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REVIEW

Age-specific causes of upper gastrointestinal bleeding in children

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Abstract

The etiology of upper gastrointestinal bleeding (UGIB) varies by age, from newborns to adolescents, with some of the causes overlapping between age groups. While particular causes such as vitamin K deficiency and cow's milk protein allergy are limited to specific age groups, occurring only in neonates and infants, others such as erosive esophagitis and gastritis may be identified at all ages. Furthermore, the incidence of UGIB is variable throughout the world and in different hospital settings. In North America and Europe, most UGIBs are non-variceal, associated with erosive esophagitis, gastritis, and gastric and duodenal ulcers. In recent years, the most common causes in some Middle Eastern and Far Eastern countries are becoming similar to those in Western countries. However, variceal bleeding still predominates in certain parts of the world, especially in South Asia. The most severe hemorrhage arises from variceal bleeding, peptic ulceration, and disseminated intravascular coagulation. Hematemesis is a credible indicator of a UGI source of bleeding in the majority of patients. Being familiar with the most likely UGIB causes in specific ages and geographic areas is especially important for adequate orientation in clinical settings, the use of proper

diagnostic tests, and rapid initiation of the therapy. The fundamental approach to the management of UGIB includes an immediate assessment of severity, detecting possible causes, and providing hemodynamic stability, followed by early endoscopy. Unusual UGIB causes must always be considered when establishing a diagnosis in the pediatric population because some of them are unique to children. Endoscopic techniques are of significant diagnostic value, and combined with medicaments, may be used for the management of acute bleeding. Finally, surgical treatment is reserved for the most severe bleeding.

Key Words: Upper gastrointestinal bleeding; Age-specific; Epidemiology; Pediatric; Unusual cause

Core Tip: This review provides general and comprehensive epidemiological data, overviewing the most common causes of upper gastrointestinal bleeding (UGIB) in children, in different age groups. The relevant literature in English on pediatric UGIB was searched until 2022, with special reference to age-related causes, unusual and rare causes, and risk factors. The literature search was performed using Medline *via* PubMed database (www.pubmed.gov), Google Scholar (www.scholar.google.com) and Cochrane Database, using the following terms: "neonates and infants" and "upper gastrointestinal bleeding"; "children" and "upper gastrointestinal bleeding"; "children" and "upper gastrointestinal bleeding" and "unusual causes"; "infants and children" and "upper gastrointestinal hemorrhage" and "unusual causes".

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INTRODUCTION

Upper gastrointestinal bleeding (UGIB) represents one of the most urgent conditions in the pediatric population. The etiologies of UGIB vary by age, from newborns to adolescents, with substantial overlap between age groups[1]. The origin of UGIB in children can be traced to any location from the esophagus to the ligament of Treitz, which represents the point of transition between the foregut and midgut[1,2] (Figure 1). Approximately 20% of all GI bleeding in children arises at those sites[3]. A significant share of patients with UGIB has a benign clinical course since approximately 80% present with self-limited bleeding[2]. About three-fourths (73%) of the patients present with hematemesis, followed by melena (21% of patients) and coffee-ground emesis (6% of patients)[1,4]. Nevertheless, some patients may also experience abdominal pain, nausea, dyspepsia, or vertigo[4,5]. Furthermore, hematochezia might be a rare sign of UGIB, except in neonates and infants who have rapid passage through the GI tract[3].

Differential diagnosis of UGIB is based on age, clinical presentation, and the amount of bleeding[6]. It must also include non-GI sources such as ingested maternal blood, epistaxis, and hemoptysis as well as food-mimicking hematemesis, coffee ground emesis, or melena[1,5]. Certain types of food may confuse children and parents due to a very similar appearance to blood in vomitus (*e.g.*, red food coloring, red candies, fruit-flavored drinks, fruit juices, and beets). Similarly, the melena-like appearance of the stool may be caused by some drugs like bismuth subsalicylate or iron supplements and food such as grape juice, spinach, beets, or blueberries[6].

Therefore, the anamnesis obtained from parents and the affected patient, if possible, must include information about associated signs and symptoms, dietary habits, and medicament use, and the attempt to quantify the bleeding. Large-volume UGIB might be encountered in non-steroidal anti-inflammatory drug (NSAID)-induced gastritis, but more frequently in variceal bleeding, both in young children and adolescents[6,7].

