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ORIGINAL ARTICLE

# Diagnostic delay in very early-onset inflammatory bowel disease: A tertiary single-center retrospective study

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## Abstract

**Background:** Very early-onset inflammatory bowel disease (VEO-IBD) may have an aggressive clinical course. Upon suspicion, an immediate transfer to a pediatric gastroenterology clinic should be made, considering that diagnostic delay (DD) in referral can have profound implications. **Objectives:** The objectives of the study are to investigate the time, proportion, and factors associated with DD in VEO-IBD and explore the symptoms at initial presentation. **Methods:** An observational, retrospective, single-center study of consecutive patients with VEO-IBD confirmed by histopathology was conducted. We measured the time to diagnosis—the interval between symptom onset and the final VEO-IBD diagnosis. DD was defined as the time to diagnosis that exceeded the 75$^{th}$ percentile. **Results**: Twenty-five children with VEO-IBD—16 with ulcerative colitis (UC) and 9 with Crohn's disease (CD)—were evaluated, with a median age of 34 months. Ages at first symptoms, first visit, and diagnosis were significantly lower for the CD group. However, there was no significant difference in the time from first symptoms to diagnosis between CD and UC. Patients with weight loss, anemia, and fistulas did not meet established criteria for DD and were referred early. **Conclusion**: Our study underscores the importance of early recognition of VEO-IBD, with bloody diarrhea, abdominal pain, and weight loss serving as crucial warning signs. Identifying these symptoms can aid in the early diagnosis and prompt referral to a specialist, potentially reducing the risk of DD. **Relevance for patients:** Early recognition of bloody diarrhea, abdominal pain, and weight loss in young children can speed diagnosis of VEO-IBD and ensure timely referral to specialist care.

***Keywords:*** Very early-onset inflammatory bowel disease; Diagnostic delay; Crohn's Disease; Ulcerative colitis; Diarrhea; Blood in stools; Abdominal pain; Weight loss

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## 1. Introduction

Pediatric inflammatory bowel disease (IBD) is a chronic condition, consisting of Crohn's disease (CD), ulcerative colitis (UC), and unclassified IBD.[1-3] In addition, pediatric IBD has a severe subgroup designated very early-onset IBD (VEO-IBD), which manifests

before 6 years of age, and is classified as infantile-onset IBD if diagnosed before 2 years of age and neonatal-onset if diagnosed by 28 days of age.[4,5] VEO-IBD is distinct in its clinical and therapeutic challenges and often follows an aggressive course that requires close specialist management. Upon suspicion of pediatric IBD, immediate referral to a pediatric gastroenterology clinic for investigation is not only necessary but also a professional responsibility that cannot be overstated. This rapid action can help prevent the development of severe complications,[6,7] underscoring the crucial role of early referral and diagnosis in managing VEO-IBD.

Diagnosing pediatric IBD involves several sequential time intervals, from the onset of symptoms to the final confirmation of VEO-IBD. Prolonged intervals between symptom onset and definitive diagnosis (diagnostic delay [DD]) can increase the risk of complications, such as more extensive disease, poorer treatment response, growth failure, and impaired health-related quality of life, accentuating the impact on patient outcomes.[8-10]

The overall time to diagnosis comprises distinct intervals: the time from symptom onset to the first visit to a healthcare provider, and the time from referral to endoscopy and histopathology. Reducing these delays may significantly improve patient outcomes. Identifying children who require timely referral to a specialist can reduce DD. Establishing a timely and accurate diagnosis is a key challenge in the management of IBD. Therefore, understanding and addressing these time intervals is crucial, as this can facilitate earlier diagnosis, timely initiation of effective treatment, and improved prognosis.

The objectives of this study are to thoroughly investigate the time and proportion of DD in children with VEO-IBD. In addition, we aim to categorize factors associated with DD, describe symptoms at initial presentation, investigate growth impairment, and examine the association between specific characteristics of the disease subtypes.

## 2. Methods

### 2.1. Study design, setting, and selection of participants

The study was an observational, retrospective, single-center, descriptive study that focused on consecutive patients referred with a suspicion of VEO-IBD between January 2012 and December 2022. These patients were all from the same geographic area and referred by the Brazilian Public Health System to the only regional tertiary center that treats children with VEO-IBD. The Botucatu Medical School Ethics Committee approved the study (CAAE 90158218.0.0000.5411). In addition, parents/caretakers provided informed consent.

### 2.2. Data collection

The data collection process was designed to extract clinical data from electronic medical records using a standardized, pre-designed protocol to ensure the comprehensive collection of sociodemographic, clinical, laboratory, radiological, and endoscopic findings. Two authors independently reviewed the medical records to ensure the completeness and accuracy of the data. The data were then stored in an Excel file (Microsoft, United States). The extracted data were entered into a database to facilitate standardized analysis.

