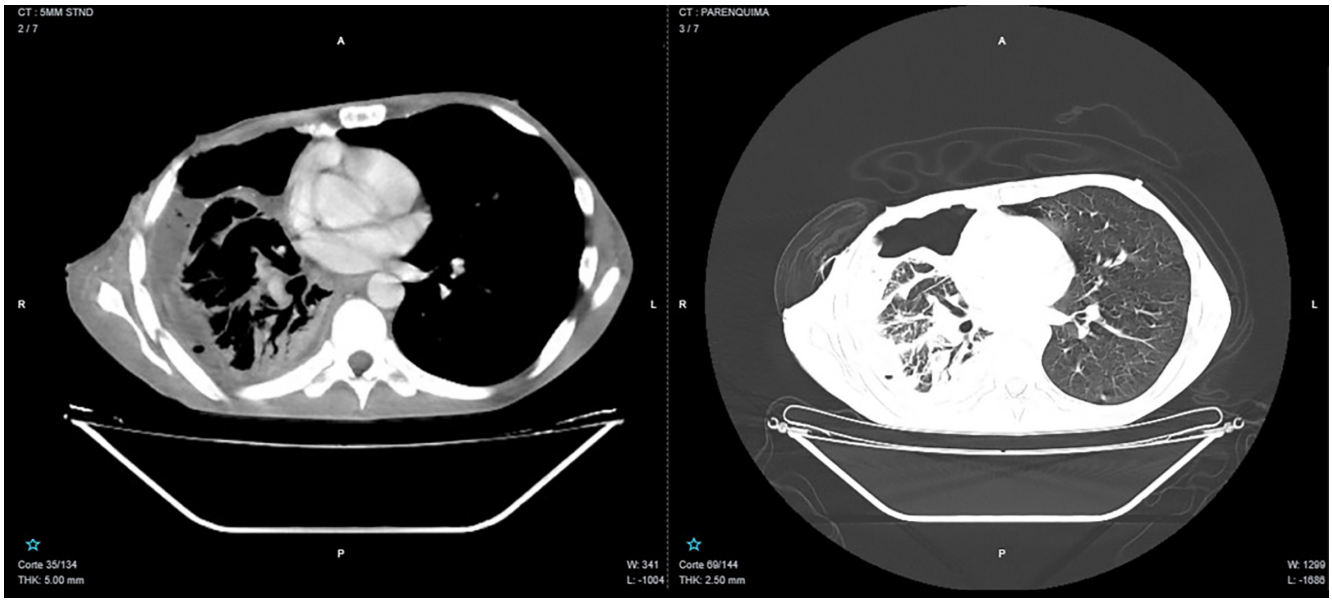


Figure 2. Contrast-enhanced chest CT with findings suggestive of multiple collections and loculated pleural effusion with residual pneumothorax. Author's file.

During the eleventh hospital day, thoracic surgery proposed a new thoracoscopy with decortication and biopsy, while clinical oncology requested a new sample to confirm the diagnosis and control the infectious source. At the end of the thirteenth hospital day, the patient again developed hemodynamic instability and impairment of respiratory mechanics and oxygenation indices, requiring high-flow oxygen therapy and readmission to the ICU. Follow-up blood cultures remained positive for *B. clausii* (**Figure 3**). The infectious diseases service indicated discontinuation of the oxazolidinone and carbapenem and initiation of therapy with a fluoroquinolone and a glycopeptide. However, the patient progressed to septic shock with multiple organ failure, requiring mechanical ventilation, continuous venovenous hemodiafiltration, and triple vasoactive support. The family signed a do-not-resuscitate order, and the patient subsequently died.

Case 2

A 68-year-old female patient with a history of myelodysplastic/myeloproliferative neoplasm was admitted due to a clinical presentation characterized by adynamia, asthenia, dizziness, and ecchymotic lesions on the upper extremities that had evolved over one month. She was evaluated by the hematology service and considered a candidate for hypomethylating therapy; therefore, hospitalization and initiation of azacitidine were indicated. On the fourth day of treatment, she developed liquid diarrheal stools and fever spikes, initially treated with loperamide plus *B. clausii*-type probiotics. However, due to persistence of symptoms, she received intravenous fluid therapy, antibiotic coverage with metronidazole, and total abdominal ultrasound, which demonstrated distended bowel loops with a large amount of fecal material, leading to the conclusion that she had intestinal obstruction.

The patient continued to deteriorate clinically, requiring vasopressor support and expansion of antibiotic coverage with meropenem and vancomycin. The general surgery service indicated emergency exploratory laparotomy, during which turbid peritoneal fluid (800 mL) was found, without other significant findings. Postoperatively, she was transferred to the intensive care unit (ICU) with a diagnosis of mixed septic and hypovolemic shock, with organ involvement evidenced by paraclinical findings, requiring vasoactive support, mechanical ventilation, and rotation to broad-spectrum antibiotics with meropenem and vancomycin. Prior to initiation of antimicrobial therapy, peripheral blood cultures and urine culture had been obtained upon admission.

The initial clinical course was favorable, and ventilatory weaning and withdrawal of support were achieved within 48 hours. However, clinical deterioration occurred during the following 24 hours, with respiratory distress and severe hypoxemia in a clinical picture compatible with acute pulmonary edema and bronchospasm. Noninvasive mechanical ventilation was required, but the response was poor, and she was intubated 20 hours after ventilatory weaning.

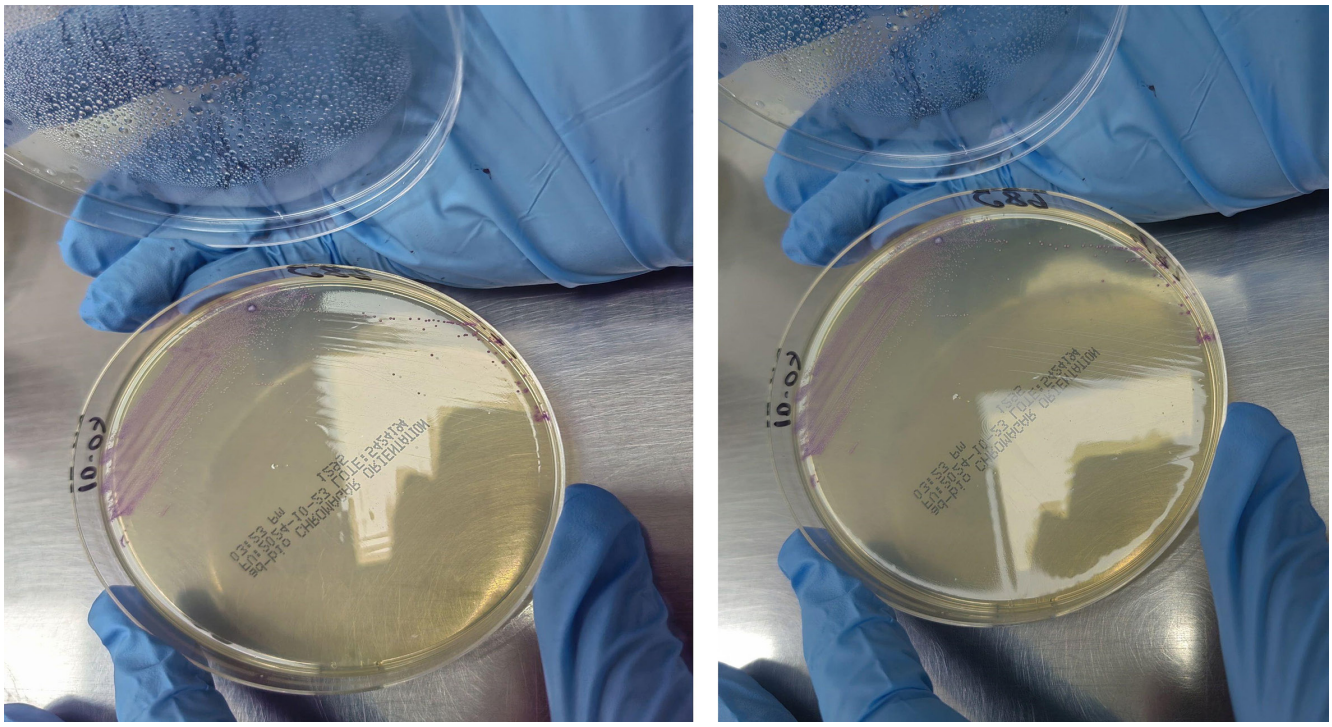


Figure 3. Chromogenic agar orientation medium showing small, round, violet-colored colonies of *B. clausii*. Author's file.

At 48 hours, blood cultures reported isolation of *B. clausii*. Samples were repeated and the same result was confirmed; therefore, the condition was classified as *B. clausii* bacteremia. Despite the antimicrobial therapy instituted, the patient showed poor clinical progression with septic shock secondary to bacteremia, requiring dual vasoactive support, but progressed to multiple organ failure and died after 19 days of ICU stay.

DISCUSSION

Two cases of bacteremia caused by *B. clausii* (*A. clausii*), a gram-positive bacillus, were presented in immunocompromised patients who had received this probiotic as part of the treatment for acute diarrheal disease. Both cases had fatal outcomes, attributable to a torpid clinical course and multiple organ dysfunction. This is an entity for which there are no clear epidemiological data regarding incidence and prevalence, given that the available literature mainly consists of case reports and a few case series at the international level, with very few cases described nationally.

The first case reported in Colombia was described by García and colleagues in 2021, in an 87-year-old patient with upper gastrointestinal bleeding, diarrhea of infectious origin, and recent use of a proton pump inhibitor. The most recent report, in 2024, described by Corredor and colleagues, corresponded to two cases in critically ill patients: one with ulcerative colitis dependent on life support and another with septic shock of pulmonary and soft tissue origin, with a history of heart failure, hypertension, and hypothyroidism, both with fatal outcomes[10,11].

A common factor in all reports was prior use of *B. clausii*-type probiotics during hospitalization, a finding that was also observed in our patients. Shared predisposing factors included immunodeficiency (invasive lung cancer and hematologic neoplasm) and critical illness, conditions that promote gastrointestinal system dysfunction and disruption of the intestinal barrier, thereby facilitating bacterial translocation. These processes may be potentiated by the use of multiple medications, antibiotics, vasoactive agents, proton pump inhibitors, and prolonged hospitalizations[12,13].

Previously reported cases were described in two regions of Colombia; however, after searching databases such as PubMed, Ovid, Google Scholar, Cochrane, and Scopus, no documented reports were found in the Caribbean region.

This is not the first time such cases have been described in immunocompromised patients, as approximately two cases involving stage IV lung cancer patients presenting with pneumonia were reported by Gargar and colleagues

in 2019[14]. These authors observed that, when facing acute or chronic diarrhea in oncology patients, there are no standard protocols for the appropriate use of these probiotics. As described by Díaz-Madriz and colleagues, whose study analyzed cases of *B. clausii* bacteremia, the mean age of affected patients was 71 years, all patients had some degree of immunosuppression, and most received treatment with levofloxacin and vancomycin, with fatal outcomes in three of the four identified patients, leading to the conclusion that extreme caution should be exercised when administering these agents in immunocompromised and elderly patients[15]. Accordingly, for cases such as ours that meet these risk factors and conditions, safe probiotic administration protocols and standardized management protocols for acute diarrheal disease should be developed in the previously mentioned settings to prevent fatal outcomes.

In our cases, both patients had fatal outcomes despite receiving early antimicrobial therapy. Given the intrinsic resistance of *B. clausii*, future therapeutic strategies are required to optimize the management of these infections. Authors such as Corredor, García, Gargar, and Díaz[10,11,14,15] have documented the need for prolonged antimicrobial regimens (longer than four weeks) in surviving patients, with persistence of positive blood cultures. These data highlight the importance of strengthening clinical recognition of this entity and developing timely prevention and management strategies.