The initial approach in the treatment of patients with significant GI bleeding involves the establishment of adequate oxygen support, placement of central or peripheral intravenous catheters, hemodynamic stabilization, transfusion of blood and blood products, as well as correction of any underlying coagulopathies[5]. Endoscopy *per se*, is both a diagnostic and therapeutic procedure that is especially important in an emergency setting[8,9]. The frequency of endoscopic therapeutic interventions is especially high in patients with esophageal varices or bulbar peptic ulcer hemorrhage[8].

EPIDEMIOLOGICAL CHARACTERISTICS OF UGIB IN CHILDREN

There is a relative paucity of data regarding the exact incidence of UGIB in children. Based on the study conducted in France in 2010, the incidence of UGIB in the pediatric population is 1-2 per 10000 children[10]. The risk of UGIB is especially high in some subpopulations such as critical care patients. Critical illness alone may be a risk factor for stress-related GI ulceration and bleeding related to systemic hypoxemia, low gastric pH, impaired splanchnic perfusion, and dysregulated mucosal cytoprotection[11]. Besides, the use of medications such as NSAIDs, aspirin, corticosteroids, and

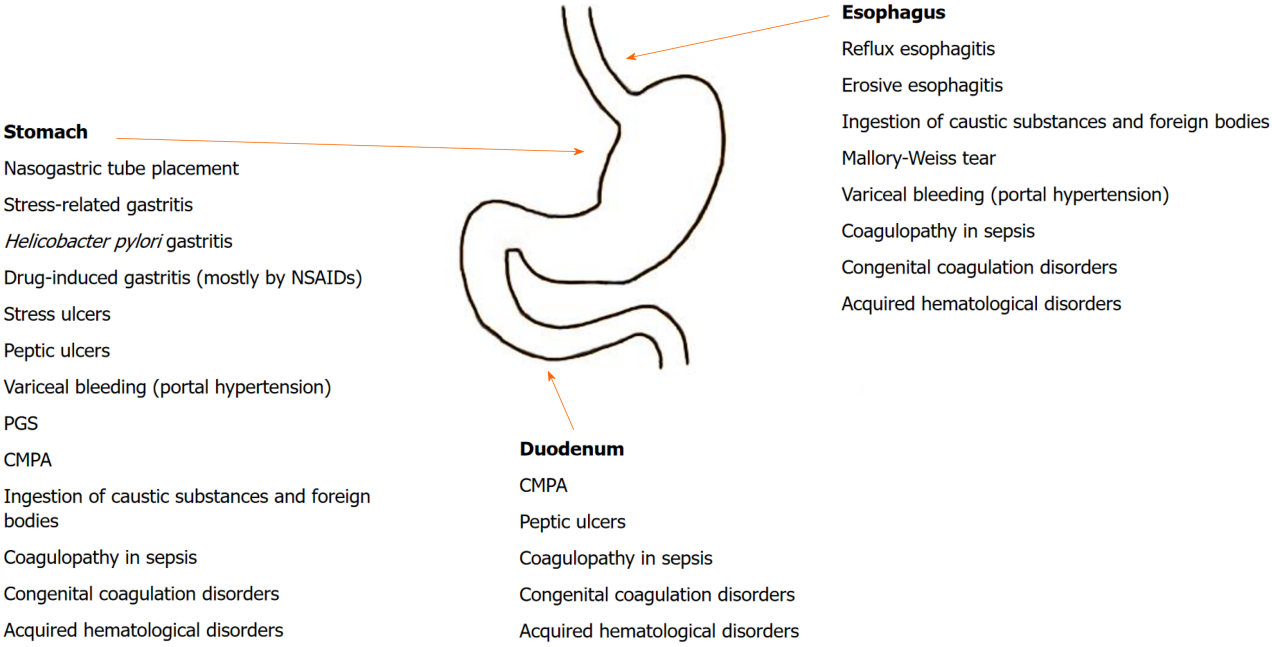

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Figure 1 Anatomic locations of upper gastrointestinal bleeding in children, with corresponding common causes. CMPA: Cow's milk protein allergy; NSAIDs: Non-steroidal anti-inflammatory drugs; PGS: Prolapse gastropathy syndrome.