Anthropometric measurements were obtained by trained pediatric nurses using standardized procedures. Body mass index (BMI) (kg/m$^2$) and corresponding BMI-for-age *z*-scores were calculated in accordance with the World Health Organization (WHO) growth assessment guidelines.[11,12] *z*-scores <−2 for any measurement were interpreted based on the WHO growth curve standards as indicative of potential growth or nutritional concerns.

### 2.3. Endoscopic evaluation

Biopsies of the colonic and ileal mucosa were obtained, and the extent of gross disease was based on the Paris Classification.[13,14] Information from colonoscopy and radiological examination reports was thoroughly and systematically utilized, further ensuring the reliability of the evaluation process.

### 2.4. Histopathological evaluation

Histopathological criteria of the European Crohn's and Colitis Organization and the European Society of Pathology were used.[15] Biopsies were fixed in buffered formalin, and 4- to 5-μm histological sections were stained with hematoxylin and eosin. Two observers performed histological examination. The histological diagnosis was based on the following characteristics: crypt (distortion, atrophy, cryptitis, and microabscesses), focal or diffuse inflammation, degree of mucosal inflammation, villiform surface, plasmacytosis, eosinophilia, presence or absence of granulomas, and lymphoid aggregates. Classifications of histological changes were performed according to a scoring system.[16] This standardized approach was used to promote reliability and consistency in histopathological evaluation.

The degrees of inflammation were recorded on a 5-point scale: 1 = no acute inflammation and no increase in chronic inflammation; 2 = only chronic inflammation; 3 = acute cryptitis, but without crypt abscesses; 4 = acute inflammation, including crypt abscesses (≤10% of crypts), and 5 = acute inflammation, crypt abscesses (>10% of crypts).

### 2.5. Diagnosis of IBD

The IBD diagnosis was based on clinical features and radiological, colonoscopic, and histopathological investigations, as proposed by the revised Porto Criteria.[14] VEO-IBD patients were divided into three age categories according to the Paris Classification, a widely accepted and validated system for classifying IBD patients by age and disease onset: neonate (<28 days), infantile (<2 years), and VEO (<6 years). Pediatric CD activity was calculated using the weighted Pediatric CD Activity Index.[17] For UC, a validated tool for assessing disease activity severity was used, measuring the Pediatric UC Activity Index.[18]

### 2.6. Time to diagnosis and DD

Signs and symptoms suggestive of IBD included diarrhea lasting ≥2–4 weeks with Bristol stool type 5–7; more than two episodes of bloody diarrhea, each lasting >1 week within the preceding 6 months; recurrent abdominal pain lasting >14 days; weight loss; and perianal diseases (abscesses, fistulas, fissures, and skin tags).[19]

The following age-related variables were used to calculate DD: age at first symptoms, age at first visit to a primary care pediatrician, duration of symptoms, age at first visit to the pediatric gastroenterology clinic, and age at diagnosis. The time interval (in months) definitions were time from the first symptoms to diagnosis and the time from the first visit to the pediatric gastroenterology clinic to diagnosis. DD in the current study was defined as the time to diagnosis in months exceeding the 75$^{th}$ percentile.[20-24] DD in pediatric IBD may lead to prolonged disease activity, increased complications, and poorer response to treatment.

### 2.7. Statistical analysis

GraphPad Prism (version 8.4.0, GraphPad Software, US) was used for statistical analysis. The Kolmogorov–Smirnov test was performed to evaluate the distribution of continuous variables. Fisher's exact test was used to analyze the categorical variables, presented as numbers and percentages. Continuous variables, expressed as medians and interquartile ranges (IQRs), were analyzed using the Mann–Whitney *U* test. All analytical tests were two-tailed, with a significance level of $p<0.05$.

## 3. Results

This study carefully evaluated 25 children diagnosed with VEO-IBD (16 with clinical and pathological features of UC and 9 with CD). Table 1 presents the baseline characteristics of the children and their parents at the first visit. The median age of all children was 34 months (IQR = 18.5–56.5). Children with CD presented at a younger age (median 14 months) than those with UC (median 48 months). This age difference was statistically significant ($p<0.001$), suggesting different disease progression or severity. Most children received breastfeeding and age-appropriate complementary feeding. However, 44% of the patients had been treated for food allergy, and 60% had been delivered by cesarean section.

