

## Etiology of Lower Gastrointestinal Bleeding in Children: A Single Center Experience from Southern Iran

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### ABSTRACT

#### BACKGROUND

This study aimed to determine the common etiologies and characteristics of lower gastrointestinal (GI) bleeding in children from Southern Iran.

#### METHODS

This five-year prospective cross-sectional study was performed from March 2006 to March 2011 in Nemazee Hospital. All pediatric patients (<18 years of age) who referred to our center with gross lower GI bleeding or two consecutive positive occult blood tests with at least a one-week interval were included in the study. Patients were categorized as neonates, infants, children and adolescents and the findings were reported separately in each group. Each patient underwent a colonoscopy and several mucosal biopsies were taken. Demographic and clinical information as well as colonoscopy and pathology findings were reported.

#### RESULTS

Overall, we included 363 pediatric patients with a mean age of 71.9±58.4 months (range: 1-216 months). There were 215 (59.2%) boys and 148 (40.8%) girls. The most common colonoscopy findings were sigmoid colon polyp in 91 (25.1%) patients followed by descending colon petechia in 78 (21.5%) patients, whitish rectal lesions in 45 (12.4%) patients, and sigmoid and rectal ulcers in 37 (10.2%) patients. Biopsy samples were non-specific in 96 (26.4%) patients. The most common pathological findings were juvenile polyp in 84 (23.1%) followed by lymphoid nodular hyperplasia in 55 (15.2%) and solitary rectal ulcers in 25 (6.9%) patients.

#### CONCLUSION

We found that lower GI bleeding was more common among 2-10 year-old children and was rarely encountered in neonates. Hematochezia was the most common form of presentation followed by bloody diarrhea and occult blood. The most common colonoscopy finding was sigmoid colon polyp and the most common pathological finding was juvenile polyp.

#### KEYWORDS

Lower gastrointestinal bleeding; Children; Colonoscopy; Iran

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## INTRODUCTION

The gastrointestinal (GI) tract is a highly vascularized organ with a large surface area. Thus any pathology involving the mucosa and the vasculature of the GI tract can lead to GI bleeding. GI bleeding is considered as an alarming sign in any age group and should be approached meticulously. Moreover, in children, GI bleeding causes panic and stress for the parents. It is categorized into upper and lower according to the site from which the bleeding originates. Lower GI bleeding is defined as bleeding originating from parts of the intestine distal to the ligament of Treitz, which is located at the duodenojejunal junction.<sup>1</sup>

There are several etiologies for lower GI bleeding in the pediatric practice ranging from mild conditions requiring little or no treatment to severe and life-threatening ones requiring immediate intervention.<sup>2</sup> The etiologies also vary according to the different age groups, which enables physicians to make appropriate differential diagnoses.<sup>3</sup> The etiologies include food allergy, infectious enterocolitis, Meckel's diverticulum, intussusception, lymphonodular hyperplasia, inflammatory bowel disease (IBD), angiodysplasia, hemorrhoids, and hemolytic-uremic syndrome (HUS).<sup>1-5</sup> Common causes of lower GI bleeding in children vary between studies.<sup>6-9</sup> Therefore, regional epidemiological data should be available in order to assist physicians with better management of these patients. As data regarding this issue is sparse in our region, we have performed this study in order to determine the common etiologies and characteristics of lower GI bleeding in children from Southern Iran.

## MATERIALS AND METHODS

This five-year prospective cross-sectional study was conducted from March 2006 to March 2011 in Nemazee Hospital, a tertiary health care center affiliated with Shiraz University of Medical Sciences. We consecutively enrolled all pediatric patients (<18 years) who referred to our center with gross lower GI bleeding or two consecutive positive occult blood tests with at least a one-week interval between tests.

We excluded those who needed emergency surgical intervention and those who had ingested red meat and peroxidase-containing fruits and vegetables such as broccoli, radishes, cantaloupes, or turnips 48 hours before the study.<sup>10-13</sup> The Institutional Review Board (IRB) as well as the Ethics Committee of Shiraz University of Medical Sciences approved the study and informed written consents were obtained from all patients or their guardians.