selective serotonin reuptake inhibitors may be additional risk factors for severe UGIB[1,5]. Moreover, other comorbidities such as cerebral palsy increase the risk of erosive esophagitis primarily due to a higher prevalence of gastroesophageal reflux[4]. Few studies have provided critical care statistics related to UGIB in children[11-15]. The cumulative incidence of UGIB in the pediatric critical care population of Canada was shown to be 10.2%[12]. Moreover, a prospective cohort study from Thailand, which included 110 pediatric intensive care unit (PICU) patients, who required mechanical ventilation longer than 48 h, revealed that the incidence of UGIB was 51.8%, among which 3.6% of the cases presented with clinically significant bleeding[13]. According to the Belgian literature review published in 2011, the incidence of significant UGIB in children admitted to the PICU was 0.4%-1.6%[14]. However, an earlier prospective comparative study from 1992 conducted in a PICU of a tertiary care university-based facility in the United States found that the prevalence of UGIB was as high as 25%[15].

UGIB may be a life-threatening condition in cases of large blood volume loss, and worldwide mortality rates in children reach up to 15%[1,4]. A study from the United States showed that the overall mortality of PICU patients was 4.8%, with significantly higher mortality observed in patients with UGIB than in those without (16% *vs* 1.3%; $P < 0.001$) [15]. To reduce the risk of GI bleeding in children hospitalized in the PICU for critical asthma, stress ulcer prophylaxis (SUP) is commonly prescribed. A retrospective, multicenter cohort study conducted in the United States from 2010 to 2019 included children 3 years to 17 years of age admitted to the PICU for critical asthma. Of the 30177 children, 10387 (34.4%) received SUP throughout the 10-year period. Gastritis was noted in 32 (0.1%) subjects, and rates did not differ for patients who had and had not received SUP (0.11% *vs* 0.1% respectively; $P = 0.706$). Moreover, no episodes of major GI bleeding events were documented for the entire study sample regardless of SUP exposure[16]. These data raise a question of a need for the routine use of SUP in this population and advocate the consideration of a more individualized approach to the prevention of GI bleeding.

MOST COMMON CAUSES OF UGIB IN THE PEDIATRIC POPULATION

Various factors influence the occurrence of UGIB in different regions and countries around the world[1,2,10,17]. According to the literature, the origin of the UGIB in the pediatric population differs in developing and developed countries[1-3,8,18-22]. Based on causes, the UGIB may be classified into two major groups: Variceal and non-variceal[5]. Previously reported data from a study conducted in the Middle East in 2012, suggested that the most common cause of UGIB is esophageal varices (in 39% of patients with UGIB)[23]. Similarly, data from India in 1996 also indicated variceal bleeding as the most common UGIB, affecting 95% of patients. The majority (92%) of these cases occurred due to extrahepatic portal vein obstruction (EHPVO)[22]. However, the data obtained from an Iranian study conducted 2012-2014 indicated that the most common etiologies of UGIB among all patients admitted for GI bleeding were prolapse gastropathy syndrome (PGS) and esophagitis, with rates of 18.6% and 15.9%, respectively, followed by esophageal varices, gastritis, and coagulopathy, with frequency of 7.1% for each[18]. Moreover, a large cross-sectional study from Turkey from 2020 showed that the most common causes of UGIB were esophagitis (47%), peptic ulcer (18.1%), and esophageal varices (11.1%)[8]. In China, a 10-year retrospective multicenter cohort study conducted 2003-2012 reported

Table 1 Common causes of upper gastrointestinal bleeding in neonates[1,3,5,24]

Cause	Bleeding source location
Swallowed blood	Non-GI bleeding
Nasogastric tube placement	Stomach
Stress-related gastritis	Stomach
CMPA	Stomach, duodenum
NEC	Lower GI tract
Vitamin K deficiency	Distinct locations
DIC	Distinct locations
Congenital coagulation disorders[1]	Distinct locations

[1]Hemophilia, Von Willebrand disease, *etc.*

CMPA: Cow's milk protein allergy; DIC: Disseminated intravascular coagulation; GI: Gastrointestinal; NEC: Necrotizing enterocolitis.

erosive gastritis as the most frequent endoscopic finding in children with UGIB (33.5%), followed by duodenal ulcer (23.2%). The same study showed that the prevalence of erosive gastritis decreased with children's age (correlation coefficient = -0.787), while duodenal ulcer showed an increasing trend regarding age (correlation coefficient = 0.958)[21].

