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Etiology and Treatment Advances of Hematochezia in Infants Aged ≤3 Months

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Abstract

The incidence of hematochezia in infants aged three months or younger has shown an upward trend in recent years. This condition is characterized by visible bloody stools, which may appear bright red, dark red, jam-like, or mucus-purulent bloody stools, and is often accompanied by positive fecal occult blood tests, with or without additional systemic clinical symptoms. The etiology is multifactorial, potentially influenced by the maternal health status during pregnancy, neonatal diseases or treatments received in the NICU, and the methods used for establishing enteral and parenteral nutrition. Notably, allergic factors have gained prominence in recent years. This paper reviews recent studies to elucidate the incidence, primary causes, and current treatment approaches for early infant hematochezia, providing a reference for clinical practice.

Keywords

Neonate, Infant, Blood in Stool, Etiology, Diagnosis and Treatment, Surgical Disease

1. Surgical Causes of Hematochezia in Early Infancy

1.1. Acute Intussusception

Acute intussusception is most prevalent in infants aged 4 to 9 months [1], with a lower incidence in those under 3 months. However, in younger infants, the condition can present acutely, progress rapidly, and lead to intestinal necrosis. This is attributed to the immature development of the digestive system in this age group, which is prone to motility disorders and instability of the mesentery at the ileocecal junction. According to a study by Li Jing'en *et al.* [1], among 7881 cases of intussusception treated at their hospital between 2008 and 2013, only 0.5% were

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infants under 3 months. In a cohort of 108 infants younger than 4 months, 68 presented with hematochezia, highlighting it as a significant clinical symptom of intussusception. While most cases are idiopathic, approximately 6% are associated with pathological intestinal conditions such as Meckel's diverticulum, Henoch-Schönlein purpura, intestinal duplication, polyps, or lymphoma [2]. Ultrasound is a reliable diagnostic tool for this condition.

1.2. Intestinal Stricture Following NEC

Intestinal stricture is a common complication following neonatal necrotizing enterocolitis (NEC), typically occurring within three months after the acute phase of NEC, with an average diagnosis time of 47.8 days post-NEC. It predominantly affects the ileum (17.7%) and colon (82.3%) and can manifest as single or multiple strictures [3]-[5]. Studies indicate that 47.3% of infants with stage II NEC develop intestinal stricture, with the incidence rising to 90% in stage III NEC [6]. The incidence of stricture is 17.0% with conservative management and 24.0% with surgical intervention [7]. The severity of the stricture may be influenced by the severity of the underlying disease and the treatment approach. Patel *et al.* [8] suggest that early enteral feeding may reduce the incidence of post-NEC intestinal stricture, whereas conditions that compromise intestinal blood supply, such as hemodynamically significant patent ductus arteriosus (hsPDA) in preterm infants and inguinal hernia, may increase the risk of developing intestinal stricture.

1.3. Intestinal Stricture Induced by Appendicitis

In neonates, recurrent abdominal distension, occult blood in stools, and elevated inflammatory markers such as white blood cells and CRP should prompt consideration of appendicitis. Although rare in the neonatal period, with an incidence ranging from 0.04% to 0.2%, it predominantly affects males (75%) and is more common in premature infants (25% to 50%). Li Jia *et al.* [9] documented a case of neonatal intestinal stricture due to appendicitis, characterized by being small for gestational age, slow fetal growth in late pregnancy, and symptoms such as recurrent abdominal distension, occult blood in stools, and elevated inflammatory markers like white blood cells and CRP by the fourth day after birth, mimicking intestinal infection and feeding difficulties. Despite interventions including anti-infective treatment and allergen avoidance, the condition persisted. Subsequent exploratory laparotomy revealed inflammatory encapsulation in the appendix region, suggesting the onset of appendicitis during the fetal period.

1.4. Extensive Intestinal Necrosis Due to Intestinal Malrotation with Gastric Wall Defect

Congenital intestinal malrotation (CIM) manifests in 80% of cases during the neonatal period, representing a common gastrointestinal malformation in newborns, with an incidence of 1 in 500 to 1 in 200. This condition arises from a disruption in the normal rotational movement around the superior mesenteric artery during embryonic intestinal development. Key symptoms include bilious vomiting,

abdominal distension, abdominal pain, and bloody stools, indicative of high intestinal obstruction and intestinal volvulus necrosis, with a mortality rate below 5% [10] [11]. CIM frequently co-occurs with congenital gastric wall defect (CGWD), which, when leading to gastric perforation, has a high mortality rate, with survival rates between 75% and 83% [12]. Wang Yuan [13] *et al.* reported a case involving a 4-day-old male neonate presenting with "bloody stools, vomiting, and abdominal distension", diagnosed with CIM and CGWD, accompanied by infectious shock, multiple organ failure, extensive intestinal necrosis, and short bowel syndrome, ultimately achieving successful treatment through three surgical interventions.