All patients were initially visited by a pediatrician. Data regarding the patients' demographic characteristics, co-morbidities, and clinical findings were recorded using a questionnaire. Patients with signs and symptoms of enterocolitis were requested to eliminate cow's milk products from their diets. Patients without good clinical responses were scheduled for colonoscopies. All patients underwent colonoscopy (small, flexible Olympus PCF-20 colonoscope) which were performed by a pediatric gastroenterologist in the Pediatric Gastroenterology Department of our center and the findings were recorded in the questionnaire. Patients received midazolam 1 mg/kg intravenously several minutes before the colonoscopy as a sedative agent. The colonoscopy was performed without prior bowel preparation for those who needed emergency intervention (those with massive and uncontrolled rectal bleeding), while other patients received 24 hours of bowel preparation prior to the colonoscopy. Several mucosal biopsies were taken under direct visualization of the mucosa and the vasculature. Phosphate-buffered formalin was used for fixing the specimens and biopsies. Paraffin embedded specimens were sectioned in 5–6  $\mu\text{m}$  slices and further stained with hematoxylin and eosin according to standard laboratory methods. All slides were reviewed by a pathologist and the results recorded in the questionnaire. The patients were categorized as neonates (1–28 days), infants (29 days–2 years), children (2–10 years) and adolescents (>10 years) and the findings were reported separately for each group.

Statistical analyses were performed using the SPSS software, version 16.0 (SPSS Inc., Chicago, IL, USA). The results were expressed as mean $\pm$ SD

and proportions as appropriate.

## RESULTS

We included 363 pediatric patients with documented lower GI bleeding who referred to our center during the study period. Patients' mean age was 71.9±58.4 months (range: 1-216 months). There was 1 (0.3%) neonate, 58 (15.9%) infants, 231 (63.7%) children, and 73 (20.1%) adolescents among the 215 (59.2%) boys and 148 (40.8%) girls.

The presenting symptoms were hematochezia in 291 (80.2%), bloody diarrhea in 66 (18.1%), and positive occult blood test in 6 (1.7%) patients. The mean duration of bleeding was 131.7±21.7 (range: 1-1460) days. The most common accompanying symptom was fever in 291 (80.2%) patients followed by abdominal pain in 89 (24.5%), weight loss in 37 (10.2%), and iron deficiency anemia in 5 (1.4%) patients. Ten (2.8%) patients needed blood transfusions during their hospital course.

Table 1 summarizes the characteristics of patients with lower GI bleeding who referred to our center. The most common colonoscopy finding was sigmoid colon polyps leading to rectal bleeding in 91 (25.1%) patients followed by descending colon petechia in 78 (21.5%), whitish rectal lesions in 45 (12.4%), and sigmoid and rectal ulcers in 37 (10.2%) patients (Table 1).<sup>9</sup>

Biopsy samples were non-specific in 96 (26.4%) patients, while the most common pathological finding was juvenile polyp in 84 (23.1%) followed by lymphoid nodular hyperplasia in 55 (15.2%), and solitary rectal ulcers in 25 (6.9%) patients (Table 1).

The colonoscopy and pathology findings of patients in each age groups are summarized in Table 2. Descending colon petechia was the most common colonoscopic finding among neonates (0.3%) and infants (9.5%), while the most common colonoscopic findings in children and adolescents were sigmoid colon polyps (23.1%) and sigmoid and rectal ulcers (4.3%), respectively.

Pathological examination of the specimens revealed that lymphoid nodular hyperplasia was the most common finding in neonates (0.3%) and infants (4.6%) while juvenile polyps and solitary rectal ulcer accounted for most pathologies that caused rectal bleeding in children (20.6%) and adolescents (3.4%), respectively.

## DISCUSSION

The presence of bloody stool is common in pediatrics. It can cause stress and panic in parents, babysitters, and even physicians. Previous studies have demonstrated that rectal bleeding in most infants and children is a benign and self-limiting condition usually requiring no treatment or one that can be managed by supportive care. The fact that etiologies of pediatric lower GI bleeding vary among different geographical regions and ethnic groups necessitates the investigation of the epidemiology and characteristics of this disorder in each region.

We found that lower GI bleeding was more common among 2–10 year-old children and rarely encountered in neonates. Hematochezia was the most common form of presentation followed by bloody diarrhea, which was similar to previous studies of Western populations.<sup>3-5</sup> In the current study, the most common colonoscopy finding was sigmoid colon polyps leading to rectal bleeding followed by descending colon petechia, and sigmoid and rectal ulcers. Juvenile polyps, lymphoid nodular hyperplasia and solitary rectal ulcers were the most common pathology findings of these patients. The etiologies of lower GI bleeding in our series varied significantly with previous reports.<sup>1,2,4,5</sup> Most previous reports have shown that constipation with fissure formation was the most common cause for rectal bleeding in toddlers and school-age children.<sup>1-3</sup> Hillemeier and coworkers<sup>3</sup> demonstrated that anal fissure and infectious diarrhea were the most common causes of lower GI bleeding in neonates, toddlers and school-age children. Milk or soy allergy as well as intussusceptions have been classified as other common causes of lower GI bleeding in children.<sup>1,3</sup>