According to the literature, the most common causes of UGIB in North America and Europe are PGS (12.7%), gastric erosions and ulcers (10.8%), erosive esophagitis (9.5%), and duodenal erosions/ulcers (8.2%), whereas less common are esophageal varices (6.3%) and Mallory-Weiss tear (3.8%)[3,4]. A retrospective cohort, single-institution study conducted in the United Kingdom 2009-2014 by Nasher *et al*[20] included 32 patients with UGIB, with an average age at presentation of 5.9 ± 5.5 years in males and 8.2 ± 6.0 years in females. Over one-half (59.3%) of patients underwent an upper GI endoscopy procedure, which identified esophageal varices and esophagitis (occurring in 26% of patients each) as the most common findings, followed by gastritis/duodenitis (identified in 15.8% of patients). Duodenal ulcer was found in 2 patients who had evidence of *Helicobacter pylori* (*H. pylori*) on biopsy and in 1 with a previous history of NSAID intake. Furthermore, 1 patient had a rare cause of UGIB, a gastric vascular malformation[20]. Moreover, a 7-year retrospective cohort study conducted from 2007 to 2013 in the northeast of Romania which included 103 patients with UGIB showed that erosive gastritis was the most common cause of UGIB (occurring in 33.9% of included patients). The other causes comprised esophagitis (14.6%), duodenitis (11.6%), duodenal ulcer (10.7%), gastric ulcer (5.8%), esophageal varices (4.8%) and Mallory-Weiss syndrome (1.9%), whereas 16.5% of patients had multicausal UGIB. Furthermore, the particular bleeding source was determined in 34.9% of patients, a possible one in 39.8%, while in 25.2% the source has not been ascertained. Finally, in the same study, NSAID consumption and *H. pylori* infection were documented in 17.5% and 36.9% of patients, respectively[19].

CAUSES OF UGIB IN NEONATES

The most common causes of UGIB in newborns include coagulation disorders such as vitamin K deficiency, cow's milk protein allergy (CMPA), stress-related gastritis, sepsis, and trauma related to nasogastric tube placement[1,3,5,6,24] (Table 1). CMPA is a common food allergy both in neonates and infants, with an incidence estimated as 1.8%-7.5% in the 1st year of life[25]. Since there is no specific diagnostic test, the diagnosis of CMPA is primarily established by clinical evaluation and the elimination diet is the preferable treatment option[26].

UGIB in neonates in the neonatal ICU (NICU) setting is not uncommon. A retrospective-prospective cohort study conducted in Finland in 2000 which included 189 newborns treated in the NICU found that approximately 20% of patients had signs of GI bleeding. Mechanical ventilation was determined to be the crucial risk factor [odds ratio (OR) = 4.06; 95% confidence interval: 1.21-12.3], with 53% of mechanically ventilated patients having gastric mucosal lesions[27].

Furthermore, vitamin K deficiency must always be considered in neonates having UGIB. Vitamin K deficiency bleeding is usually categorized into three major groups: Early-onset (1st 24 h of life), classical (2nd to 7th d), and late-onset (2nd to 12th wk). Special attention should be given to the late-onset form, which exerts a greater burden in low- and middle-income countries where the median incidence is 80/100000, compared with high-income countries where the median incidence is significantly lower, 8.8/100000[28]. Besides, all neonates with hematemesis should also be screened for other bleeding disorders such as maternal thrombocytopenic purpura, hemophilia, and Von Willebrand disease, which are well-known risk factors for possible GI bleeding. Furthermore, the large amount of UGIB in newborns may also be caused by gastric erosion due to the placement of a nasogastric tube, sepsis, and/or disseminated intravascular coagulation[5]. When major UGIB occurs in neonates, parenteral vitamin K and proton pump inhibitors administration are recommended empirically[29]. Moreover, it is very important to initially exclude ingestion of blood of maternal origin that may be swallowed during delivery or from cracked nipples, which can be perceived as UGIB. Therefore, alkali denaturation testing (known as the Apt test) should be performed whenever available to distinguish maternal from fetal blood[30]. If maternal blood ingestion is excluded, another source of UGIB should be sought in this age group.