CONCLUSION

B. clausii bacteremia represents an emerging infection with high clinical impact, characterized by elevated mortality and difficulty in eradication, as observed in the cases described. Before indicating the use of probiotics, the therapeutic decision should be individualized by considering each patient's risk factors, especially in immunocompromised individuals. It is essential to promote studies that allow better understanding of this entity and to establish institutional and international protocols for the safe and rational use of probiotics in both outpatient and inpatient settings.

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Case report

The Role of Colonoscopy in a Hostile Abdomen: Successful Management of a Coloatmospheric Fistula Due to Late Iatrogenic Perforation

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Abstract

Objective: To report the contribution of endoscopic management in the therapeutic approach to a patient with complex late colonic perforation and enteroatmospheric fistula, highlighting its impact on treatment, clinical course, and relevance as a minimally invasive tool in medical practice. **Case report:** We present the case of a patient with a fistula at the splenic flexure of the colon, secondary to a late perforation caused by a retroperitoneal and perisplenic abscess following nephrectomy. The clinical course was marked by a hostile abdomen resulting from multiple surgical interventions, including peritoneal lavage and the use of negative pressure therapy. Despite these measures, adequate fistula control was not achieved. Given the complexity of the condition and lack of response to conventional treatment, the patient underwent endoscopic management as a therapeutic alternative. **Conclusion:** Endoscopic management using hemoclips represents an effective and safe alternative for the closure of colonic fistulas in patients with a hostile abdomen. It reduces hospital stay and avoids major surgical reinterventions, thereby promoting full recovery.

Keywords

Colonoscopy; clips; endoscopy; intestinal perforation.

INTRODUCTION

Coloatmospheric fistulas are traditionally managed surgically, either through primary repair in acute settings or by means of more extensive colonic resections and stoma creation, which increases morbidity and mortality in these patients. The literature describes successful endoscopic management of early colonoscopic colonic perforations treated immediately with hemoclips or over-the-scope clips (OTSC), depending on the size of the perforation[1,2]. However, the available literature provides limited data regarding the effectiveness of endoscopic management in the setting of coloatmospheric fistulas, particularly in patients with a hostile abdomen. We present a case of successful endoscopic closure of a fecal fistula using hemoclips, which resulted in favorable and satisfactory clinical outcomes.

CASE PRESENTATION

A 60-year-old female patient was initially managed at a lower-complexity institution with left nephrectomy and drainage of a psoas abscess through a lumbotomy. She was subsequently referred to a higher-level center, where the general surgery team performed a laparotomy with drai-

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nage of a perisplenic abscess, splenectomy, and placement of a subatmospheric pressure system because of persistent contamination of the abdominal cavity.

During one of the peritoneal washouts, a colonic fistula at the splenic flexure was identified, which could neither be controlled nor localized (**Figure 1**), resulting in ongoing intra-abdominal contamination in the setting of a hostile abdomen. Its location was confirmed by a contrast enema study (**Figure 2**). An endoscopic closure attempt was subsequently performed, and during colonoscopy indigo carmine was applied, allowing precise identification of the fistulous site at the splenic flexure of the colon, a region that is difficult to approach because of its anatomical configuration. Two hemoclips were placed, achieving complete closure of the fistula (**Figure 3**). The effectiveness of the procedure was confirmed by contrast enema (**Figure 4**). This allowed progressive closure of the abdominal cavity, with favorable clinical evolution (**Figure 5**).

DISCUSSION

The management of intestinal fistulas continues to represent one of the greatest challenges in gastrointestinal surgery, particularly when they occur in the setting of a hostile abdomen or after delayed colonic perforation. Their management requires a comprehensive evaluation that considers anatomical, physiological, and clinical factors, including the location of the defect, its size, duration, degree of peritoneal contamination, and the patient's overall condition. Traditionally, surgical management has constituted the cornerstone of treatment, aimed at controlling the septic focus, resecting the affected segment, and restoring intestinal continuity whenever possible[3,4]. However, this strategy is associated with considerable morbidity and mortality, particularly in patients with established sepsis secondary to extensive contamination of the peritoneal cavity, which triggers a systemic inflammatory cascade and rapid clinical deterioration, increasing mortality to as high as 40% in cases of severe sepsis[5].

In this setting, technological advances in therapeutic endoscopy have enabled the development of less invasive alternatives for the management of gastrointestinal fistulas and have consolidated clip closure as a minimally invasive alternative to conventional surgical treatment. Endoscopic clip closure, whether using conventional devices or OTSC systems, has demonstrated promising results in the upper gastrointestinal tract, particularly in esophageal and gastroduodenal fistulas and perforations of iatrogenic, postoperative, or spontaneous origin (6–8).

In the colon, the application of this technique has been described mainly for the management of perforations secondary to colonoscopic procedures and has



Figure 1. Open abdomen with a subatmospheric pressure system and a non-localized coloatmospheric fistula. Author's file.

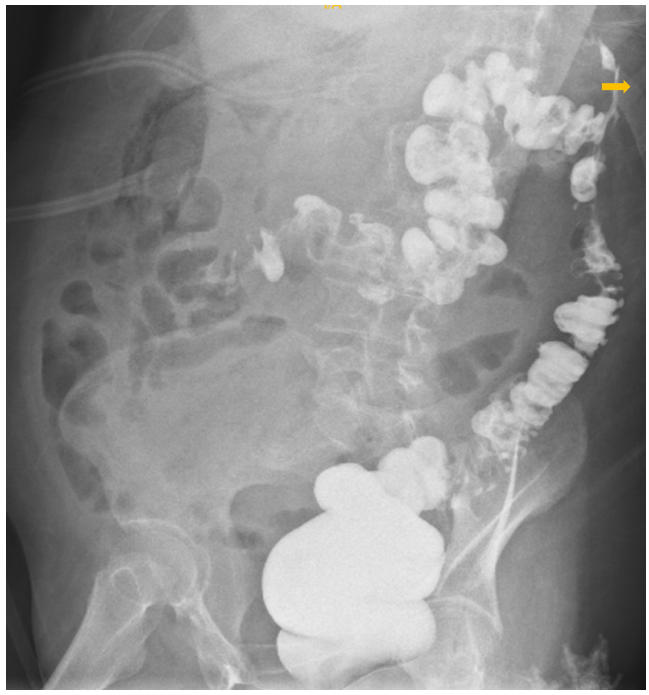


Figure 2. Fistula at the splenic flexure of the colon (yellow arrow). Author's file.

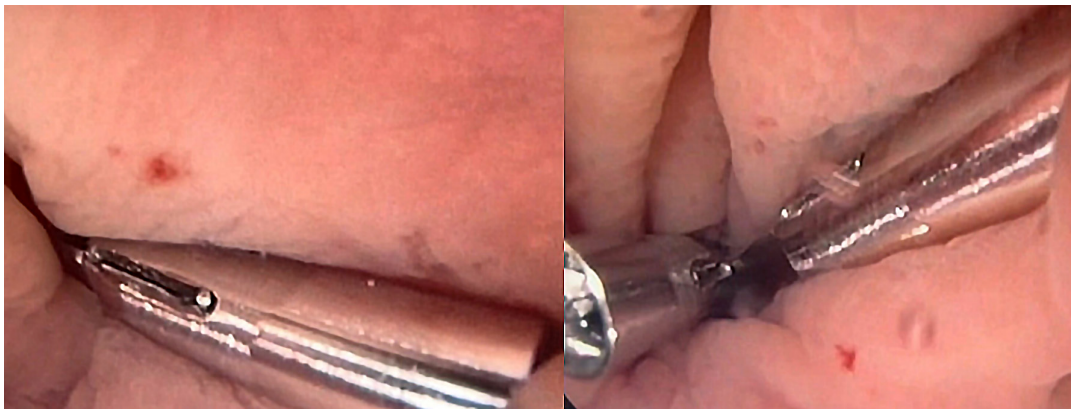


Figure 3. Endoscopic closure of the coloatmospheric fistula using two hemoclips. Author's file.

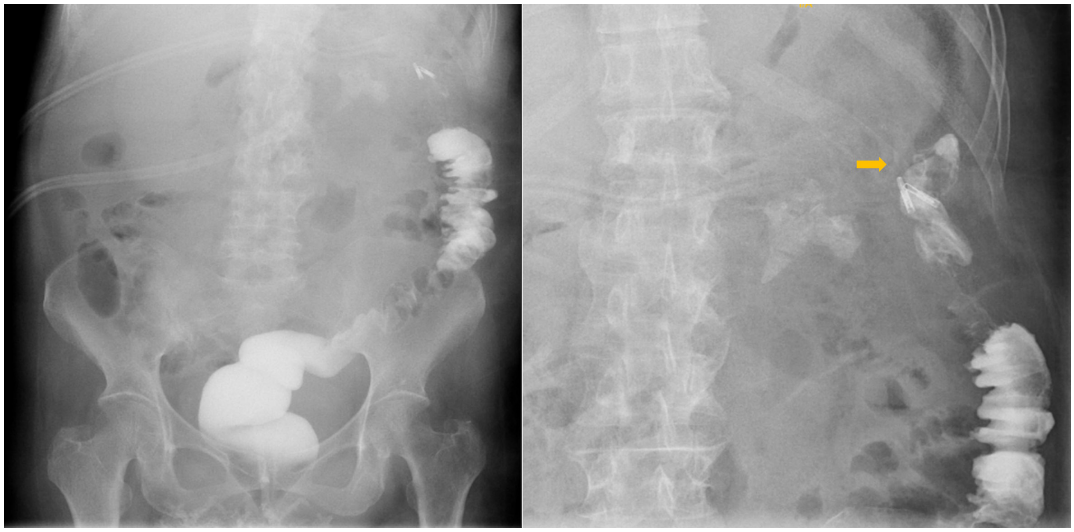


Figure 4. Adequate filling of the rectal ampulla and the sigmoid and descending colon. Passage of contrast medium through the site of hemoclip placement is observed, with no evidence of fistulous tracts (yellow arrow). Images property of the authors. Author's file.



Figure 5. Progressive closure of the abdominal cavity with adequate control of contamination. Author's file.

shown encouraging results in terms of efficacy and safety. Nevertheless, the success of this strategy depends largely on appropriate patient selection, and ideal candidates are those without established fecal peritonitis who maintain stable hemodynamic and physiological conditions. In this context, early identification of the lesion, tissue edge viability, and the availability of an experienced colonoscopist are key determinants of a favorable prognosis[9–11].

The available evidence regarding endoscopic repair of colocutaneous fistulas in the setting of a contaminated and hostile abdomen remains limited. Although some successful cases have been reported in postoperative settings (12–14), the available data are still insufficient to establish strong recommendations for its implementation. Preprocedural assessment using imaging studies such as fistulography, contrast enema, and contrast-enhanced computed tomography allows more accurate planning of the therapeutic strategy, optimizing localization of the fistulous tract and reducing the risk of therapeutic failure[15]. Assessment of defect characteristics, including size, anatomical location, and edge viability, constitutes a critical aspect in selecting the therapeutic approach. Furthermore, the choice of endoscopic device should be individualized according to the size and morphology of the defect: conventional clips are useful for small perforations (<10 mm), whereas OTSC systems or endoscopic suturing are reserved for larger lesions or those with irregular edges[15,16].