Although polyps were the most common cause of lower GI bleeding in our study, they were less common in Western populations.<sup>1-5</sup> Haghi Ashtiani and colleagues<sup>7</sup> have shown that polyps are common among Iranian children and juvenile polyps account for most cases. Further studies are required to investigate the possible etiologies for the high prevalence of polyps in Iranian children. A study in 80 children who were managed with lower GI bleeding from January 2005 to December 2007 in various hospitals in Karachi has shown the most common causes of lower GI bleeding to be rectal polyps, infectious colitis, ulcerative colitis and non-specific colitis.<sup>11</sup> In Egyptian children the most common cause of

**Table 1: Characteristics and findings of study patients presenting with lower GI bleeding.**

Variable	Value
<b>Age (mean±SD, months)</b>	71.9±58.4
Neonates (%)	1 (0.3%)
Infants (%)	58 (15.9%)
Children (%)	231 (63.7%)
Adolescents (%)	73 (20.1%)
<b>Sex</b>	
Boys (%)	215 (59.2%)
Girls (%)	148 (40.8%)
<b>Presenting symptoms</b>	
Hematochezia (%)	291 (80.2%)
Bloody diarrhea (%)	66 (18.1%)
Positive occult blood (%)	6 (1.7%)
<b>Colonoscopy findings</b>	
Sigmoid colon polyps (%)	91 (25.1%)
Descending colon petechia (%)	78 (21.5%)
Rectal whitish lesions (%)	45 (12.4%)
Sigmoid and rectal ulcers (%)	37 (10.2%)
Rectal erythematous lesions (%)	33 (9.1%)
Rectal and sigmoid erosions (%)	22 (6.1%)
Normal mucosa (%)	17 (4.7%)
Diffuse nodularity with edema (%)	13 (3.6%)
Loss of vascular markings and mucosal fragility (%)	10 (2.8%)
Aphthous mucosal lesions (%)	7 (1.9%)
Diffuse colitis with pseudopolyp (%)	5 (1.4%)
Anal fissure (%)	3 (0.8%)
Hemorrhoidal tag (%)	2 (0.4%)
<b>Pathology findings</b>	
Non-specific (%)	96 (26.4%)
Juvenile polyp (%)	84 (23.1%)
Lymphoid nodular hyperplasia (%)	66 (18.2%)
Solitary rectal ulcers (%)	25 (6.9%)
Ulcerative colitis (%)	21 (5.8%)
Normal	18 (5.2%)
Crohn's disease	16 (4.4%)
Allergic colitis (%)	7 (1.9%)
Pseudomembranous colitis (%)	6 (1.7%)
Graft-versus-host disease (GVHD) (%)	5 (1.4%)
Post-infection colitis	5 (1.4%)
Proctitis	5 (1.4%)
Drug-induced colitis (%)	5 (1.4%)
Hemorrhoidal tag (%)	2 (0.4%)
Post-transplant lymphoproliferative disorder (%)	2 (0.4%)