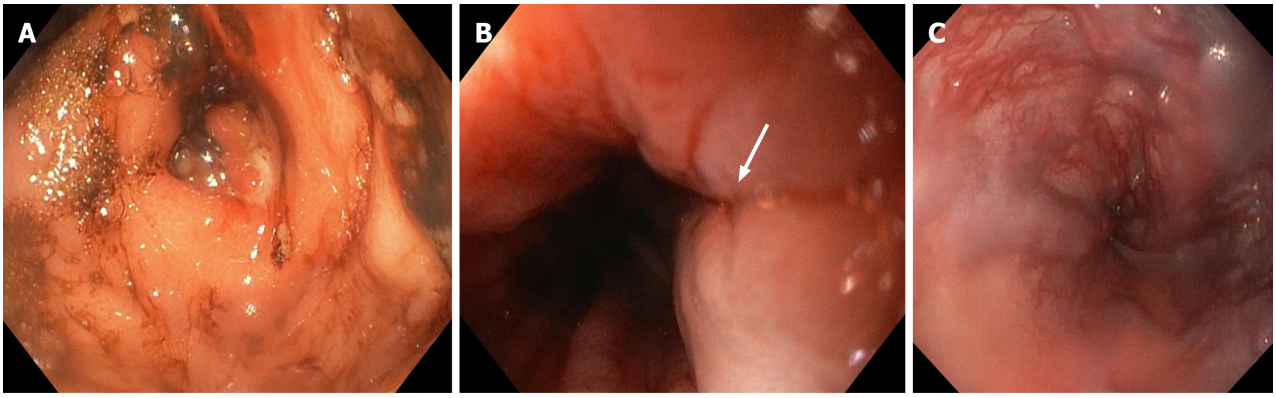

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Figure 2 The most common causes of upper gastrointestinal bleeding in children from 1-year-old to 3-years-old. A: Gastric ulcer in a 3-year-old boy who presented with hematemesis; B: Mallory-Weiss tear in a 3-year-old boy; C: Esophageal varices grade II in a 2-year-old boy with extrahepatic portal vein obstruction after cardiac surgery.

Finally, preterm infants represent a delicate pediatric population, in whom bright red blood in nasogastric aspirate may be a presenting sign of necrotizing enterocolitis (NEC)[3], although the source of hemorrhage caused by NEC is mostly located in the lower GI tract[31,32]. NEC usually develops in preterm infants with usual onset between 2 wk and 3 wk of life. On the other hand, full-term infants comprise about 10% of all babies with NEC, and in this subgroup NEC may appear within the 1st wk of life[33]. Because of insufficient reliable data due to inconsistencies in diagnosis and/or data collection of different studies, the precise incidence of NEC is undetermined[32]. When diagnosed, NEC must be treated rapidly with nasogastric decompression, proper antimicrobial therapy, and other supportive measures. If there is a suspicion of advanced NEC, surgical treatment is necessary[3].

CAUSES OF UGIB IN INFANCY

In younger infants, during the early months of life, the causes of UGIB are related to reflux and erosive esophagitis, PGS, CMPA, and stress-related gastritis[1,3,17,18,25] (Table 2). Gastritis with subsequent mucosal bleeding and stress ulcers are especially common causes of UGIB in infants hospitalized in PICU[3,27]. Less frequent causes include caustic and foreign body ingestion, coagulation disorders, medication-induced bleeding (mostly caused by NSAIDs), and rarely peptic ulcers and esophageal varices[5,17,34]. The presence of melena, particularly in the youngest children, points to significant GI hemorrhage[10,20]. The source of bleeding in these patients usually can be identified by flexible endoscopy, though drug-induced ulceration should be suspected from detailed medical history data and usually does not require endoscopic confirmation. An age-related retrospective study, which was conducted 2000-2010 in Iran and included children and adolescents aged 0-18 years, showed that erosive esophagitis was the most common cause of GI bleeding in all patients. This was also the most common finding in patients less than 1-year-old, with a prevalence of 37%, followed by gastritis (25.9%)[17]. On the other hand, the same study identified peptic ulcer disease (PUD) as a cause of UGIB in only 7.4% of infants, which significantly differed from older children. In concordance with these findings are the results from a national case-crossover study, conducted in France over a 2-year period, where a similar prevalence of the most common UGIB causes in this age group was reported[10].