1.5. Meckel's Diverticulum

Over half of Meckel's diverticulum (MD) cases are diagnosed in children under the age of two, with hematochezia being the most prevalent complication, occurring at a rate of 2% - 4%. This condition arises from the failure of the yolk stalk or vitelline duct to close at the intestinal end during the 5th to 7th week of gestation. The incidence is similar between genders, although complications are more frequently observed in males [14] [15]. A study by Tian Yanhui *et al.* [16] involving 264 surgically confirmed MD patients found that 17% were under six months old. In infants and young children, MD is often an incidental finding during abdominal surgery for conditions such as intussusception, intestinal obstruction, volvulus, internal hernia, adhesions, inguinal hernia, gastrointestinal bleeding, diverticulitis, and perforation. Honig J [17] and colleagues reported a case involving a 5-day-old male infant presenting with "bloody stool and vomiting". An abdominal X-ray indicated intestinal obstruction, and surgery revealed a 24 cm segment of the ileum, tightly adhered to the fibrotic and ischemic tip of the diverticulum, which was subsequently resected. Histological examination post-surgery confirmed the diagnosis of MD.

1.6. Congenital Megacolon

Congenital megacolon, or Hirschsprung's disease (HSCR), also referred to as aganglionic megacolon, occurs in approximately 1 in 5000 live births, with 80% of cases manifesting within the first few months of life. Severe cases may lead to complications such as intestinal perforation, obstruction, and Hirschsprung-associated enterocolitis (HAEC), with a mortality rate of approximately 2% - 5% [18]. HAEC represents the most severe complication of HSCR, presenting with explosive bloody stools, fever, and abdominal distension, posing a significant threat to life. Factors such as prematurity, delayed diagnosis, the extent of the aganglionic segment, trisomy 21, and congenital anomalies of the heart and nervous system increase susceptibility. Although there is no consensus on the associated risk factors, they are crucial for early clinical recognition and diagnosis [19] [20].

1.7. Midgut Volvulus

Midgut volvulus (MV) has an annual incidence rate of 1.7 to 5.7 per 100,000

individuals, with approximately 75% of cases occurring within the first year of life, predominantly during the neonatal period. The primary clinical manifestations include bilious vomiting and abdominal distension, while hematochezia is exceedingly rare [21]. The presence of hematochezia often signifies a critical condition, potentially necessitating intestinal resection, and may result in short bowel syndrome or mortality. In a study by Guan Qiansi [22] *et al.*, involving 231 pediatric MV cases, 9.1% exhibited intestinal necrosis at the time of surgery, with only two cases initially presenting with hematochezia, which were preoperatively considered as necrotizing enterocolitis (NEC). Research indicates that MV may be linked to preterm birth, low Apgar scores, and delayed meconium passage [21]. Furthermore, the etiology of preterm birth may involve intermittent prenatal volvulus causing intestinal ischemia, leading to fetal stress, premature rupture of membranes, chorioamnionitis, placental insufficiency, and fetal heart rate abnormalities. Consequently, in preterm infants who experience sudden clinical deterioration with marked abdominal distension and hematochezia, clinicians should consider the possibility of MV-induced intestinal necrosis in addition to NEC.

1.8. Vascular Malformation

Children presenting with persistent hematochezia and anemia may also suffer from colorectal vascular malformation (CRVM). Huang Y [23] *et al.* documented 23 pediatric cases of CRVM, with a median age of 1.4 years (ranging from 1 month to 12 years). Fourteen of these cases were initially misdiagnosed as anal fissure, rectal polyp, inflammatory bowel disease, portal hypertension, or Meckel's diverticulum, and were ultimately diagnosed through colonoscopy, enhanced CT, and angiography, with all 23 cases undergoing surgical intervention. CRVM is a rare benign vascular anomaly, typically located in the rectosigmoid region, primarily consisting of venous malformations. These are often isolated lesions but may also be part of systemic syndromes such as Klippel-Trenaunay syndrome, making them highly susceptible to misdiagnosis [24]. Wang [25] *et al.* discovered that over 50% of adult CRVM cases can be traced back to childhood or even infancy.

1.9. Diseases of the Sigmoid Colon/Rectum and Anus

Anal-rectal fissures and polyps are potential causes of bloody stools in infants. Research has indicated [26] that the incidence of anal fissures is lower in newborns compared to older children. Common contributing factors include certain laxative treatments, excessive wiping, and hard stools, all of which can increase pressure in the internal anal sphincter.