In our case, the location of the fistula was confirmed through both clinical evaluation and imaging studies, which enabled pre-colonoscopy planning and facilitated localization of the fistula. Endoscopic closure was successfully performed using two hemoclips guided by indigo carmine staining, and adequate exclusion of the fistulous tract with passage of contrast medium into the proximal colon was subsequently confirmed. This result favored progressive closure of the abdominal cavity by controlling the source of contamination, thereby avoiding the need for proximal diversion and resulting in a satisfactory clinical outcome. The experience of the colonoscopist and appropriate patient selection are consolidated as fundamental factors for the success of this strategy, especially in complex scenarios such as a hostile abdomen. Although surgery continues to be the therapeutic cornerstone in most cases, endoscopic closure may be considered a valid alternative in carefully selected patients, provided that the necessary resources and expertise are available.

Nevertheless, the absence of prospective studies and large case series constitutes a significant limitation, emphasizing the need for additional research to more precisely define the role of endoscopic management within the therapeutic algorithm for colocutaneous fistulas.

CONCLUSION

In cases of delayed colonic perforation, surgical management remains the first-line therapy. Endoscopic management constitutes an effective and safe alternative, in expert hands, for the closure of colonic fistulas in patients with a hostile abdomen, allowing reduction of hospital stay and avoidance of major surgical reinterventions, thereby promoting complete patient recovery.

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Case report

Gastric Adenocarcinoma in Two Adolescents with Genetic Predisposition: A Case Report

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Abstract

Introduction: Gastric tumors in pediatric patients are extremely rare, posing diagnostic and therapeutic challenges due to limited medical literature and nonspecific clinical presentation. **Case report:** Two cases of 13-year-old adolescents with no relevant medical history are reported, both presenting with nonspecific gastrointestinal symptoms. Both were diagnosed with stage IV diffuse gastric adenocarcinoma through upper gastrointestinal endoscopy with biopsy and immunohistochemistry. Rapid tumor progression and resistance to chemotherapy were observed. The first case was associated with Lynch syndrome, and the second met criteria for hereditary diffuse gastric cancer (HDGC). **Discussion:** These tumors exhibit high aggressiveness and poor response to treatment, which is associated with delayed diagnosis and probable genetic predisposition. Currently, no specific pediatric protocols exist; therefore, management is based on adult guidelines, with limited outcomes in this population. **Conclusion:** It is essential to maintain a high index of clinical suspicion in the presence of persistent or nonspecific symptoms, implement early genetic screening, and adopt a multidisciplinary approach. Further research on hereditary syndromes and the development of pediatric-specific guidelines are needed to achieve earlier diagnosis and improve prognosis.

Keywords

Gastric cancer; adenocarcinoma; adolescent; pediatrics; abdominal pain.

INTRODUCTION

Gastrointestinal malignant tumors commonly occur during the sixth and seventh decades of life, whereas in childhood and adolescence they are extremely rare and aggressive, accounting for approximately 5% of all pediatric neoplasms. Gastric adenocarcinoma represents 0.05% of all gastrointestinal neoplasms[1]. Gastric carcinoma exhibits aggressive behavior and is usually diagnosed at advanced stages because its initial symptoms are nonspecific, including abdominal pain, emesis, anemia, diarrhea, and weight loss[2,3].

In children and adolescents, the genetic factor becomes more relevant and is usually present in 10% of cases[4]. Clinical aggressiveness may be associated with hereditary syndromes such as hereditary diffuse gastric cancer (HDGC) caused by a mutation in the CDH1 gene, or Lynch syndrome due to loss of expression of MLH1, MSH2, MSH6, or PMS2. Both exhibit an autosomal dominant inheritance pattern and extensive metastatic dissemination. The diffuse subtype, characterized by the presence of signet ring cells, confers a poorer prognosis and poor response to chemotherapy, sometimes associated with a family history of cancer or occurring in its absence[5,6].

In Lynch syndrome, cancer may develop in different areas of the gastrointestinal tract, including the stomach, small intestine, and pancreas, although in most cases the

cancer is detected in the colon[7]. Isolated breast cancer is not typically associated with pathogenic variants in the MSH6 gene; however, such cases have been reported[8].

Although *Helicobacter pylori* infection and certain lifestyle habits have been recognized as relevant risk factors for the development of gastric cancer in adults, this association is less clear in the pediatric population. Nevertheless, in regions with a high prevalence of *H. pylori*, a hereditary mutation in the E-cadherin gene has been identified, suggesting a possible genetic and environmental relationship in the early onset of this disease[1,9]. In Colombia, 50% of middle-class children and nearly 80% of children from low socioeconomic backgrounds are infected with *H. pylori* before 10 years of age, and the infection is associated with positive cagA, vacA, and iceA genes[10].

The genetics of gastric cancer reveal significant heterogeneity with distinct molecular subtypes, including Epstein-Barr virus (EBV)-positive tumors, microsatellite instability (MSI), chromosomal instability (CIN), and genomically stable (GS) tumors[11]. This highlights the importance of considering molecular classification together with the evaluation of hereditary syndromes in adolescents with gastric cancer in order to establish targeted therapies and avoid unfavorable outcomes. For these reasons, we present the report of two cases of adolescents with metastatic diffuse gastric adenocarcinoma in whom molecular alterations associated with hereditary genetic predisposition were identified.

CASE REPORT

Case 1

This was a previously healthy 13-year-old female patient with a maternal history of breast cancer. She was referred to a tertiary care center in Cali, Colombia, due to a clinical presentation of severe persistent osteomuscular pain in the dorsolumbar region of approximately 10 days' duration, which had been associated with sports-related trauma, accompanied by mucocutaneous pallor and one episode of mild hematemesis. The patient also reported diffuse moderate-intensity abdominal pain, loss of appetite, and nonspecific weight loss. On admission physical examination, generalized mucocutaneous pallor, abdominal tenderness on palpation, and tachycardia were observed. She subsequently experienced syncope and was hospitalized.

Admission laboratory tests showed severe anemia with a hemoglobin level of 5.0 g/dL, requiring blood product transfusion. Given the suspicion of gastrointestinal bleeding, an upper gastrointestinal endoscopy (UGE) was performed, revealing an extensive exophytic lesion involving the lesser curvature up to the antropyloric junction, with multiple sites of erosion and scant layered bleeding, along with a report of chronic superficial gastritis and negative *H. pylori* testing. A myeloproliferative syndrome was initially suspected; therefore, a bone marrow biopsy was performed, in which no cellular populations suspicious for neoplasia were identified. Infectious diseases were ruled out.

Imaging studies, including magnetic resonance imaging of the abdomen and chest, demonstrated a nodal conglomerate involving multiple thoracic and lumbar vertebral bodies, as well as the iliac wings. Consequently, the patient underwent greater omentum biopsy by pediatric surgery because of suspicion of gastric lymphoma. Histopathological examination revealed poorly differentiated diffuse gastric adenocarcinoma with signet ring cells. Immunohistochemistry (IHC) showed negative microsatellite instability and programmed death-ligand 1 (PD-L1), negative fluorescence *in situ* hybridization (FISH) for human epidermal growth factor receptor 2 (HER2), and loss of nuclear expression of mutS homolog 2 (MSH2), findings suggestive of Lynch syndrome.

Subsequently, during hospitalization, the patient developed bilateral breast masses. Given the family history and suspicion of Lynch syndrome, breast ultrasonography was performed, reporting bilateral BI-RADS 5 solid focal lesions, with pathology compatible with metastatic adenocarcinoma, possibly originating from the upper gastrointestinal tract as the primary site. The patient was classified as stage IV disease, and palliative chemotherapy with the FLOT regimen (fluorouracil, leucovorin, oxaliplatin, and docetaxel) was initiated (**Table 1**). However, disease progression occurred during treatment; palliative sedation was started, and the patient died two months after diagnosis.

Case 2

A previously healthy 13-year-old male patient, with no relevant personal history or reported family history of cancer, was referred to a tertiary care center in Cali, Colombia, because of severe colicky abdominal pain of one and a half months' duration. On admission physical examination, he appeared with mild mucocutaneous pallor, adynamia, mesogastric abdominal pain, and tachycardia, without palpable abdominal masses or lymphadenopathy; therefore, he was hospitalized. Subsequently, the patient developed hematemesis and melena. He required blood product transfusion because of severe anemia with a hemoglobin level of 6.4 g/dL.

An upper gastrointestinal endoscopy (UGIE) was performed, reporting an extensive excavated gastric ulcer measuring 2.5 to 3 cm in diameter, located on the greater curvature at the antropyloric junction, with raised borders and positive *H. pylori* testing, which was treated with triple

therapy. Complementary tests were performed, including a negative infectious profile and diagnostic imaging with abdominal computed tomography (CT), which showed gastric wall thickening with lymphadenopathy adjacent to the celiac trunk and scant free fluid in the pelvic cavity. In addition, positron emission tomography (PET scan) demonstrated metastatic involvement of the bone marrow. Pediatric hematology-oncology requested bilateral bone marrow aspiration, which was negative for malignancy, as well as immunohistochemistry (IHC) to confirm the diagnosis, reporting HER2 negativity and a pathogenic variant in CDH1. Variants of uncertain significance in MSH2 and MUTYH were also identified.

The patient was diagnosed with stage IV hereditary diffuse gastric cancer (HDGC), and neoadjuvant chemotherapy with 5-fluorouracil and cisplatin was initiated for three cycles (**Table 1**). Surgical local tumor resection was considered; however, the patient showed stable disease progression, and a repeat PET scan demonstrated signs of tumor progression in the bone marrow, with persistence of nodal and gastric disease. The patient was considered chemotherapy-resistant, subsequently received palliative radiotherapy, and died nine months after diagnosis.

Table 1. Stage-Based Treatment of Pediatric Gastric Cancer

Stage	Treatment
I	Radical gastrectomy with lymphadenectomy. Adjuvant chemotherapy may be considered in high-risk cases.
II	Radical surgery if resectable. Neoadjuvant chemotherapy ± radiotherapy according to tolerance.
III	If resectable: surgery + neoadjuvant chemotherapy. If unresectable: systemic chemotherapy. Radiotherapy may be added as palliative or neoadjuvant treatment.
IV	Palliative treatment: supportive surgery (obstruction, bleeding), palliative chemotherapy, and radiotherapy. Clinical trials are strongly recommended. Comprehensive management in specialized pediatric oncology centers.

Author's own research.

DISCUSSION

Primary gastric tumors in children are uncommon, and gastric carcinoma is even more unusual. Its prognosis depends on the extent of disease at the time of diagnosis and the appropriateness of treatment, which has resulted in limited available information regarding this pathology in the pediatric population. Nevertheless, one of the largest studies conducted was performed by Tessler and colleagues[3] in 2019 using records from the National Cancer Data Base between 2004 and 2014. Their objective was to compare the clinical presentation, management, and outcomes between pediatric patients (≤21 years) and adults (>21 years) with gastric adenocarcinoma. They identified that, among the 129,024 total cases, only 129 cases (0.10%) corresponded to pediatric patients. In addition, these patients more frequently presented with advanced-stage disease (stage IV) (56%) compared with adults (41%). They concluded that although children had more advanced disease and more aggressive histological types, their survival rates were similar to those of adults.

Likewise, reports of this disease in the pediatric population are rare in Colombia[15]. However, two case reports from 2007 and 2021 were identified. The first involved a 12-year-old male adolescent from Popayán, Cauca, who presented with a one-year history of diffuse symptoms (abdominal pain, vomiting, melena, hematemesis), and biopsy revealed diffuse-type adenocarcinoma with positive *H. pylori* immunohistochemistry and the presence of cagA and vacA genes. He underwent total gastrectomy, and metastases to the spleen, pancreas, and colon were identified[12]. The second case involved a 10-year-old girl from Medellín, Antioquia, who presented with constitutional syndrome (abdominal pain, postprandial emesis, and weight loss); studies revealed poorly differentiated diffuse gastric adenocarcinoma with signet ring cells, and diagnostic laparoscopy showed signs of peritoneal carcinomatosis, for which palliative chemotherapy was offered[13].