Table 2 presents the signs and symptoms at the first visit. Diarrhea and blood in the stools were the most prevalent, with half of the children experiencing weight loss. Perineal fistulas were present in 20% of children with

**Table 1. Baseline characteristics of children and their parents at the first visit**

| Variables | Value (*n*=25) |
|---|---|
| Child characteristics | |
| Sex: Female/male, *n* (% female) | 21/04 (84) |
| Child age (months) | 34 (18.5–56.5) |
| Firstborn, *n* (%) | 13 (52) |
| Breastfeeding (months) | 6 (4–9) |
| Complementary diet (months) | 6 (5–6) |
| Previous treatment for FA, *n* (%) | 11 (44) |
| Antibiotic use in UC/CD (%) | 69/100 |
| Parental characteristics | |
| Mother's age (years) | 34.5 (28–38.5) |
| Father's age (years) | 38 (30–42.5) |
| Mother's education (years) | 8 (8–12) |
| Father's education (years) | 8 (8–12) |
| Family history of IBD, *n* (%) | 4 (16) |
| Birth characteristics | |
| Vaginal/cesarean (Cesarean %) | 10/15 (60) |
| Term, *n* (%) | 16 (64) |
| Preterm, *n* (%) | 9 (36) |
| Birth weight (g) | 3,280 (2,520–3,520) |
| Birth length (cm) | 49 (47.75–50) |
| Anthropometric variables at first visit | |
| Weight (kg) | 12.9 (7.79–19.15) |
| Weight (*z*-score) | −0.87 (−1.680–0.215) |
| Height (cm) | 87.5 (75.25–108.00) |
| Height (*z*-score) | −0.84 (−2.22–0.23) |
| BMI/A (kg/m$^2$) | 15.5 (14.7–15.9) |
| BMI/A (*z*-score) | −0.23 (−0.88–0.42) |

Note: Continuous variables are expressed as median (interquartile range) and categorical variables as number (percentage).
Abbreviations: BMI/A: Body mass index-for-age; CD: Crohn's disease; FA: Food allergy; IBD: Inflammatory bowel disease; IQR: Interquartile range; UC: Ulcerative colitis.

CD, underscoring the urgent need for effective and timely diagnosis and treatment.

Table 3 presents comparisons of the ages and time intervals between CD and UC. The ages at first symptoms, first visit, and diagnosis were all significantly lower for the CD group. In addition, the time from the first visit to the pediatric gastroenterology clinic to diagnosis was shorter for children with CD. There was no statistical difference in the time from first symptoms to diagnosis between CD and UC.

Table 4 compares clinical, laboratory, and anthropometric variables in patients with and without DD. DD (greater than the 75$^{th}$ percentile, i.e., 28 months) was observed in seven patients. Interestingly, the proportion of children with weight loss (67%) and low hemoglobin levels (<11 g/dL; 72%) was significantly higher in children without DD, highlighting the importance of early diagnosis in improving patient outcomes.

## 4. Discussion

The current study examined symptoms at initial presentation and identified factors associated with DD in children with VEO-IBD. Based on a widely accepted standard, diagnoses of IBD were made using laboratory, radiological, endoscopic, and histological criteria, as outlined in the revised Porto Criteria.[14]

Our study's main finding is that there is no significant difference in the time from the first symptoms to diagnosis between CD and UC. However, the time from first visit to the pediatric gastroenterology clinic to diagnosis was shorter for children with CD. The proportion of patients with DD at the ≥75$^{th}$ percentile (≥28 months) was 28%. The ages at first symptoms, first visit, and diagnosis were significantly lower for the CD group. Diarrhea and blood in stool were present in >90% of children. Previous treatment for food allergy was reported in 44% of patients, a family history of IBD in 16%, and delivery by cesarean section in 60%.

**Table 2. Symptoms and signs at the first visit**

| Symptoms/signs | *n* (%) |
|---|---|
| Diarrhea | 24 (96) |
| Blood in stool | 23 (92) |
| Abdominal pain | 16 (64) |
| Weight loss | 13 (52) |
| Perineal disease | 10 (40) |
| Plicoma | 5 (20) |
| Fistulas | 5 (20) |
| Genital fistula | 3 (12) |
| Perineal abscess | 2 (8) |
| Perianal fissure | 9 (36) |
| Extraintestinal symptoms | 3 (12) |