CAUSES OF UGIB IN TODDLERS

The most common causes of UGIB in children from 1-year-old to 3-years-old include reflux and erosive esophagitis, gastritis, caustic ingestions, peptic ulcer (Figure 2A), esophageal varices, vomiting-induced bleeding similar to ones from Mallory-Weiss tear (Figure 2B), and PGS[1,3,4,18] (Table 3). PGS represents a retrograde prolapse of a part of gastric mucosa from the proximal stomach into the distal esophagus[35]. A study by Cleveland *et al*[4] found the erosion caused by prolapse of a portion of the gastric cardia along the lesser curvature found in PGS represents a more common source of bleeding than PUD or nonspecific gastritis in children.

It is well known that NSAIDs (including aspirin) and corticosteroids can increase the risk of UGIB, causing impairment of the gastric mucosal barrier by reduction and alteration of mucous secretion and promoting tissue fragility[5,36]. A group of French researchers performed a national case-crossover study with a total of 177 children with UGIB involved. The study reported that UGIB in one-third of the cases occurred due to exposure to NSAIDs at doses used for analgesic or antipyretic purposes. According to the age groups, the observed risk was more than four times higher in children up to 7-years-old (OR = 14.1) than in patients 8-years-old to 16-years-old (OR = 3.4)[10]. Although gastric ulcers have been associated with the chronic use of NSAIDs, reports from a single center in the United States over a 1-year period described UGIB in patients aged 16 mo to 36 mo (median age of 23.5 ± 9.0 mo) who developed hematemesis within 24 h

Table 2 Common causes of upper gastrointestinal bleeding in infants[1,3,5,17,26]

Cause	Bleeding source location
Erosive esophagitis	Esophagus
Reflux esophagitis	Esophagus
Ingestion of caustic substances and foreign bodies	Esophagus, stomach
Erosive gastritis	Stomach
Stress ulcers	Stomach
Drug-induced gastritis (most commonly by NSAIDs)	Stomach
PGS	Stomach
CMPA	Stomach, duodenum

CMPA: Cow's milk protein allergy; NSAIDs: Non-steroidal anti-inflammatory drugs; PGS: Prolapse gastropathy syndrome.

Table 3 Common causes of upper gastrointestinal bleeding in toddlers[1,4,18]

Cause	Bleeding source location
Erosive esophagitis	Esophagus
Mallory-Weiss tear	Esophagus
Ingestion of caustic substances and foreign bodies	Esophagus, stomach
Variceal bleeding associated with portal hypertension	Esophagus, stomach
Erosive gastritis	Stomach
Peptic ulcers	Stomach
PGS	Stomach
Drug-induced gastritis (most commonly by NSAIDs)	Stomach

NSAIDs: Non-steroidal anti-inflammatory drugs; PGS: Prolapse gastropathy syndrome.

after receiving just one or two age- and weight-appropriate doses of ibuprofen. In each of those patients, esophagogastroduodenoscopy demonstrated an antral gastric ulcer[36].

Furthermore, it is reported that the consumption of NSAIDs combined with infection with *H. pylori* is associated with a higher risk of gastroduodenal ulceration and bleeding[19]. A study from Tunis showed that the severity of gut mucosal damage in a population with a high prevalence of *H. pylori* infection is correlated with NSAID level intake, especially in children younger than 24 mo. However, the presence of *H. pylori* infection did not worsen gut mucosal injury severity in patients receiving NSAIDs[37].