**Table 2: Characteristics and findings of study patients presenting with lower GI bleeding according to age.**

Variable%	Neonates (n=1)%	Infants(n=58)%	Children (n=231)%	Adolescents(n=73)%
<b>Sex</b>				
Boys	0 (0)	32 (8.8)	139 (38.3)	44 (12.1)
Girls	1 (0.3)	26 (7.2)	92 (25.3)	29 (8)
<b>Presenting symptoms</b>				
Hematochezia	0 (0)	56 (15.4)	179 (19.3)	56 (15.4)
Bloody diarrhea	1 (0.3)	16 (4.4)	35 (9.6)	15 (4.1)
Positive occult blood	0 (0)	1 (0.3)	3 (0.8)	2 (0.6)
<b>Colonoscopy findings</b>				
Sigmoid colon polyps	0 (0)	3 (0.9)	80 (23.1)	8 (2.3)
Descending colon petechia	1 (0.3)	33 (9.5)	42 (12.1)	2 (0.6)
Whitish rectal lesions	0 (0)	8 (2.3)	24 (6.9)	13 (3.8)
Sigmoid and rectal ulcers	0 (0)	2 (0.6)	20 (5.8)	15 (4.3)
Rectal erythematous lesions	0 (0)	2 (0.6)	16 (4.6)	15 (4.3)
Rectal and sigmoid erosions	0 (0)	1 (0.3)	11 (3.2)	10 (2.9)
Normal mucosa	0 (0)	4 (1.1)	10 (2.9)	3 (0.8)
Diffuse nodularity with edema	0 (0)	3 (0.9)	8 (2.3)	2 (0.6)
Loss of vascular markings and mucosal fragility	0 (0)	0 (0)	8 (2.3)	2 (0.6)
Aphthous mucosal lesions	0 (0)	0 (0)	7 (2)	0 (0)
Diffuse colitis with pseudopolyp	0 (0)	2 (0.6)	2 (0.6)	1 (0.3)
Anal fissure	0 (0)	0 (0)	2 (0.6)	1 (0.3)
Hemorrhoidal tag	0 (0)	0 (0)	1 (0.3)	1 (0.3)
<b>Pathology findings</b>				
Non-specific	0 (0)	20 (5.7)	54 (15.5)	22 (6.3)
Juvenile polyp	0 (0)	2 (0.6)	75 (20.6)	7 (2)
Lymphoid nodular hyperplasia	1 (0.3)	23 (6.6)	41 (11.7)	1 (0.3)
Solitary rectal ulcers	0 (0)	0 (0)	13 (3.7)	12 (3.4)
Ulcerative colitis	0 (0)	1 (0.3)	9 (2.6)	11 (3.2)
Normal	0 (0)	4 (1.1)	11 (3.1)	3 (0.9)
Crohn's disease	0 (0)	0 (0)	6 (1.7)	10 (2.9)
Allergic colitis	0 (0)	3 (0.9)	1 (0.3)	3 (0.9)
Pseudomembranous colitis	0 (0)	2 (0.6)	4 (1.1)	0 (0)
Graft-versus-host disease (GVHD)	0 (0)	5 (1.4)	0 (0)	0 (0)
Post-infection colitis	0 (0)	2 (0.6)	2 (0.6)	1 (0.3)
Proctitis	0 (0)	1 (0.3)	4 (1.1)	0 (0)
Drug-induced colitis	0 (0)	0 (0)	4 (1.1)	1 (0.3)
Hemorrhoidal tag	0 (0)	0 (0)	0 (0)	2 (0.6)
Post-transplant lymphoproliferative disorder	0 (0)	0 (0)	2 (0.6)	0 (0)

rectal bleeding was infectious enterocolitis. Colorectal polyps and chronic colitis were the next common causes of bleeding per rectum respectively.<sup>12</sup>

A systematic analysis of Chinese literature found an additional 160 studies that provided relevant data in 53 951 patients showed that the three most common etiologies for GI bleeding in children were colorectal polyps (49%), chronic colitis (11%), and intussusception (9%). Colorectal cancer was extremely rare in children, with only one patient that was diagnosed with colorectal cancer.<sup>13</sup>

Ojuawo and colleagues reported that diarrhea, vomiting, abdominal pain, anorexia, and failure to thrive were the most common accompanying symptoms of bloody diarrhea and rectal bleeding.<sup>14</sup> In another case-control study, Arvola and coworkers reported that loose and mucous stools, abdominal pain, and vomiting were frequently detected in those children with bloody stools.<sup>5</sup> In our study, fever, abdominal pain, loose stool, weight loss, and iron deficiency anemia were the most common symptoms that accompanied bloody stool.

It is believed that rectal bleeding in children should not affect the growth pattern negatively, because of the mild and transient nature of the disorder. However we found that 37 (10.2%) patients suffered from weight loss and 5 (1.4%) had iron deficiency anemia, which was suggestive of the chronic nature of the disease. Lower GI bleeding in children is usually an acute condition that rarely results in hemodynamic or hemoglobin changes. Peptic ulcers, cow's milk allergy and arteriovenous malformations are conditions which may cause chronic occult bleeding leading to iron deficiency anemia in children.<sup>1,2</sup> Pasricha and colleagues have found that most children with iron deficiency anemia suffer from low iron intake; less commonly a source of occult bleeding may be found.<sup>15</sup> Thus we believe that our patients with iron deficiency anemia were suffering from this condition before developing lower GI bleeding; in other words, iron deficiency anemia in our study was not a result of lower GI bleeding, which was consistent with previous studies.<sup>5-8,15</sup>