As occurred in the previously described cases, our patients presented with metastatic disease from the time of diagnosis and showed resistance to chemotherapy, demonstrating more aggressive tumor behavior than that observed in the adult population[3]. This underscores the need to implement interventions that enable early detection of gastric cancer in this population because, as reported in the literature and also observed in these patients, the clinical manifestations of this type of cancer are highly nonspecific in the early stages. More striking symptoms, such as severe epigastric abdominal pain, weight loss, and hematemesis, are observed in advanced stages, which is generally when the disease is diagnosed[14].

Another exceptionally rare gastrointestinal tumor in children is esophageal carcinoma. Suárez and colleagues reported the first case of a 14-year-old male adolescent with a history of intellectual disability and Barrett's esophagus who was admitted in February 2015 to the Instituto Nacional de Cancerología de Colombia and developed esophageal adenocarcinoma. Similar to our two patients with gastric adenocarcinoma, this adolescent presented with nonspecific gastrointestinal symptoms, such as dysphagia, weight loss, and emesis, leading to delayed diagnosis and consequently

complicating both treatment and prognosis. Unlike our cases, esophageal adenocarcinoma in adolescents appears to have a stronger association with environmental and inflammatory factors rather than genetic predisposition, and its therapeutic approach is also generally based on protocols designed for adults[17,18].

Furthermore, it is important to highlight that molecular testing was performed in our patients, allowing for better stratification and consideration of more specific treatments despite the current limitations of targeted therapies. However, rapid disease progression was observed, underscoring the need to consider diagnoses such as Lynch syndrome and HDGC when variants in the MSH2 and CDH1 genes are detected in young patients. This becomes especially relevant in the context of chemotherapy resistance, given the characteristic aggressiveness of these tumors in the pediatric population, even in the absence of a family history of cancer.

Consequently, targeted studies for pathogenic variants are recommended in first- and second-degree relatives, along with genetic and oncologic counseling[2,3]. In addition, HER2 and PD-L1 negativity currently limits access to targeted therapies, reinforcing the importance of performing early molecular studies and implementing personalized therapeutic strategies[16]. These strategies should include genetic screening in patients with a history of hereditary cancer and the development of new therapeutic alternatives adapted to the molecular characteristics of tumors in this age group[9].

Finally, the presence of *H. pylori* in one of the cases supports its possible role as a cofactor in predisposed individuals and in high-prevalence populations, suggesting that early eradication could represent a relevant preventive measure.

CONCLUSIONS

The management of gastric adenocarcinoma in pediatric patients remains limited and poorly understood because of the lack of specific guidelines and the reliance on adult treatment protocols. Advancing research, including genetic studies in patients and their families, is essential to improve knowledge and optimize treatment strategies in this population.

By presenting these cases, we hope to contribute to the literature regarding the importance of early diagnosis of gastric cancer in the pediatric population, based on the need to perform early diagnostic studies even in the presence of nonspecific symptoms such as hematemesis, abdominal pain, weight loss, or lumbar pain. These measures will facilitate early detection and the development of appropriate therapeutic strategies and, ultimately, improve the clinical prognosis of these patients.

Conflict of Interest

No conflicts of interest were reported.

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Case report

Ileocecal Tuberculosis (Surgical and Pathological Diagnosis) Mimicking Inflammatory Bowel Disease: A Case Report and Literature Review

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Abstract

Introduction: We report the case of a patient with suspected inflammatory bowel disease (IBD) who failed to respond to vedolizumab therapy and was subsequently diagnosed with *Clostridioides difficile* infection and gastrointestinal tuberculosis (GITB). **Case Presentation:** A 21-year-old woman with IBD receiving biological therapy and corticosteroids presented with vomiting, abdominal pain, and bloody diarrhea. *C. difficile* toxin testing was positive, and vancomycin therapy was initiated. Given the persistence of symptoms, colonoscopy was performed and revealed segmental ulcerative colitis. Biopsy specimens and cultures confirmed the presence of *Mycobacterium tuberculosis*, and a four-drug antituberculous regimen was subsequently initiated. **Conclusion:** GITB and Crohn's disease share overlapping clinical and histological features, making diagnosis particularly challenging. Considering GITB in cases of refractory IBD, as well as the possibility of its coexistence with *C. difficile* infection, is essential for appropriate management and for preventing complications associated with the inappropriate use of immunosuppressive agents and biological therapies.

Keywords

Tuberculosis; gastrointestinal tuberculosis; Crohn's disease; stenosis.

INTRODUCTION

In emerging countries such as Colombia, the use of biologic therapy for inflammatory bowel disease (IBD) is increasing, although tuberculosis remains more prevalent. In patients who do not improve with initial treatment, it is essential to rule out infectious causes, particularly those associated with biologic or immunosuppressive therapy.

CASE DESCRIPTION

A 21-year-old woman with no known medical history presented in another city with a one-month history of generalized abdominal pain predominantly located in the right iliac fossa. An upper gastrointestinal endoscopy was performed, showing moderate congestive antral gastropathy and moderate bulboduodenitis, while colonoscopy revea-

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led multiple discontinuous ulcers with irregular borders in the cecum, ascending colon, and transverse colon, predominantly involving the cecum. Biopsies were obtained, demonstrating severe chronic active inflammation with focal architectural distortion, ulcer fragments, and granulation tissue, without evidence of granulomas, cryptitis, or microorganisms. The findings were negative for dysplasia or neoplastic involvement.

Treatment was initiated for probable IBD consistent with Crohn's disease (CD) with prednisolone 40 mg and oral mesalazine 500 mg every 24 hours for one month. However, due to lack of improvement, she sought care at another institution. Given the lack of response to first-line therapy, her case was discussed in a multidisciplinary medical board, and initiation of treatment with an integrin receptor antagonist (vedolizumab 300 mg intravenously) using an induction regimen was considered pending infectious disease approval. Serologic testing showed negative hepatitis B and C virus antibodies, negative hepatitis B surface antigen, nonreactive human immunodeficiency virus (HIV) testing, and a negative tuberculin skin test. Additionally, chest radiography demonstrated interstitial opacities and thickening of the peribronchovascular interstitium, without other relevant findings (**Figure 1**).



Figure 1. Chest radiograph obtained prior to initiation of vedolizumab treatment. Author's file.

The patient was admitted to the emergency department at our institution two months later due to worsening abdominal pain associated with bloody watery stools. Upon evaluation, an abdominal computed tomography scan was requested (**Figure 2**), which showed infectious inflammatory changes involving the ascending colon and cecum, along with an increased number of lymph nodes at the mesenteric root. Given the suspicion of gastrointestinal infection in the context of CD, a toxin assay was requested and returned positive. Inpatient management with oral vancomycin was initiated; however, one week later, the patient developed fever spikes and a significant increase in pain predominantly located in the right iliac fossa. A repeat colonoscopy was performed, revealing multiple segmental ulcers with fibrin in the cecum, ascending colon, and transverse colon (**Figure 3**), with involvement of the ileocecal valve and sparing of the ileum. Cultures and biopsies were therefore obtained, respectively.

Laboratory testing demonstrated the presence of *Mycobacterium tuberculosis* on the acid-fast bacillus (AFB) test (**Figure 4**), with subsequent isolation in culture. The patient was therefore evaluated by the Infectious Diseases Department, and quadruple therapy with isoniazid, rifampin, ethambutol, and pyrazinamide was initiated.

Due to lack of improvement with antituberculous therapy and signs of intestinal obstruction, the patient underwent surgery, during which 70 cm of small intestine were resected starting from the ileocecal valve, followed by side-to-side mechanical anastomosis. Pathology findings (**Figure 5**) revealed chronic inflammation with necrotizing granulomas, ruling out CD and confirming gastrointestinal tuberculosis (GITB).

DISCUSSION

GITB occurs in 20%–25% of patients with concomitant pulmonary tuberculosis. It is the sixth most common form of extrapulmonary tuberculosis after lymphatic, genitourinary, bone and joint, miliary, and meningeal tuberculosis[1]. It may affect any segment of the gastrointestinal tract; however, most cases occur at the jejunal and ileocecal levels, accounting for 64% of cases, which is explained by the high concentration of lymphoid aggregates and possibly by prolonged mucosal contact with the bacilli[1].

Transmission may occur following primary tuberculosis through hematogenous or lymphatic spread, or through swallowed sputum mediated by macrophages. Epithelial cells are also involved in direct infection through microfold cells (M cells) and with the assistance of dendritic cells[2]. Previously, GITB was associated with *Mycobacterium bovis* rather than *Mycobacterium tuberculosis*, probably due to the consumption of contaminated dairy products. Following the introduction of milk pasteurization and improvements in detection methods, the number of gastrointestinal tuberculosis infections decreased dramatically, as this process is generally sufficient to eliminate mycobacteria[3].



Figure 2. Contrast-enhanced abdominal and pelvic computed tomography showing concentric mural thickening of the cecum and distal ascending colon segment (7.5 mm) with hyperenhancement, surgical absence of the cecal appendix, and an increased number of lymph nodes at the mesenteric root. Author's file.

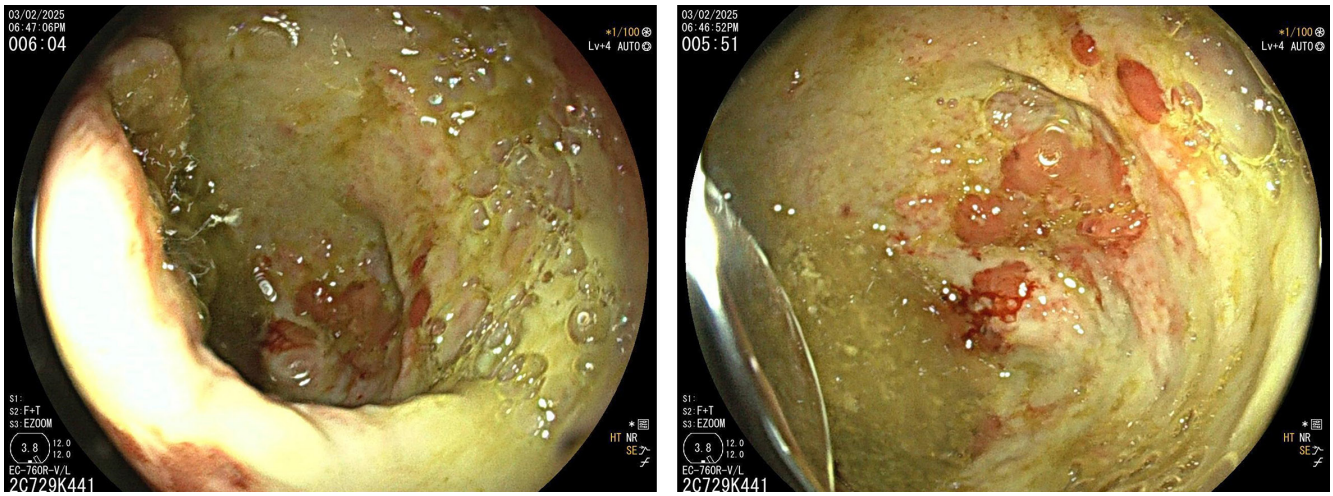


Figure 3. Segmental ulcerative colitis involving the cecum. Author's file.

In Colombia, case reports of gastrointestinal tuberculosis have been published in patients with HIV and in another patient with previous pulmonary tuberculosis[4,5].

The most common clinical manifestations of GITB are abdominal pain (30%–88%), fever (21%–73%), diarrhea (5%–47%), loss of appetite (30%–90%), weight loss (8%–80%), and rectal bleeding (5%–15%). Patients may also present with obstructive symptoms, pain in the right iliac fossa, or a palpable mass in the right iliac fossa[6].