**Table 3. Comparisons of clinical variables between Crohn's disease and ulcerative colitis**

| Parameters | Median (IQR) | | *p*-value |
|---|---|---|---|
| | Crohn's disease | Ulcerative colitis | |
| Age (months) | | | |
| At first symptoms | 2.5 (1.0–12.0) | 36.0 (9.0–51.0) | 0.006 |
| At the first visit | 22.0 (5.0–32.0) | 46.5 (33.2–69.0) | 0.003 |
| Duration of symptoms | 16.0 (3.5–22.5) | 10.0 (3.7–24.7) | Ns |
| At diagnosis | 22.9 (5.0–32.7) | 58.1 (34.5–71.6) | 0.0006 |
| Time interval (months) | | | |
| The first symptoms of diagnosis | 16.8 (3.6-23.2) | 25.3 (6.7–32.8) | Ns |
| The first visit to PGEC for diagnosis | 0.8 (0.3–0.9) | 1.2 (0.7–13.0) | 0.007 |

Abbreviations: IQR: Interquartile range; ns: Non-significant; PGEC: Pediatric gastroenterology clinic.

**Table 4. Comparisons between clinical, anthropometric, and laboratory variables based on the presence or absence of diagnostic delay**

| Parameters | Diagnostic delay | | *p*-value |
|---|---|---|---|
| | Yes (*n*=7) | No (*n*=18) | |
| Family history of IBD, *n* (%) | 1 (14) | 3 (17) | ns |
| Vaginal section, *n* (%) | 2 (29) | 8 (44) | ns |
| Breastfeeding (mo), median (IQR) | 7 (6–26) | 5.5 (3.7–7.7) | ns |
| Food allergy treatment, *n* (%) | 5 (71) | 6 (33) | ns |
| Weight loss, *n* (%) | 1 (14) | 12 (67) | 0.03 |
| Weight-for-age *z*-score, median (IQR) | −0.87 (−1.6–0.3) | −0.7 (−2.0–0.2) | ns |
| Height-for-age *z*-score, median (IQR) | −0.61 (−1.8–0.3) | −0.9 (−2.7–0.1) | ns |
| Perineal fistula | 0 (0) | 5 (28) | ns |
| Hemoglobin <11 g/dL, *n* (%) | 1 (14) | 13 (72) | 0.02 |
| Positive CRP (mg/dL) | 5 (71) | 12 (67) | ns |
| Elevated ESR (mm/h) | 6 (86) | 16 (89) | ns |
| Albumin <3,5 g/dL | 2 (29) | 7 (39) | ns |
| Fecal calprotectin (µg/g), median (IQR) | 242 (141–3,000) | 1,107 (825–2,159) | ns |

Note: Percentages are calculated relative to the *n* number of the subgroup (Yes [*n*=7]; No [*n*=18]).
Abbreviations: CRP: C-reactive protein; ESR: Erythrocyte sedimentation rate; IBD: Inflammatory bowel disease; IQR: Interquartile range.

These findings have significant implications for the management of VEO-IBD, suggesting that early diagnosis and intervention could significantly reduce disease severity and improve patient outcomes. Timely diagnosis is measured as the difference between the time of first symptom onset and the time of diagnosis. Pediatricians and pediatric gastroenterologists must be motivated to emphasize the importance of early diagnosis, as it holds the promise of better outcomes for their patients.

The time from disease onset to established IBD diagnosis in children and adults may take several months, as described in existing systematic reviews.[25-27] One systematic review in pediatric IBD has emphasized delays in diagnosis, with a median of 2–10 months (range 2–18 months) for UC and 4–24 months for CD.[25] In another recent systematic review, DD was quantified at 4.5 months for IBD overall, with medians of 5 and 3 months, respectively, for children with CD and UC.[27]

In addition, age at diagnosis is clinically important. It appears that VEO-IBD is usually considered to be more severe when diagnosed later in life. In pediatric IBD overall (not specifically VEO-IBD), the median of DD was 5.0 months.[9,10,28-30] with significantly longer delays in children with CD than in those with UC. In the current study, the DD was 16 months for CD and 25 months for UC, which are substantially higher than the median reported in the literature. Two factors may contribute to DD in IBD in our country: the low prevalence of VEO-IBD and the prioritization of more common diseases.[19]

In the current study, DD is defined as being greater than or equal to 28 months (i.e., greater than the 75$^{th}$ percentile). However, when comparing CD and UC, there is no significant difference in the time from the onset of first symptoms to diagnosis, differing from the published data.[10,25] The discrepancy may be related to the similar duration of symptoms between CD and UC in our cohort, suggesting that the IBD investigation is unbiased. Indeed, prior studies indicate that with access to specialty care, disparities among minority and low-income patients with IBD may be reduced or improved.[31] The Red Flags index—a set of symptoms that indicate a high likelihood of IBD—when used in conjunction with fecal calprotectin, is practical for physicians in recognizing early CD and reducing DD.[32] Investigations for the diagnosis of IBD involve a combination of clinical, hematological, endoscopic, and histological approaches, as well as imaging studies.[33] These tools provide reassurance and confidence in the diagnostic process.