2. Medical Causes of Early Infant Hematochezia

2.1. Systemic Hemorrhagic Disorders: Some Cases Are Identified Due to Hematochezia Occurring in Early Infancy [27]

2.1.1. Vitamin K Deficiency Bleeding

In infants under six months, sudden spontaneous bleeding with normal platelet

and fibrinogen levels, and an international normalized ratio (INR) of ≥4 or a prothrombin time exceeding four times the normal value, can be diagnosed as vitamin K deficiency bleeding (VKDB) [28]. This condition has received considerable attention from clinicians and is subject to proactive prevention and effective treatment. Huang Xin [29] *et al.* conducted a comparative study involving 60 infants aged 0 - 3 months with unexplained gastrointestinal bleeding and healthy controls, demonstrating that deficiencies in VitK 1 and VitK 2 are linked to unexplained gastrointestinal bleeding in infants. TT, PT, APTT, and FIB serve as crucial clinical monitoring parameters.

2.1.2. Genetic Coagulation Disorders

In the neonatal period, unexplained bleeding at skin or venipuncture sites, subcutaneous bleeding, visceral bleeding, and gastrointestinal bleeding, with normal platelet count and function, after excluding other causes, often indicate congenital coagulation factor deficiencies. Hemophilia A and B are the most prevalent, frequently with a family history. Diagnosis can be confirmed through coagulation factor activity levels and genetic testing [30] [31].

2.1.3. Acquired Coagulation Disorders

Severe medical conditions such as severe infections, sepsis, severe asphyxia, severe hemolytic disease, and shock can lead to disseminated intravascular coagulation (DIC) and liver dysfunction, which may result in bleeding. The pathophysiology of DIC involves the activation and dysregulation of the coagulation and inflammatory systems, leading to excessive thrombin production. This is accompanied by widespread fibrin deposition and the consumption of coagulation proteins and platelets, ultimately causing multiple organ dysfunction. Clinically, this can manifest as spontaneous bleeding at various sites.

2.1.4. Immune-Mediated Thrombocytopenia

Immune thrombocytopenia (ITP) is a relatively common hemorrhagic disorder characterized by isolated thrombocytopenia, though it is less frequently observed in the neonatal period. In cases of severe bleeding associated with ITP, intracranial hemorrhage is the most prevalent, followed by gastrointestinal bleeding. Zhou F [32] and colleagues conducted an analysis of 663 pediatric ITP cases, revealing that severe bleeding occurred in 3.8% of cases. Among these, 6 children experienced gastrointestinal bleeding, with 1 case presenting with hematemesis and shock, and 5 cases presenting with melena, all occurring in infants under 6 months of age.

2.2. Inflammatory Bowel Disease in the Neonatal Period

Inflammatory bowel disease (IBD) encompasses a group of non-specific inflammatory disorders affecting the intestines, characterized clinically by persistent abdominal pain, diarrhea (which may or may not be accompanied by bloody stools), growth retardation, and occasionally extraintestinal symptoms. The etiology

remains unknown. Very early-onset IBD (VEO-IBD) is defined as IBD occurring in children under the age of 6, while infantile-onset IBD (IO-IBD) occurs in those under 2 years old, representing 6% to 15% and 1% of pediatric IBD cases, respectively [33]. Monogenic mutations play a significant role in the pathogenesis of IBD, with over 50 gene mutations identified as being associated with VEO-IBD [3].

2.2.1. VEO-IBD Associated with IL-10 or IL-10 Receptor Mutations

This condition typically manifests as recurrent episodes of bloody diarrhea, marked weight loss, growth retardation, and recurrent perianal issues. Studies by Xiao Y. [34] and Guan Dexiu [35] have reported IL-10 R mutation rates of 38.5% and 45.8% in children with VEO-IBD, respectively, indicating a notably high prevalence among Chinese pediatric patients. Recently, hematopoietic stem cell transplantation has emerged as a promising treatment for IL-10 deficiency, with some patients achieving clinical remission following the procedure. Nonetheless, there are significant risks associated with the treatment, including transplant failure, septic shock, and idiopathic pneumonia [36].