Although it is considered a disease of developing countries, cases continue to be reported in developed countries due to migration and in immunocompromised individuals;

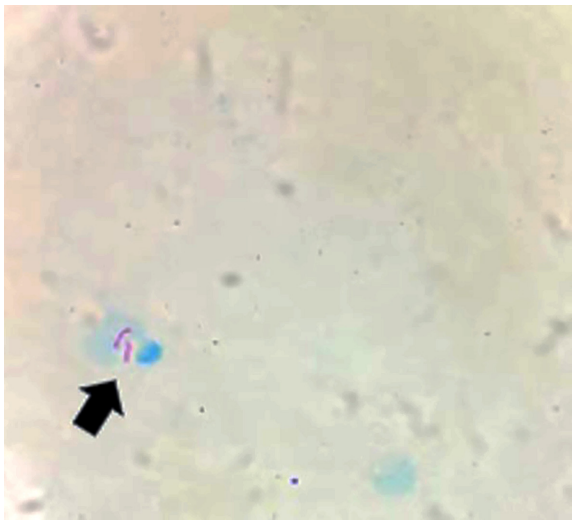


Figure 4. Isolation of *Mycobacterium tuberculosis* (AFB) in the cecum. Author's file.

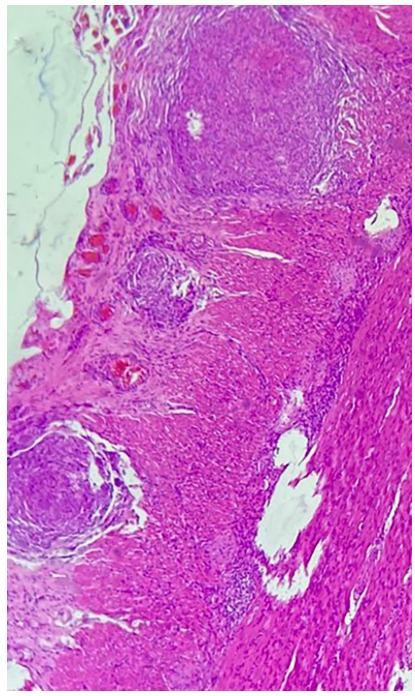


Figure 5. Ileal resection biopsy stained with hematoxylin and eosin showing necrotizing granulomatous chronic inflammation. Author's file.

for example, immunosuppression related to HIV and associated therapies, including anti-tumor necrosis factor (anti-TNF) agents and steroids[7]. GITB results in chronic intestinal inflammation that, like CD, is associated with granuloma formation[8]. Distinguishing gastrointestinal tuberculosis from CD is difficult because of the similarities in clinical manifestations and the low sensitivity of microbiological tools for the diagnosis of GITB. Seo H and colleagues showed that approximately 11% of patients with GITB were misdiagnosed with CD, whereas approximately 18% of patients with CD received a diagnosis of GITB[9]. These findings raise the following question: should greater caution be exercised when administering biologic therapy for suspected IBD in our setting?

In our case, the patient underwent chest radiography and tuberculin skin testing, taking into account the reported sensitivity and specificity of approximately 80% and 97%–98%, respectively[10]. However, several causes of false-negative results have been reported in a retrospective cohort, including HIV infection, chronic kidney disease, alcohol abuse, drug use, and age ≥65 years[11].

According to a meta-analysis that included 316 patients with gastrointestinal tuberculosis and 376 patients with CD, three histological features with high specificity for diagnosing GITB compared with CD were identified. These features included caseous necrosis, confluent granulomas, and ulcers lined by macrophages, with combined sensitivities of 21%, 38%, and 41%, and combined specificities of 100%, 99%, and 95%, respectively[12].

For the treatment of GITB, patients should receive a complete course of antituberculous therapy. Currently, a two-month treatment course is recommended for uncomplicated digestive tract tuberculosis. Longer treatment regimens should be avoided because they are associated with poor adherence and a higher risk of adverse effects from potentially toxic medications[13]. Surgical intervention is reserved for complications such as fibrosis, stenosis, and acute abdomen, or when diagnostic uncertainty persists[13].

For its part, *Clostridioides difficile* infection is the most common infectious cause of hospital-acquired diarrhea, generally preceded by the use of antibiotics such as fluoroquinolones, cephalosporins, broad-spectrum penicillins, and clindamycin[11,14]. Several studies estimate the incidence of *C. difficile* infection at between 2.8% and 3.73% in patients with ulcerative colitis (UC), and around 1% in CD, compared with rates below 0.5% in the general population. In addition, it is estimated that 8.2% of patients with UC and 1% of patients with CD are asymptomatic carriers of *C. difficile* without clinical manifestations of active infection[15]. This makes our clinical case even more noteworthy, given its rarity.

CONCLUSIONS

GITB and CD are chronic granulomatous diseases that primarily affect the terminal ileum. These conditions are

often confused in clinical practice because of the increasing emergence of IBD in developing countries. It is important to emphasize that the clinical, endoscopic, and imaging findings are not pathognomonic for either condition, creating a challenge for the treating physician. Considering the above, and given that this is an uncommon presentation reported in the literature, we describe this case with the aim of raising awareness within the medical community, since distinguishing GITB from CD is of immense importance because of the consequences that biologic therapy and immunosuppression may have in patients with an incorrect diagnosis.

Conflict of Interest

All authors declare that there are no conflicts of interest.

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Use of Artificial Intelligence

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Case report

Primary Biliary Cholangitis Associated with Celiac Disease, Lupus, and Hashimoto's Thyroiditis: A Case Report

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Abstract

Introduction: The coexistence of two or more autoimmune diseases defines multiple autoimmune syndrome. Primary biliary cholangitis (PBC) may occur in association with other immune-mediated conditions. A case of PBC associated with systemic lupus erythematosus (SLE), celiac disease (CD), and Hashimoto's thyroiditis (HT) is described. **Case report:** A 45-year-old woman presented with cholestatic liver enzyme abnormalities and positive autoantibodies. She had a history of HT and a family history of CD. Serology showed positive anti-endomysial antibodies, anti–tissue transglutaminase IgA 117 U/mL, positive AMA-M2, ANA 1:320, positive anti-dsDNA, and decreased C3/C4. Duodenal biopsy revealed villous atrophy, and liver biopsy demonstrated granulomas, bile duct injury, and portal inflammation with portal fibrosis, confirming PBC. A gluten-free diet, ursodeoxycholic acid (15 mg/kg/day), hydroxychloroquine (400 mg/day), prednisone (0.5 mg/kg with taper), and azathioprine were initiated. The patient showed normalization of liver biochemistry and clinical improvement. **Discussion:** Polyautoimmunity in PBC is well recognized and commonly involves thyroid disorders, SLE, and CD. This case illustrates the need for targeted screening for associated autoimmune diseases and multidisciplinary management. The presence of multiple autoantibodies and characteristic histological findings guided diagnosis and treatment. **Conclusion:** In patients with PBC, concomitant autoimmune diagnoses should be considered; early detection and comprehensive management optimize outcomes.

Keywords

Primary biliary cholangitis; systemic lupus erythematosus; celiac disease; Hashimoto's thyroiditis.

INTRODUCTION

Primary biliary cholangitis (PBC) is a chronic cholestatic cholangiopathy of autoimmune origin that predominantly affects middle-aged women(1). The coexistence of autoimmune diseases is common in PBC and may be part of the so-called multiple autoimmune syndrome or polyautoimmunity(2). Polyautoimmunity is defined as the presence of two or more autoimmune diseases in the same patient(3). In this context, the most common extrahepatic autoimmune conditions associated with PBC are, in order of frequency, Sjögren's syndrome (affecting approximately one-third of patients), Raynaud's phenomenon, Hashimoto's thyroiditis (and, less frequently, Graves' disease), scleroderma/CREST

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syndrome, rheumatoid arthritis, systemic lupus erythematosus (SLE), celiac disease, autoimmune skin diseases (e.g., lichen planus), and vasculitis. These associations appear to reflect shared immunopathogenic mechanisms and a clear female predominance, although, overall, they do not appear to significantly affect survival compared with patients with PBC without autoimmune comorbidities[4]. Recognizing these associations is essential for timely diagnosis, risk stratification, and comprehensive management.

In celiac disease, the autoimmune disorders most frequently associated are type 1 diabetes *mellitus* and autoimmune thyroid diseases (Hashimoto's thyroiditis and, less frequently, Graves' disease). Autoimmune liver diseases have also been described, particularly autoimmune hepatitis and PBC, in addition to Sjögren's syndrome and SLE. This spectrum reinforces the need for targeted surveillance in celiac disease, especially during the first years after diagnosis, as well as confirmation of celiac disease through positive anti-endomysial antibodies (EmA) and/or anti-tissue transglutaminase antibodies (tTG), followed by duodenal biopsy demonstrating typical histologic findings. Furthermore, it underscores the importance of strict gluten avoidance, since more rapid normalization and sustained low tTG levels are associated with a lower subsequent risk of developing new autoimmune diseases[5]. Despite the above, the simultaneous coexistence of all four conditions (Hashimoto's thyroiditis, celiac disease, SLE, and PBC) is uncommon. This rarity gives the present case particular clinical and academic relevance, highlighting the need for an integrative diagnostic approach and interdisciplinary management in the setting of polyautoimmunity.

METHOD

Retrospective descriptive study based on medical record review. Approved by the CEPSH/UFSC. Opinion No. 7.670.068.

CASE

A 45-year-old woman presented with persistent elevation of liver biochemical tests. Overall, she remained asymptomatic and reported no jaundice, pruritus, or abdominal pain (chief complaint), except for the presence of arthralgias. In the history of present illness, she reported laboratory abnormalities detected several months earlier, without identifiable triggers, and denied the use of herbal products, anabolic agents, or cholestatic drugs, as well as alcohol consumption. She denied fever, weight loss, choluria, or acholia. Her comorbidity consisted of treated Hashimoto's thyroiditis, with euthyroid status. Her past medical history was negative for abdominal surgeries, previous hepatitis, cholelithiasis, or known biliary disease. Family history was positive for celiac disease in a first-degree relative. Regarding lifestyle habits, she was a non-smoker, followed an omnivorous diet, engaged in irregular physical activity, and denied recreational drug use. On physical examination, she was in good general condition, afebrile, and hemodynamically stable, without mucocutaneous stigmata of cholestasis or signs of advanced liver disease. The abdomen was flat, soft, and non-tender, with no palpable visceromegaly, clinical jaundice, or lymphadenopathy.

Laboratory tests (**Table 1**) showed a cholestatic pattern, with elevated alkaline phosphatase and γ-glutamyltransferase, mildly increased alanine aminotransferase (ALT) and aspartate aminotransferase (AST), normal bilirubin, and preserved synthetic function (albumin and coagulation tests within normal range). The immunologic profile revealed positive EmA, tTG IgA: 117 U/mL, positive antimitochondrial antibodies type M2 (AMA-M2), antinuclear antibody: 1:320 reticular speckled pattern, positive anti-DNA antibodies, and reduced C3/C4 levels; serum IgA was within the normal range. Viral hepatitis serologies were negative. Endoscopic imaging studies and intestinal histology demonstrated that upper endoscopy with duodenal biopsy showed Marsh 3 villous atrophy consistent with celiac disease. Liver biopsy revealed granulomas, bile duct injury, portal infiltrate, and portal fibrosis, findings consistent with PBC, with mild to moderate histologic activity. Concurrently, she was being followed by Rheumatology, which established the diagnosis of SLE based on a presentation of polyarthralgia.