Foreign body ingestion represents a significant risk factor for major complications, including UGIB. The occurrence of UGIB in these patients was shown to be time-related regarding the diagnosis establishment. Ingestion of a button battery is especially hazardous because it often results in secondary complications such as mucosal erosions, bleeding, gastric outlet obstruction, mediastinitis, or abscess formation[34,38]. Even in the case of a button battery lodging in the esophagus only transiently, severe erosion and ongoing necrosis of the esophagus and surrounding tissues may occur after the removal. Therefore, batteries that are in the esophagus must be removed within 2 h to avoid potentially fatal complications such as perforation and, the most severe one, aorto-esophageal fistula formation and subsequent bleeding [34]. Exsanguination from aorto-esophageal fistula has been reported in infants and toddlers[39].

Severe UGIB bleeding may be caused by esophageal varices rupture, which develops as a result of portal hypertension [40,41]. The most frequent causes of portal hypertension and its complications in children are EHPVO (Figure 2C) and liver cirrhosis. Liver cirrhosis in infancy is most commonly caused by biliary atresia (BA) and metabolic disorders, whereas in older children, the most common causes are alpha-1-antitrypsin deficiency, autoimmune hepatitis, primary sclerosing cholangitis, and Wilson's disease[42]. In patients with BA, esophageal varices may develop earlier compared to other causes of cirrhosis in children, with the median age of the first bleeding at 17 mo[43]. The management of variceal bleeding comprises both prophylaxis and acute emergency treatment and includes the use of drugs (*e.g.*, propranolol, vasopressin, and somatostatin), endoscopic procedures (*e.g.*, periodic surveillance endoscopies, endoscopic sclerotherapy, and band ligation), interventional radiology (*e.g.*, transjugular intrahepatic portosystemic shunt), and surgery (*e.g.*, portosystemic shunting)[44].

CAUSES OF UGIB IN CHILDREN OLDER THAN 3-YEARS-OLD

In children older than 3-years-old, bleeding most commonly arises from Mallory-Weiss tear, reflux and erosive esophagitis, erosive gastritis (Figure 3A), chronic PUD, caustic ingestions, esophageal varices, gastric varices (Figure 3B), and foreign body ingestion[1,4,5,24]. Besides, younger children and adolescents may experience bleeding from severe coagulopathy due to hematological disorders such as leukemia and idiopathic thrombocytopenic purpura[3] (Table 4).

PUD in children is similar to that in adults; however, there are some differences, especially in the prevalence of etiologies, clinical presentation, and complications. PUD is usually categorized as primary when associated with *H. pylori* and hypersecretory conditions including Zollinger-Ellison syndrome (ZES), short-bowel syndrome, cystic fibrosis, hyperparathyroidism, *etc*. Primary PUD is more often found in the duodenum, whereas secondary ulcers are more frequently localized in the stomach. On the other hand, secondary PUD is usually associated with systemic disease and drug ingestion and comprises stress ulcers, drug-induced ulcers, ulcers associated with infections other than *H. pylori*, Crohn's disease (CD) ulcers, ulcers associated with foreign body ingestion, *etc*[45]. A retrospective analysis performed in a single Endoscopy Center in China in 2021 included 173 children who were found to have upper GI ulcer. Primary ulcer was found in 148 (85.6%) patients and secondary in 25 (14.4%) patients. Of those with secondary ulcers, foreign body in the digestive tract was the most common cause, and was observed in 17 children (68%), followed by Henoch-Schönlein purpura (HSP) in 5 children (20.0%) and CD in 3 children (12.0%)[46].