In certain pediatric cohorts, DD was associated with bowel stenosis, fistulas, and decreased height-for-age.[10,22] Consequently, DD would compromise therapy.[34,35] The National Institute for Health and Clinical Excellence (NICE) recommends that IBD be considered in patients with gastrointestinal symptoms lasting at least 6 weeks, such as (a) abdominal pain or discomfort, (b) bloating, and (c) changes in bowel habits.

In children with IBD, the most common symptoms are chronic diarrhea, rectal bleeding, abdominal pain, and weight loss. Because UC classically presents with rectal bleeding, its recognition and subsequent referral for investigation may be more straightforward.[36,37] Children with VEO-IBD often present with non-specific gastrointestinal symptoms that may be associated with a DD. In this cohort, rectal bleeding was present in >90% of children and weight loss in > 50%, underscoring the need for rapid referral when these symptoms are observed.

The definition of growth failure was based on inspection of growth curves at the discretion of the treating physician ($z$-scores <−2, or curve crossing two major percentiles). While the $z$-scores for both weight and length were slightly negative, mothers reported weight loss in more than 50% of cases. Thus, avoiding the decreased weight and height is a crucial part of good patient care.[36]

Misinterpretation of symptoms, especially those attributed to infection or food allergy, is common and may delay recognition of severe colitis. In this study, previous treatment for food allergy occurred in 44% of patients, while antibiotic therapy was prescribed to 69% of children with UC and to all with CD. Similar rates (48%) of previous food allergy treatment have been reported in children with IBD-VEO. On the other hand, antibiotic therapy for diarrhea was reported in 25% of children with IBD-VEO.[38]

Extraintestinal manifestations may occur, primarily in CD patients, who are twice as likely to develop them as those with UC, potentially leading to misdiagnosis. Many patients develop at least one extraintestinal manifestation before diagnosis.[39-41]

Laboratory tests to guide referral to a specialist pediatric gastroenterologist for suspected IBD are not yet available. Published summaries of alarm symptoms highlight the most frequently reported clinical features, and recommendations are available for interpreting fecal calprotectin levels in conjunction with other diagnostic measures. In addition, symptoms and signs were assessed to identify predictors of DD by comparing patients with and without DD. Weight loss and anemia did not meet both established criteria for DD. In addition, the presence of a fistula did not indicate DD. These features may have prompted earlier consultation, leading to more timely diagnosis and initiation of treatment.

The current study has some limitations. First, the study had a limited sample size. Nonetheless, standardized data collection permitted an objective analysis of the results. Second, only children diagnosed at a single tertiary center were included, which may limit the generalizability of the results. Third, the retrospective design was an inevitable limitation that may have compromised the accurate assessment of the DD. However, these data were recorded at the time of the first visit in routinely maintained clinical records, which may have improved accuracy. Fourth, DD may result from various factors, including patients delaying healthcare seeking, healthcare professionals failing to recognize IBD promptly, and delays in conducting investigations. Finally, this study's comparison was limited by the scarcity of publications on DD in VEO-IBD.

The strengths of this study include the following: first, our hospital is the only referral site for cases with clinical suspicion of VEO-IBD. Second, the study cohort comprises well-defined, consecutive VEO-IBD patients. Third, a single center can provide more uniform diagnostic procedures. Fourth, to the best of our knowledge, this study is the first to evaluate DD in VEO-IBD in Brazilian children.

## 5. Conclusion

The main conclusions were:

(a) The median time to diagnosis in children with VEO-IBD in this cohort was prolonged.
(b) Children with CD or UC can experience several months of DD.
(c) Most of the DD in VEO-IBD accrued before specialist consultation.
(d) Children often wait several months for a final diagnosis.
(e) UC cases are predominant in this study cohort.
(f) Bloody diarrhea is the most common symptom among children with VEO-IBD.

Overall, DD is associated with deleterious health outcomes. Therefore, general pediatricians must recognize symptoms, laboratory parameters, and risk factors to identify cases needing referral to a pediatric gastroenterologist. Rectal bleeding, weight loss, family history of IBD, and perianal disease should prompt active case-finding. Finally, further research is needed to identify factors influencing the length of DD in VEO-IBD and to develop strategies to minimize the DD.

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## Conflict of interest

The authors declare that they have no competing interests.

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## Ethics approval and consent to participate

The Ethics Committee from Botucatu Medical School approved the study (CAAE 90158218.0.0000.5411). Written informed consent was obtained from the parents/caretaker.

## Consent for publication

All authors consented to publication.

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