Table 1. Laboratory Tests Throughout Clinical Follow-up*

Date	AST (RV <37)	ALT (RV <56)	ALP (RV <136)	GGT (RV <55)
Aug/09	**38**	**60**	**197**	**97**
Nov/09	**41**	**61**	**213**	**112**
Jan/12	33	52	**171**	**102**
Feb/15	22	29	**141**	35
Sep/16	29	30	105	37
Aug/18	36	40	133	53
Dec/20	31	27	98	30
Sep/22	20	25	70	25
Feb/25	20	24	73	27

*Values in bold correspond to results above the reference value for each test. ALT: alanine aminotransferase; AST: aspartate aminotransferase; ALP: alkaline phosphatase; GGT: γ-glutamyltransferase; RV: reference value. Author's own research.

Based on the integrated clinical, serologic, and histologic findings, a gluten-free diet, ursodeoxycholic acid 15 mg/kg/day, hydroxychloroquine 400 mg/day, prednisone 0.5 mg/kg with gradual tapering, and azathioprine as a steroid-sparing agent were initiated. During follow-up, progressive improvement in liver biochemistry was documented, culminating in normalization of liver enzymes, along with sustained clinical improvement during follow-up visits through 2025 (**Table 1**). During clinical follow-up, negativization of EmA and tTG autoantibodies was also observed, as well as normalization of the duodenal biopsy (Marsh 0).

DISCUSSION

In the present case, the presence of AMA-M2 and the characteristic histologic findings established the diagnosis of PBC, while the systemic autoantibodies and clinical manifestations supported concomitant SLE. Villous atrophy together with positive EmA and tTG confirmed celiac disease. According to the classical classification of autoimmune polyglandular syndromes, this constellation of diseases corresponds to APS-III (MAS-3), specifically within subgroups IIIb (which include the association of autoimmune thyroiditis with gastrointestinal/hepatobiliary disease) and IIId (characterized by the coexistence of autoimmune thyroiditis with systemic rheumatologic diseases such as SLE). In light of the contemporary association-network analysis proposed by Pham-Dobor and colleagues, these combinations align with the clusters centered on Hashimoto's thyroiditis, in which gastrointestinal, hepatobiliary, and systemic manifestations converge. This integrated approach underscores the importance of early recognition of these patterns of polyautoimmunity in order to anticipate new manifestations, optimize clinical follow-up, and ensure timely interventions[6].

This case reflects the complexity of polyautoimmunity, given that the vast majority of patients with autoimmune polyglandular syndromes present with two and, less frequently, three manifestations. Endocrine diseases are the most common, followed by gastrointestinal disorders and, thirdly, systemic conditions such as rheumatoid arthritis (RA), Sjögren's syndrome (SS), and SLE[6]. In this context, the simultaneous coexistence of four autoimmune diseases (Hashimoto's thyroiditis, celiac disease, PBC, and SLE) constitutes an exceptional finding that broadens the clinical spectrum described in the literature.

Celiac disease is a systemic immune-mediated disorder triggered by gluten in genetically predisposed individuals and is associated with a broad spectrum of extraintestinal manifestations and an increased risk of other autoimmune diseases. Evidence suggests that early diagnosis and treatment are associated with a lower subsequent development of autoimmunity, whereas unrecognized or untreated celiac disease is linked to a greater occurrence of autoimmune and liver disorders over time[7].

At the intersection between celiac disease and PBC, population-based studies have reported elevated bidirectional prevalences. In a United Kingdom cohort, approximately 3% of patients with celiac disease had PBC, and nearly 6% of individuals with PBC had celiac disease[8]. Furthermore, Irish series reported that celiac disease in patients with PBC was at least 10 times more frequent than in the general population, while Scandinavian registries demonstrated very high relative risks of PBC in celiac disease (incidence ratios on the order of approximately 25–28)[9]. Although negative findings have been reported in some series (Sweden, Italy, and Greece), the overall body of evidence supports a clinically relevant association between these two entities[10–13]. These findings justify active screening for celiac disease in patients with PBC and marked autoimmunity and, conversely, hepatologic surveillance in individuals with celiac disease[14].

In this regard, metabolomic analyses by nuclear magnetic resonance of serum and urine demonstrated that PBC exhibits a distinctive metabolic fingerprint compared with healthy controls and celiac disease, with higher serum levels of pyruvate, citrate, glutamate, glutamine, serine, tyrosine, phenylalanine, and lactate, as well as lower urinary levels of hippurate and trigonelline. These findings suggest alterations in energy metabolism and possible intestinal dysbiosis. Furthermore, the profiles allowed discrimination between PBC and celiac disease with high accuracy (approximately 82%–92% in serum, depending on the experiment), supporting the notion that, despite their clinical association, PBC and celiac disease exhibit different metabolic signatures that may provide pathogenic insights and future therapeutic targets[15].

In this setting, it is crucial to differentiate "pure" PBC from a PBC-autoimmune hepatitis (AIH) overlap syndrome, since the presence of systemic autoantibodies related to SLE may complicate interpretation. The Paris criteria propose ALT/IgG thresholds and hepatocellular histologic features to define overlap[16]. In our case, the mildly elevated transaminases, positive AMA-M2, and typical cholangiopathic histology supported PBC without significant overlap, reserving immunosuppression for the management of SLE rather than as a specific strategy for PBC.

From a therapeutic perspective, the cornerstone of treatment remains ursodeoxycholic acid (UDCA 13-15 mg/kg/day), with assessment of biochemical response using validated criteria (Barcelona, Paris I/II, Toronto)[17]. A strict gluten-free diet is mandatory in confirmed celiac disease and may optimize liver parameters in certain subgroups, but it does not replace UDCA as the standard of

care in PBC. Hydroxychloroquine, tapering prednisone, and azathioprine were directed toward the control of SLE; any improvement in liver enzymes under these agents should be interpreted within the context of the primary response to UDCA.

CONCLUSION

This case illustrates how polyautoimmunity may mask or mimic overlap syndromes, requiring a disciplined diagnostic algorithm and the integration of serology, histology, and clinical context. In PBC, complete response to UDCA remains the central prognostic determinant. Concurrently, timely screening and treatment of celiac disease, as well as appropriate control of SLE, contribute decisively to clinical and biochemical improvement. In light of contemporary classifications of autoimmune polyglandular syndromes, this case exemplifies a phenotype of multiple polyautoimmunity centered on Hashimoto's thyroiditis, with hepatobiliary, intestinal, and systemic involvement. Early identification of these associations not only allows anticipation of new autoimmune manifestations, but also optimizes longitudinal follow-up and ensures timely therapeutic interventions, reinforcing the clinical and academic relevance of this case within the spectrum of diseases requiring early detection and comprehensive management.

Conflict of Interest

The authors declare that there are no conflicts of interest related to this manuscript.

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Use of Artificial Intelligence

Artificial intelligence-assisted technologies (ChatGPT) were used exclusively to support drafting, style standardization, and linguistic review. All scientific decisions, data analysis and interpretation, and drafting of substantive content were performed by the authors. Artificial intelligence was not used for data analysis or image generation.

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Case report

Arteriovenous Malformation Associated with a Jejunal Diverticulum: An Uncommon Cause of Small Bowel Bleeding

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Abstract

Jejunal diverticulosis is an uncommon cause of small bowel bleeding, and its coexistence with an arteriovenous malformation (AVM) is exceedingly rare. We report the case of an 81-year-old man presenting with overt gastrointestinal bleeding and hemodynamic instability. Conventional endoscopy and initial imaging studies failed to localize the bleeding source. Exploratory laparoscopy combined with intraoperative enteroscopy identified a large jejunal diverticulum with mucosal ulceration and associated vascular congestion. Histopathological analysis confirmed a true diverticulum with an underlying AVM. Surgical resection of the affected segment resulted in complete resolution, with no recurrence of bleeding during clinical follow-up. This report underscores the importance of considering uncommon combined etiologies in patients with obscure small bowel bleeding of unclear origin.

Keywords

Diverticulum; gastrointestinal hemorrhage; vascular malformations; capsule endoscopy; balloon enteroscopy.

INTRODUCTION

Small bowel bleeding refers to hemorrhage originating between the ampulla of Vater and the ileocecal valve. Clinically, it may present as melena or hematochezia, or manifest as obscure gastrointestinal bleeding suspected on the basis of iron deficiency anemia or a positive fecal occult blood test without an identifiable source on initial studies. This diagnosis should be considered when upper gastrointestinal endoscopy and colonoscopy fail to establish the cause, representing a highly complex diagnostic challenge[(1)].

Among the uncommon causes of small bowel bleeding, jejunal diverticula constitute the rarest form of small bowel diverticulosis. These lesions correspond to saccular herniations of the mucosa through focal defects in the intestinal wall at sites of reduced resistance. Although most patients remain asymptomatic, recognition of this condition becomes clinically relevant when complications such as diverticulitis, gastrointestinal bleeding, intestinal obstruction, or perforation occur[(1,2)].

Bleeding associated with jejunal diverticula typically results from erosion of adjacent vessels. However, in excep-

tional cases, an arteriovenous malformation may coexist. This uncommon vascular abnormality further increases the complexity of both the clinical presentation and the diagnostic process[3].

We present a case of obscure gastrointestinal bleeding ultimately attributed to a jejunal diverticulum concomitant with an arteriovenous malformation, which required the sequential use of different imaging modalities and surgical exploration to achieve a definitive diagnosis and provide curative treatment. Written informed consent was obtained from the patient, and the study was approved by the Institutional Ethics Committee (CCEI 17789-2025).

CASE PRESENTATION

An 81-year-old male patient with a history of hypertension, hiatal hernia, gastritis, coronary artery disease, and diverticulosis, as well as a recent hospitalization for Mallory-Weiss syndrome, was readmitted three days after discharge because of a seven-hour episode of profuse melena associated with asthenia, adynamia, dizziness, emesis, vomiting, and diffuse abdominal pain. On admission, hypotension (90/64 mm Hg) and tachycardia (110 beats per minute [bpm]) were documented, without fever, and with a respiratory rate of 16 breaths per minute. Laboratory studies revealed a hemoglobin level of 9.4 g/dL, without leukocytosis, thrombocytopenia, or other cytopenias. Electrolytes, liver enzymes, acid-base status, and lactate levels were within normal ranges. The patient was transferred to the intensive care unit (ICU), where initial hemodynamic stabilization was achieved with crystalloid administration and proton pump inhibitors. Due to persistent anemia, he required multiple packed red blood cell transfusions.

Given the recent history of Mallory-Weiss syndrome, upper gastrointestinal endoscopy was performed and ruled out active bleeding or stigmata of recent hemorrhage. Colonoscopy revealed extensive pancolonic diverticulosis, including diverticula in the distal ileum, without identification of a clear bleeding source. Persistence of melena suggested a more proximal gastrointestinal origin.

In light of these findings, capsule endoscopy was indicated for evaluation of the small bowel. The study demonstrated an image suggestive of a space-occupying lesion in the proximal jejunum, without signs of active bleeding (**Figure 1**). Antegrade enteroscopy advanced approximately three meters and revealed multiple wide-based diverticula without endoscopic stigmata of recent hemorrhage. No masses, polyps, or findings suggestive of neoplasia were observed. Magnetic resonance enterography ruled out associated focal lesions or signs of diverticulosis-related complications.

Given the unfavorable clinical course and persistent diagnostic uncertainty, the patient underwent exploratory laparoscopy with intraoperative enteroscopy. Multiple adhesions between the small bowel and the transverse mesocolon were identified, along with jejunal diverticula in the explored segment. A large diverticulum with marked vascular congestion and intradiverticular blood clots was identified (**Figure 2**), without other associated pathological findings. Segmental resection of the affected bowel was performed.