2.2.2. CYBB Gene Mutation Associated with VEO-IBD in Chronic Granulomatous Disease

Mingran Mi and colleagues [37] documented two cases of "Very Early Onset Inflammatory Bowel Disease" (VEO-IBD) with initial symptoms appearing at 1 month and 1 year 7 months of age. The patients exhibited symptoms such as mucus, pus, and bloody stools, along with recurrent fevers and perianal abscesses, indicating extraintestinal infections. Colonoscopic examination revealed multiple ulcers in the rectum and colon, but standard IBD treatments were largely ineffective. Genetic sequencing eventually identified a heterozygous mutation in the CYBB gene, leading to a diagnosis of chronic granulomatous disease (CGD). This condition is an X-linked primary immunodeficiency disorder characterized by recurrent infections and heightened inflammatory responses. Consequently, for pediatric patients showing symptoms of IBD along with extraintestinal infections, it is crucial to conduct thorough endoscopic evaluations early on, and genetic testing should be considered when necessary to achieve a definitive diagnosis.

2.2.3. IL2RG Gene Mutation and Its Role in Infantile IBD

A pioneering case in the country [38] involved a 1-month-old male infant who was hospitalized with symptoms of "recurrent diarrhea for one month, bloody stools for 15 days, and fever for 3 days". Colonoscopy revealed changes resembling inflammatory bowel disease (IBD), alongside a reduction in both cellular and humoral immunity. High-throughput sequencing identified a hemizygous mutation in the IL2RG gene, leading to a diagnosis of X-linked severe immunodeficiency disease. This condition, resulting from IL2RG gene mutations, is noted for its rarity and poor prognosis. Cases of very early-onset IBD (VEO-IBD) due to this mutation have only been documented in isolated reports [38]. Early recognition and genetic testing are crucial for achieving a timely and accurate diagnosis.

2.3. Neonatal Necrotizing Enterocolitis

The pathogenesis of necrotizing enterocolitis (NEC) in neonates remains unclear, with hematochezia being one of its most prevalent clinical symptoms. Current understanding suggests that NEC results from the interplay of multiple factors, including feeding practices, ecological imbalance, and excessive inflammatory responses. It is associated with conditions such as preterm birth, low birth weight, feeding methods, asphyxia, intrauterine growth restriction, chorioamnionitis, delivery mode, and alterations in intestinal microbiota [39]. The incidence of NEC among preterm infants ranges from 1.7% to 10.8%, with a mortality rate of 23.5% among diagnosed cases, which is even higher in low birth weight preterm infants [39] [40]. Survivors are at increased risk of developing complications such as short bowel syndrome, intestinal stenosis, growth and developmental disorders, and neurodevelopmental abnormalities.

2.4. Cow's Milk Protein Allergy

In infants aged 0 to 3 months, the presence of blood in the stool is frequently associated with cow's milk protein allergy (CMPA). In China, the prevalence of CMPA in children aged 0 to 2 years ranges from 0.83% to 3.5% [41]. CMPA can be mediated by IgE, non-IgE, or a combination of both mechanisms [42]. It can manifest during the neonatal period, predominantly as a non-IgE-mediated delayed allergic reaction, with gastrointestinal symptoms being the most common. This condition can affect multiple systems and is characterized by food protein-induced proctocolitis (FPIP), food protein-induced enterocolitis syndrome (FPIES), food protein-induced enteropathy (FPE), and Heiner syndrome, among others. IgE-mediated CMPA is exceedingly rare in the neonatal period, while the mixed-mediated type may present solely as atopic dermatitis [41] [43]. It is crucial to differentiate neonatal CMPA from infectious diseases such as necrotizing enterocolitis (NEC), sepsis, and enteritis, as clinical presentations may involve mixed factors that necessitate careful evaluation.

2.5. Infectious Enteritis and Antibiotic-Associated Diarrhea

For infants aged 0 to 3 months who exhibit visible blood streaks or mucus-pus-blood in their stools, it is crucial to rule out intestinal infections. Common pathogens responsible for such infections include Escherichia coli, Shigella, Salmonella, Campylobacter, Vibrio, Yersinia, Listeria monocytogenes, Entamoeba histolytica, enteric viruses, and fungi. Moreover, antibiotic-associated diarrhea (AAD) is another potential cause of bloody stools, with incidence rates ranging from 16.80% to 70.59%. Nearly all antibacterial medications can induce AAD, and the risk is heightened in infants under 3 years of age, those who are artificially fed, have low birth weight, are premature, or have undergone invasive intestinal procedures [44].

2.6. Pseudo-hematemesis and/or Melena

Bleeding from nasopharyngeal or tracheal injuries, often due to intubation or

trauma, can be swallowed into the digestive tract, leading to pseudo-hematemesis or melena. Meconium or transitional stools may appear black if left for 1 - 2 days after birth. Other causes include vaginal bleeding contaminating the stool or the rare ingestion of substances such as iron supplements, bismuth, charcoal, or phenolphthalein. If vomiting and black stools occur before the initiation of breastfeeding, neonatal swallowing syndrome, resulting from the ingestion of maternal blood during delivery, should be considered. Additionally, in breastfed infants, it is important to check for maternal nipple fissures that might lead to the ingestion of maternal blood.