Age is considered an important factor in differentiating the etiologies of lower GI bleeding in pediatrics. As shown in previous studies polyps are considered the most common causes of lower GI bleeding in ages fol-

lowing infancy.<sup>1,2</sup> Bleeding from polyps are usually fresh and painless (hematochezia) but minimal in amount when resulting from stalk vasculature rupture or surface abrasions. Juvenile polyps are the most common types of polyps among children and adolescents.<sup>7</sup> These polyps are usually hamartomatous and account for 90% of all polyps found in children.<sup>16</sup> Juvenile polyps are usually solitary and are located in the rectosigmoid area, as we have reported. Several syndromes including familial polyposis coli, Gardner syndrome, and Turcot syndrome result in adenomatous polyps.<sup>17</sup> In our study, we have found that lymphoid nodular hyperplasia was the most common cause of bleeding in infants. It results in GI infections or protein allergies characterized by multiple, yellowish lymphoid follicles. Lymphoid nodular hyperplasia is usually asymptomatic and resolves spontaneously but needs dietary restriction and occasional steroid medication. It is accompanied by fresh rectal bleeding in infants which is self-limited. The incidence of these findings decreases with increasing age.<sup>18</sup>

Gastroenteritis and GI infections are considered as the most common causes of lower GI bleeding and dysentery in any age group.<sup>2</sup> Several microbial agents have been found to be responsible for dysentery including salmonella, shigella, *Campylobacter jejuni*, *Yersinia enterocolitica*, *Escherichia coli* (0157:H7), *Clostridium difficile*,<sup>4</sup> *Entamoeba histolytica*, rotavirus, and Norwalk virus.<sup>5</sup> In our report, infections were the eleventh most common cause of bloody diarrhea while in other studies they have been classified as the first or second most common causes of lower GI bleeding in children.<sup>19,20</sup> This finding has possibly resulted from selection bias because we included those who referred to our center, a tertiary referral center in Southern Iran where patients with more critical conditions would visit.

Food allergy is also considered as one of the most common causes of lower GI bleeding in neonates and infants.<sup>2</sup> The mechanisms responsible for rectal bleeding secondary to food allergy include food-induced enterocolitis syndrome, food-induced colitis, and allergic eosinophilic gastroenteritis.<sup>21</sup> Protracted vomiting and bloody diarrhea are classic symptoms of cow's milk allergy in infants which usually leads to dehydration, especially in younger infants (<3 months of age).<sup>22</sup> In severe cases, malabsorption, protein-losing enteropathy, and

failure to thrive may result. The most common agents responsible for food allergies include cow's milk and soy protein. These allergies frequently occur in first three months of life secondary to milk proteins and soy hypersensitivity.<sup>22</sup> Food allergy in these children is self-limited and does not cause weight loss or failure to thrive. These children present with occult blood in their stools and fresh bleeding is rare. In our study, 7 (1.9%) patients have been diagnosed with food allergies, most were infants who presented with positive occult blood. It has been shown that breast and cow's milk hydrolysate protect against cow's milk allergy or allergic diseases in neonates.<sup>23</sup> The prevalence of breastfeeding in Iran is favorable compared to countries that are members of the European Union, and is reported to be approximately 90% in the first year of life.<sup>24</sup> This may be the reason for the low prevalence of cow's milk allergy in our study compared to previous studies.<sup>1-9</sup>

IBD including ulcerative colitis and Crohn's disease are also common etiologies of lower GI bleeding in children. Previous studies have shown that approximately 20% of patients with IBD are diagnosed before the age of 20 years, among whom most are below 15 years of age.<sup>13</sup> Rectal bleeding is the main presenting symptom in most patients with ulcerative colitis and 25% of those with Crohn's disease.<sup>25</sup> In our study, ulcerative colitis and Crohn's disease were the fifth and seventh most common causes of rectal bleeding and accounted for 10.2% of all patients. This was higher compared with previous studies from Western populations, which was an alarming finding that requires further investigation.<sup>3-5</sup>

Our study has some limitations. First, it was a cross-sectional study that included all children who referred to our tertiary center with lower GI bleeding. This selection method possibly resulted in selection bias because only patients with more critical illnesses referred to our center. Future studies should be population-based in order to avoid this type of bias. Second, we have excluded those who needed immediate surgical intervention. Thus there is no data available on patients who had lower GI bleeding secondary to surgical impressions including intussusception, volvulus, necrotizing enterocolitis, and toxic megacolon. A cross-sectional survey including surgical cases is recommended in this region of Iran. However, this is the first report from Southern Iran on the charac-

teristics of lower GI bleeding in the pediatric population. We found that lower GI bleeding was more common among 2–10 year-old children and rarely encountered in neonates. Hematochezia was the most common form of presentation followed by bloody diarrhea and occult blood, which was similar to Western populations. The most common colonoscopy finding was sigmoid colon polyps that lead to rectal bleeding followed by descending colon petechia, whitish rectal lesions, and sigmoid and rectal ulcers. The most common pathological finding was juvenile polyp followed by lymphoid nodular hyperplasia and solitary rectal ulcers.

#### CONFLICT OF INTEREST

The authors declare no conflict of interest related to this work.

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