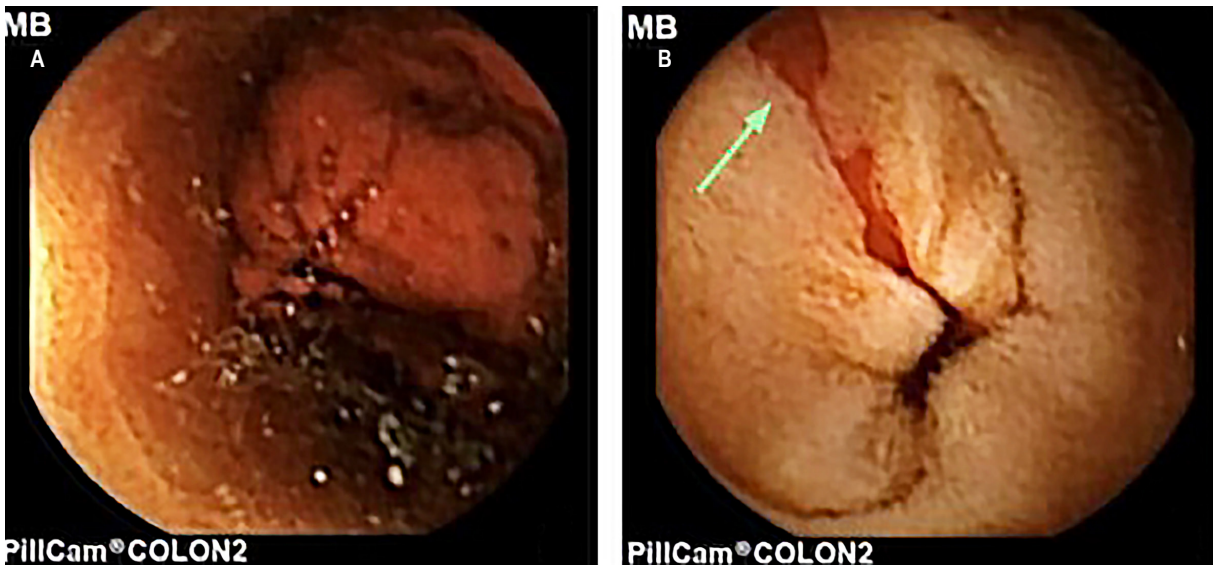


Figure 1. Capsule endoscopy findings. **A.** Image suggestive of a lesion in the proximal jejunum with focal mucosal disruption. **B.** Erosive lesion with visible blood residues, consistent with recent bleeding. Author's file.

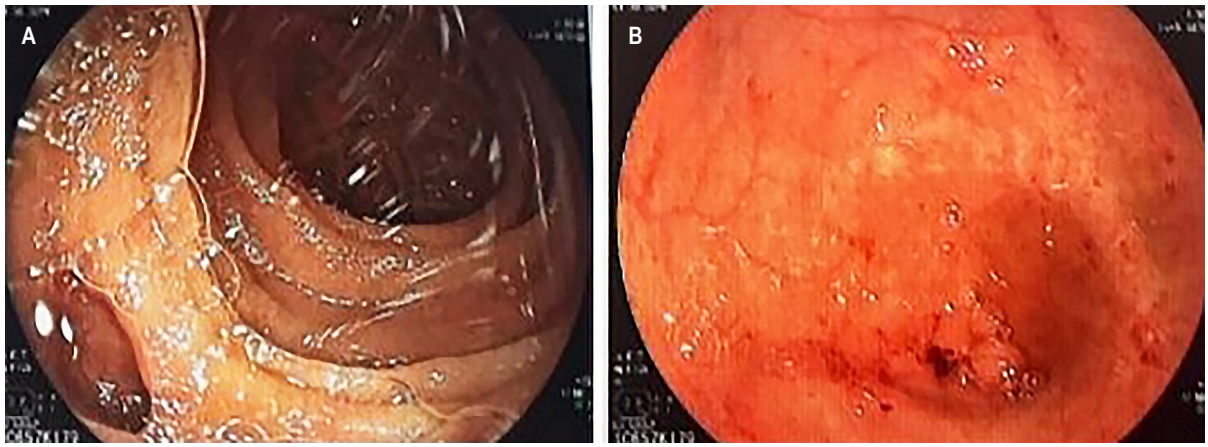


Figure 2. Intraoperative enteroscopy findings. **A.** Wide-necked jejunal diverticulum identified during surgical exploration. **B.** B. Intraluminal view of the diverticulum with clots and stigmata of recent hemorrhage. Author's file.

Histopathological analysis demonstrated true diverticula and pseudodiverticula with superficial mucosal erosion, acute serositis, submucosal edema, vascular ectasia and congestion, as well as a lesion consistent with an arteriovenous malformation. No further bleeding episodes occurred after surgery.

DISCUSSION

Few cases of gastrointestinal hemorrhage secondary to the coexistence of an arteriovenous malformation and jejunal diverticulosis have been described[3–8]. Small bowel bleeding is an uncommon event, accounting for approximately 5%–10% of all gastrointestinal bleeding cases[1,2]. The etiology varies according to patient age. In individuals younger than 40 years, vascular causes predominate, mainly angiodysplasia and Dieulafoy lesions, followed by inflammatory diseases, including Crohn's disease, intestinal ulcers, Meckel's diverticulum, and nonspecific enteritis, as well as tumors and polyposis syndromes. In patients older than 40 years, vascular etiologies remain the most common, particularly angioectasias and Dieulafoy lesions, together with ulcerative disease associated with nonsteroidal anti-inflammatory drug (NSAID) use and gastrointestinal neoplasms such as gastrointestinal stromal tumors (GISTs), lymphomas, carcinoid tumors, and adenocarcinoma. Other even less frequent causes include portal hypertensive enteropathy, intestinal varices, systemic vascular syndromes, and infiltrative or connective tissue diseases[1,2].

The diagnostic evaluation of persistent small bowel bleeding should begin with assessment of hemodynamic status. Although most patients are hemodynamically stable, this male patient required critical care management, ICU admission, and transfusional support because of persistent anemia. When upper gastrointestinal endoscopy and colonoscopy fail to localize the bleeding source, repeating these procedures may be considered if technical limitations were present, given that up to 30% of cases may originate outside the small bowel. Capsule endoscopy is the subsequent method of choice because of its high diagnostic yield and its value in excluding disease. If bleeding persists or recurs, deep enteroscopy and magnetic resonance enterography complement the evaluation according to clinical relevance and local availability. Intraoperative enteroscopy is reserved for selected cases in which clinical suspicion remains high despite previous nondiagnostic studies[2].

This case illustrates the value of a stepwise, adaptive, and methodical approach. Although the patient initially presented with melena and marked anemia, the initial studies were inconclusive. Capsule endoscopy suggested a jejunal lesion that was subsequently not confirmed by antegrade enteroscopy or magnetic resonance imaging. Clinical deterioration, together with persistent obscure bleeding, justified surgical exploration assisted by intraoperative enteroscopy, which identified a large jejunal diverticulum with superficial erosions, dilated congestive vessels, and intradiverticular clots. Histological examination confirmed pseudodiverticula and a vascular lesion consistent with an arteriovenous malformation as the cause of bleeding.

Although uncommon, the association between jejunal diverticulosis and arteriovenous malformation should be considered in the differential diagnosis of unexplained persistent small bowel bleeding. This report highlights the importance of maintaining clinical suspicion, integrating

fragmented findings, and adapting the diagnostic evaluation according to disease progression in order to achieve accurate diagnoses and curative treatment, even in uncommon clinical scenarios.

Informed Consent

Written informed consent was obtained from the patient, and the study was approved by the Institutional Ethics Committee (CCEI-17789-2025).

Conflict of Interest

The authors declare no conflicts of interest.

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Use of Artificial Intelligence Technologies

No artificial intelligence tools were used.

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Case report

Arcanobacterium haemolyticum as an Unusual Etiology of Hepatic Abscesses: A Case Report

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Abstract

Introduction: *Arcanobacterium haemolyticum* is an infrequent Gram-positive, catalase-negative bacillus, typically associated with pharyngitis and mild cutaneous infections. Systemic infections caused by this microorganism are uncommon, and hepatic abscess formation is particularly rare. **Case report:** We present the case of a 30-year-old man with human immunodeficiency virus (HIV) infection on antiretroviral therapy who presented with diarrhea, fever, and abdominal pain. During hospitalization, jaundice, hepatomegaly, and cholestasis were observed. Magnetic resonance cholangiography revealed hepatic abscesses and portal thrombophlebitis. Blood cultures were positive for *A. haemolyticum*, with no additional isolates. Given the inability to perform drainage, antibiotic therapy was administered for six weeks, resulting in an adequate clinical response and progressive resolution of the lesions. **Conclusions:** *A. haemolyticum*, typically considered a low-virulence pathogen, can cause severe invasive infections, including hepatic abscesses and pylephlebitis, and should be considered a potential etiologic agent in immunocompromised populations.

Keywords

Arcanobacterium; hepatic abscess; venous thrombosis; HIV infections; sepsis.

INTRODUCTION

Hepatic abscess is an infectious inflammatory space-occupying lesion of the liver[(1)]. The bacteria most frequently associated with the development of hepatic abscesses are gram-negative bacilli, enterococci, and *Streptococcus spp*[(1,2)]. However, over recent decades, less common pathogens have been described, posing diagnostic and therapeutic challenges, particularly in immunosuppressed patients, individuals with diabetes, or those with alcoholism[(2)]. Among these pathogens, *Arcanobacterium haemolyticum* is a catalase-negative gram-positive bacillus usually associated with pharyngitis and cutaneous infections[(3)], especially in young adults. Clinical presentations of *A. haemolyticum* involving deep or visceral infections are unusual, while endocarditis, osteomyelitis, meningitis, and pneumonia are more commonly reported[(3)]. We present the case of a patient with multiple hepatic abscesses secondary to *A. haemolyticum* infection, highlighting the importance of recognizing this atypical pathogen in hepatobiliary infections among immunosuppressed patients.

CLINICAL CASE

A 30-year-old male patient presented with an eight-day history of frequent, low-volume diarrheal bowel movements with mucus and no blood, associated with nausea and vomiting of food contents, as well as subjective fever, chills, and poor oral intake tolerance. He had a history of human immunodeficiency virus (HIV) infection diagnosed three years earlier, with good adherence to treatment with tenofovir/emtricitabine/efavirenz (TDF/FTC/EFV), and a most recent CD4 count of 230 cells/μL. Review of systems revealed odynophagia at the onset of symptoms. On admission, the patient appeared in fair general condition and was febrile, hypotensive, jaundiced, and had diffuse abdominal pain with voluntary guarding and hepatomegaly. Initial laboratory tests showed severe thrombocytopenia and hyperlactatemia. Gastrointestinal sepsis was suspected; therefore, fluid resuscitation was initiated and antibiotic therapy with ceftriaxone 2 g IV daily was started for a planned five-day course. A gastrointestinal FilmArray panel was negative.

Given the findings of jaundice and hepatomegaly, a liver profile was ordered, showing aspartate aminotransferase (AST): 26, alanine aminotransferase (ALT): 32, alkaline phosphatase (ALP): 350, total bilirubin (TB): 1.66, direct bilirubin (DB): 1.16, and indirect bilirubin (IB): 0.50, consistent with a cholestatic pattern. Abdominal computed tomography demonstrated haustral dilatation, pneumobilia, and intrahepatic biliary duct dilatation (which had not been documented on the initial hepatobiliary ultrasound), as well as a 9 mm cecal appendix and portal pylephlebitis, probably secondary to septic emboli. Treatment with piperacillin-tazobactam 4.5 g IV every 6 hours was initiated, and the patient underwent exploratory laparotomy because of suspected appendicitis; however, no abnormalities were identified.