3. Diagnosis and Management of Early Infant Hematochezia

Accurate diagnosis of the underlying cause of hematochezia in early infancy is crucial. This involves a comprehensive approach that includes detailed medical history taking, physical examination, and the use of appropriate diagnostic tools such as laboratory tests, imaging studies, ultrasound, colonoscopy, and genetic testing when necessary [45]-[47]. Treatment should be etiology-specific, with surgical conditions managed through surgical intervention or conservative approaches, while medical conditions require both etiological and symptomatic treatment. Key advancements in treatment are outlined below.

3.1. Air Enema for Intussusception Reduction

Air enema has a reduction success rate of 90% [48], making it highly effective, though it poses a risk of intestinal perforation, particularly in infants younger than 6 months. Consequently, air enema is not the preferred initial treatment for neonatal intussusception. Factors such as the duration of the condition, presence of hematochezia, compromised intestinal blood supply, the location of the intussusception lead point, and the morphology of the intussusception mass significantly influence the success of air enema reduction [1]. For infants with intussusception, excluding neonates, once a clear diagnosis is established and the infant is in good general condition without dehydration, shock, or signs of peritoneal irritation, and abdominal X-ray rules out pneumoperitoneum, an attempt at air enema reduction should be made. Even if reduction is unsuccessful, it can facilitate subsequent surgical intervention.

3.2. Surgical Treatment

Surgery serves as the primary therapeutic approach for surgical diseases and is the sole treatment option for certain congenital gastrointestinal malformations. Over 30% to 50% of children with NEC require surgical intervention [49]. Determining the optimal timing for surgery remains a significant challenge; while intestinal perforation, complete obstruction, and peritonitis are widely accepted as absolute indications for surgery, the disease is often advanced by this stage, resulting in a poor prognosis. Most research [50] suggests that the ideal timing for NEC surgery is before intestinal necrosis occurs and before perforation, although the postoperative

mortality rate at this stage is not lower than that for perforated NEC, and recovery time post-surgery is extended. Wang Jiali *et al.* [50] recommend using Bell staging, standardized physical examination scoring, the MD7 scale, the Detroit scale, abdominal X-ray scale, the neonatal acute physiology scoring perinatal supplement II score (SNAPPE-II), and bedside real-time ultrasound (POCUS) to evaluate and determine the timing of surgery. In recent years, ultrasound, in particular, has provided significant clinical value in diagnosing NEC and determining the timing for surgical intervention [49] [50].

3.3. Targeted Treatment of NEC

Research has identified elevated levels of miRNA-124 expression and a decrease in ROCK 1 and MYPT 1 in rat NEC tissues. Inhibition of miR-124 leads to a significant increase in the expression of ROCK 1 and MYPT 1, along with a marked reduction in tissue damage. This suggests that miR-124 expression facilitates the progression of NEC, and genetic and epigenetic factors have been extensively investigated as potential therapeutic targets [51].

3.4. Treatment of VKDB

Vitamin K (VitK) therapy can correct prolonged PT and APTT within 4 to 6 hours, with PT levels returning to 30% - 50% of normal within 1 hour, generally achieving rapid hemostasis. Recent international studies [52] suggest administering VitK intravenously at a dose of 250~300 μg/kg for VKDB, with a total dosage of 1~2 mg. Infants under 6 months with VKDB can be completely cured, although those experiencing severe bleeding may require blood product transfusions.

3.5. Dietary Management of CMPA [41]

For breastfed infants with CMPA, it is advised to continue breastfeeding while the mother eliminates foods containing milk protein for 2 to 4 weeks. If severe allergic reactions occur, switching to amino acid-based formula (AAF) or extensively hydrolyzed formula (eHF) is recommended. Formula-fed infants with CMPA can directly use eHF or AAF. For those with mild to moderate symptoms, eHF is preferred as the initial alternative. If eHF is not tolerated, symptoms persist, or severe allergies develop, transitioning to AAF should be considered.

In summary, bloody stools in infants are a common clinical symptom with complex causes. While some severe congenital gastrointestinal malformations and immunodeficiencies can have poor or life-threatening outcomes, most infants with bloody stools have a favorable prognosis when diagnosed and treated early. This underscores the importance for clinicians not to overlook uncommon causes of rectal bleeding and to carefully evaluate each case.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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