Due to persistent thrombocytopenia and splenomegaly, a portal Doppler ultrasound was requested to evaluate for portal hypertension. The study revealed acute thrombosis of the already known left branch of the portal vein, and full anticoagulation was initiated after surgery.

As no clear infectious focus had been identified as the source of the septic pylephlebitis, and given the presence of pneumobilia and intrahepatic biliary duct dilatation, magnetic resonance cholangiography was performed (**Figure 1**). The study showed an abnormal hepatic parenchymal signal with an image suggestive of a developing abscess in the periphery of hepatic segments VI and VII. In addition, blood culture results ultimately documented bacteremia caused by *A. haemolyticum*. Therefore, the condition was interpreted as pharyngeal (more common) and gastrointestinal (colitis) colonization with secondary bacteremia in the context of an immunosuppressed patient, ultimately leading to abscess formation and septic thrombophlebitis.

A six-week course of antibiotic therapy with ampicillin/sulbactam 3 g IV every six hours was completed. Follow-up abdominal computed tomography performed at three weeks documented enlargement of one of the hepatic collections, reaching a volume of 54 mL (**Figure 2**). However, imaging characteristics suggested that the abscess was organized, making drainage unfeasible. Given the favorable clinical course, resolution of abdominal pain, disappearance of diarrheal bowel movements, improvement in liver function tests (**Table 1**), and sustained reduction in the inflammatory response, antibiotic therapy was continued. A subsequent follow-up computed tomography scan performed two weeks later (**Figure 3**) demonstrated a

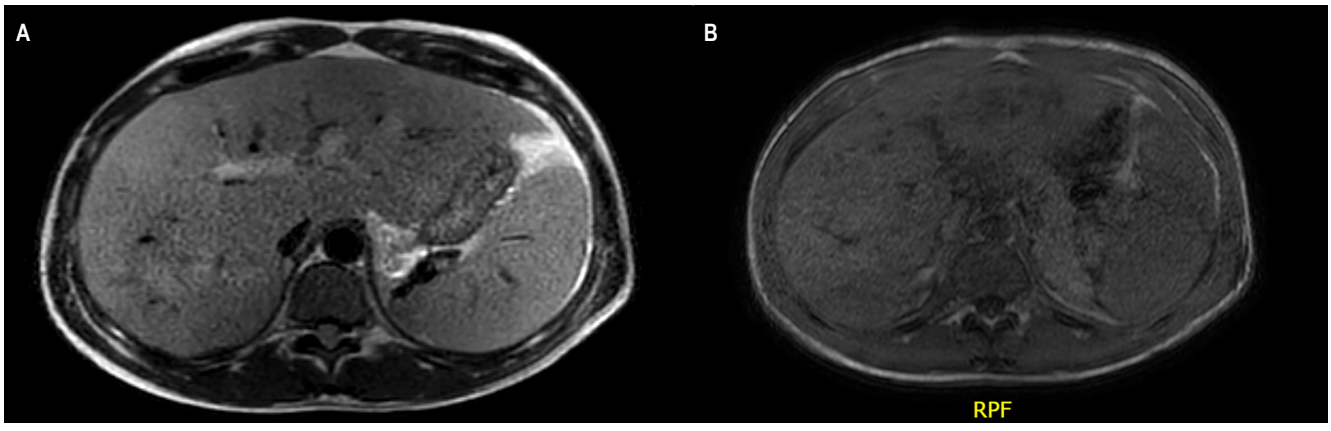


Figure 1. Magnetic resonance cholangiography. **A.** Peripheral focal lesion in hepatic segment VII, suggestive of an organizing abscess. **B.** Poorly defined peripheral hepatic lesions in segments VI–VII. Author's file.

reduction in the size of the hepatic abscesses, and follow-up blood cultures were negative. A total of six weeks of antibiotic treatment was completed. Outpatient follow-up at three months demonstrated complete resolution of symptoms.

Table 1. Evolution of Laboratory Parameters During Follow-up

Laboratory Tests	Admission	Day 3	Week 3	Week 6
Leukocytes (/µL)	9,800	17,330	4,600	5,000
Hemoglobin (g/dL)	13.5	11.9	10.0	12.3
Platelets (/µL)	42,000	29,000	345,000	400,000
AST (U/L)	25	127	26	17
ALT (U/L)	26	59	32	15
ALP (U/L)	185	329	350	130
Total bilirubin (mg/dL)	5.59	8.18	4.88	1.25
Creatinine (mg/dL)	1.54	1.12	0.88	0.98
Lactic acid (mmol/L)	3.2	2.2	1.3	0.8

ALT: alanine aminotransferase; AST: aspartate aminotransferase; ALP: alkaline phosphatase. Author's own research.

DISCUSSION

We present the case of a systemic *A. haemolyticum* infection in a patient with HIV infection, manifesting as sepsis accompanied by septic pylephlebitis of the portal vein and the formation of hepatic abscesses. The coexistence of this microorganism in the bloodstream, together with the observed thrombotic and hepatic complications, represents an unusual presentation distinct from the more commonly reported clinical picture of self-limited pharyngeal infections in young adults or mild cutaneous infections[2–4]. This clinical presentation may be associated with the patient's immunocompromised status, which predisposed him to invasive infection[4]. The literature reports few cases of hepatic abscesses caused by *A. haemolyticum*[2,3], suggesting an uncommon tropism for hepatic parenchyma.

In this case, the most likely pathophysiological sequence involved bacteremia secondary to pharyngeal or gastrointestinal colonization, followed by hepatic seeding and subsequent formation of multiple abscesses. The local inflammatory process and endothelial infection likely favored the development of pylephlebitis and portal vein thrombosis, findings that support the septic progression and organ dysfunction observed.

Early microbiological diagnosis enabled targeted antimicrobial management. Identification of *A. haemolyticum* in blood cultures, together with its susceptibility profile to penicillins(6–8), prompted optimization of antibiotic therapy to ampicillin/sulbactam, resulting in an adequate clinical and radiological response. This finding highlights the importance of maintaining active microbiological surveillance when unusual gram-positive cocci or bacilli are identified in immunosuppressed patients, avoiding underestimation of these organisms as contaminants.

Regarding management, hepatic abscesses associated with pylephlebitis usually require prolonged antibiotic therapy (four to six weeks)[5,9], with drainage when feasible. In the present case, radiological follow-up demonstrated

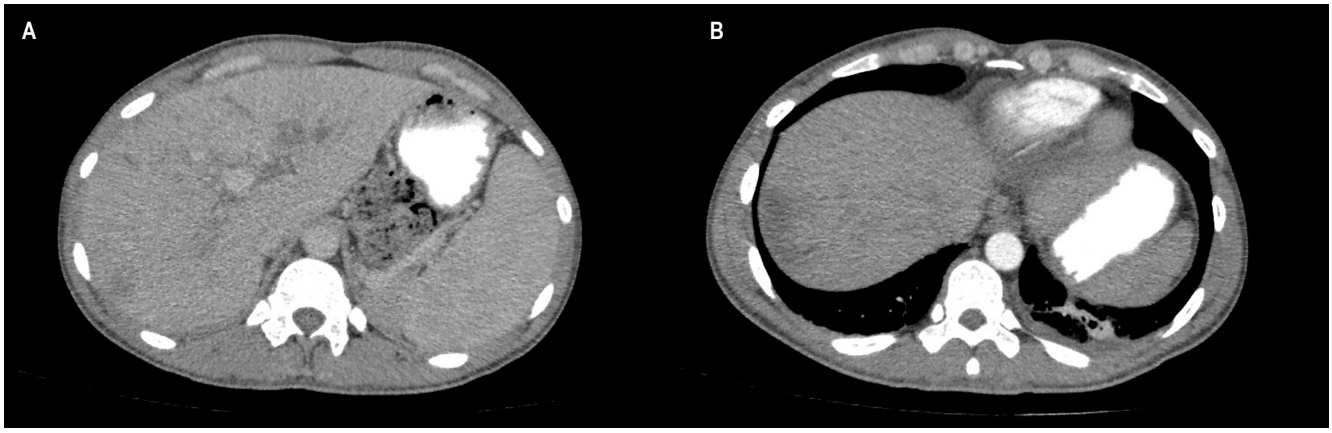


Figure 2. Contrast-enhanced computed tomography of the abdomen and pelvis. **A.** Peripheral caudal collection in segment VII measuring 19 × 19 × 16 mm (L × AP × T), consistent with a hepatic abscess, with an approximate volume of 8 mL. **B.** Additional collection in segment VII, located more superiorly and with poorly defined borders, measuring 57 × 59 × 31 mm, with an approximate volume of 54 mL. Thrombosis of the left portal vein and right portal branches. Heterogeneous enhancement of the hepatic parenchyma, predominantly during the arterial phase. Splenomegaly. Author's file.

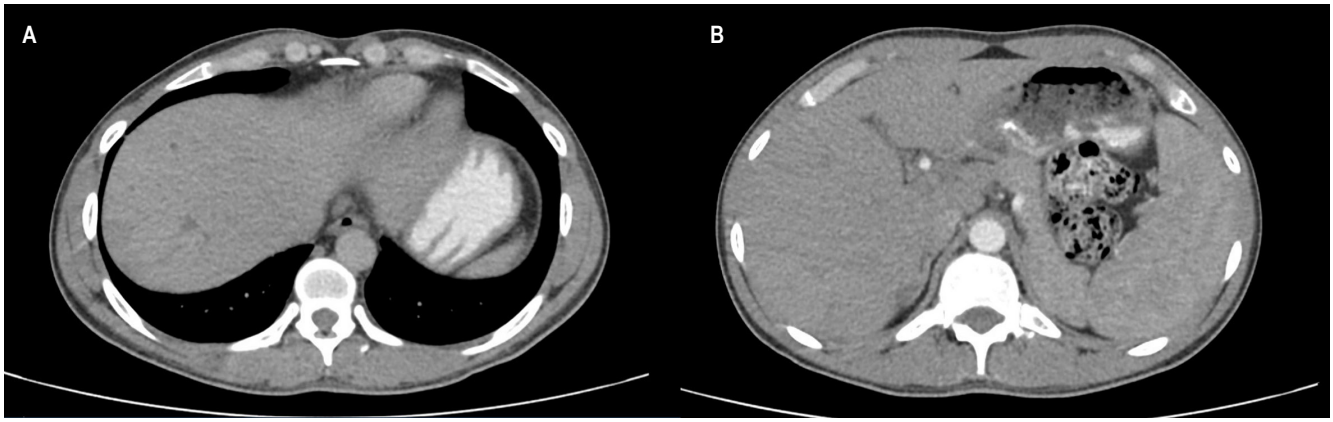


Figure 3. Follow-up computed tomography of the abdomen and pelvis. **A.** Irregular subcapsular hypodense lesion in segment VII measuring 23 × 18 mm. **B.** Additional rounded hypodense lesion in segment VII measuring approximately 15 × 18 mm. Findings were primarily attributable to hepatic abscesses, with a reduction in size compared with the previous study. Author's file.

apparent initial enlargement followed by regression, probably reflecting the liquefaction and organization process of the abscess. Since the lesions were not amenable to percutaneous drainage, exclusive medical management was chosen, with favorable clinical evolution and progressive reduction of the lesions during follow-up.

This case provides additional evidence of the capacity of *A. haemolyticum* to cause severe invasive infections outside the respiratory tract, particularly in immunocompromised hosts. It also emphasizes the need to consider this pathogen in the differential diagnosis of bacteremia caused by unusual gram-positive organisms and of hepatic infections without an evident biliary source.

CONCLUSION

This case demonstrates that *A. haemolyticum*, typically considered a low-virulence pathogen, can cause severe invasive infections, including hepatic abscesses and pylephlebitis, underscoring the importance of early microbiological identification and targeted antimicrobial management in immunocompromised populations.

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