H. pylori infection has been found in 50% of the world's population (approximately in 70% of the population in developing countries and 30%-40% in developed countries)[47] (Figure 3C). In children, the majority of *H. pylori* infections are asymptomatic, regardless of being associated with microscopic gastric inflammation[48]. Spontaneous eradication of the infection is noted mainly in infants and young children, and it decreases with age[49]. Besides, due to a rising resistance of *H. pylori* to antimicrobials and lack of symptom improvement in the absence of PUD, testing for *H. pylori* presence and application of eradication therapy are recommended only for the subset of patients with a high suspicion of PUD[47]. Therapy should be based on antibiotic resistance profiles and tailored accordingly using sufficiently high doses and treatment durations of 10-14 d, to achieve an initial eradication success rate of ≥ 90%[48]. In case of unknown susceptibility, high-dose triple therapy with proton pump inhibitors, amoxicillin, and metronidazole for 14 d is recommended as first-line therapy[48]. In a retrospective cohort study from the Middle East (conducted 1993-2002), which included 521 patients younger than 18-years-old who presented with UGIB, 24 (5%) children were diagnosed by endoscopy with PUD. The average age was 15 (range: 5-18 years). Primary PUD was found in 79% of the children, and according to the available histopathological data, the main finding was antral gastritis highly associated with *H. pylori*[50]. Moreover, a retrospective cohort study conducted in Japan 1995-2001, which included 283 patients aged 9 mo to 16 years, showed that the prevalence of *H. pylori* was highest in children with nodular (antral) gastritis (98.5%) and duodenal PUD (83%). *H. pylori* infection strongly correlated with gastric and duodenal ulcers in the age group of 10-years-old to 16-years-old compared to children 9-years-old or younger, in whom this correlation was not identified (OR = 12.1 *vs* 4.1 for duodenal ulcer, and OR = 8.2 *vs* 0.7 for gastric ulcer). Besides, researchers identified a low frequency of hematemesis or tarry stools (occurring in 9% of all patients), suggesting that there was no association with significant acute GI blood loss in the majority of patients[51]. Moreover, it has been reported that several hematological diseases may be associated with *H. pylori* infection, such as iron deficiency anemia, immune thrombocytopenia, and vitamin B12 deficiency, which can lead to additional GI disorders and subsequent UGIB[52].

EHPVO represents an important cause of portal hypertension in developing countries, and some data suggest that it is responsible for the occurrence of up to 80% of portal hypertension in children[53]. It commonly presents as incidental splenomegaly on physical examination (in 43.3% of cases) and in 40% as UGIB manifested as hematemesis and/or melena due to gastroesophageal varices[41]. Gastroesophageal varices caused by portal hypertension as a consequence of EHPVO were shown to be the most common source of significant UGIB in children above 3-years-old in South Asian countries[22,54]. A retrospective cohort study from India, conducted from 2002 to 2012, found 30 patients with EHPVO (5-years-old to 14-years-old). The peculiarity of these results was that delivery at home, which was one of the risk factors, was reported in all 30 cases, while the other risk factors, umbilical sepsis and a history of cow dung application over the umbilical cord were identified in 27% and 6.7% of patients, respectively. Almost 75% of all patients in that study had UGIB. Endoscopy findings revealed esophageal varices in all enrolled patients, gastric varices in 38.5%, and portal hypertensive gastropathy in 20%[55].

BA is a common cause of portal hypertension in older children as well as in children 3-years-old or younger. A cross-sectional multicentric study conducted between May 2006 and December 2009, as a part of the Childhood Liver Disease Research and Education Network, enrolled a total of 163 patients with BA (aged 1-25 years). The 43/163 (26.3%) patients with portal hypertension had complications, and 19.6% manifested with esophageal varices bleeding. Among the 32 patients with esophageal varices bleeding, most (34.4%) had their first bleeding episode between 6-years-old and 10-years-old, followed by equal portions (21.8% each) between birth and 2-years-old, between 2-years-old and 5-years-old, and ≥ 10-years-old[40].

UNUSUAL CAUSES OF UGIB

Unusual causes of UGIB (Table 5) are as clinically challenging in pediatric patients as in their adult counterparts. The incidence of unusual etiologies could be higher in pediatric practice since most of the rare diseases initially present during childhood. Unusual causes comprise various congenital anomalies, acquired diseases, and unusual foreign body ingestion.

Table 4 Common causes of upper gastrointestinal bleeding in children ages > 3 yr[1,4,5,24,50]

Cause	Bleeding source location
Erosive esophagitis	Esophagus
Reflux esophagitis	Esophagus
Mallory-Weiss tear	Esophagus
Variceal bleeding associated with portal hypertension	Esophagus, stomach
Erosive gastritis	Stomach
Stress ulcers	Stomach
Drug-induced gastritis (most commonly by NSAIDs)	Stomach
Helicobacter pylori gastritis	Stomach
Peptic ulcers	Stomach, duodenum
Acquired hematological disorders (ITP, leukemia, *etc*.)	Distinct locations

ITP: Idiopathic thrombocytopenic purpura; NSAIDs: Non-steroidal anti-inflammatory drugs.

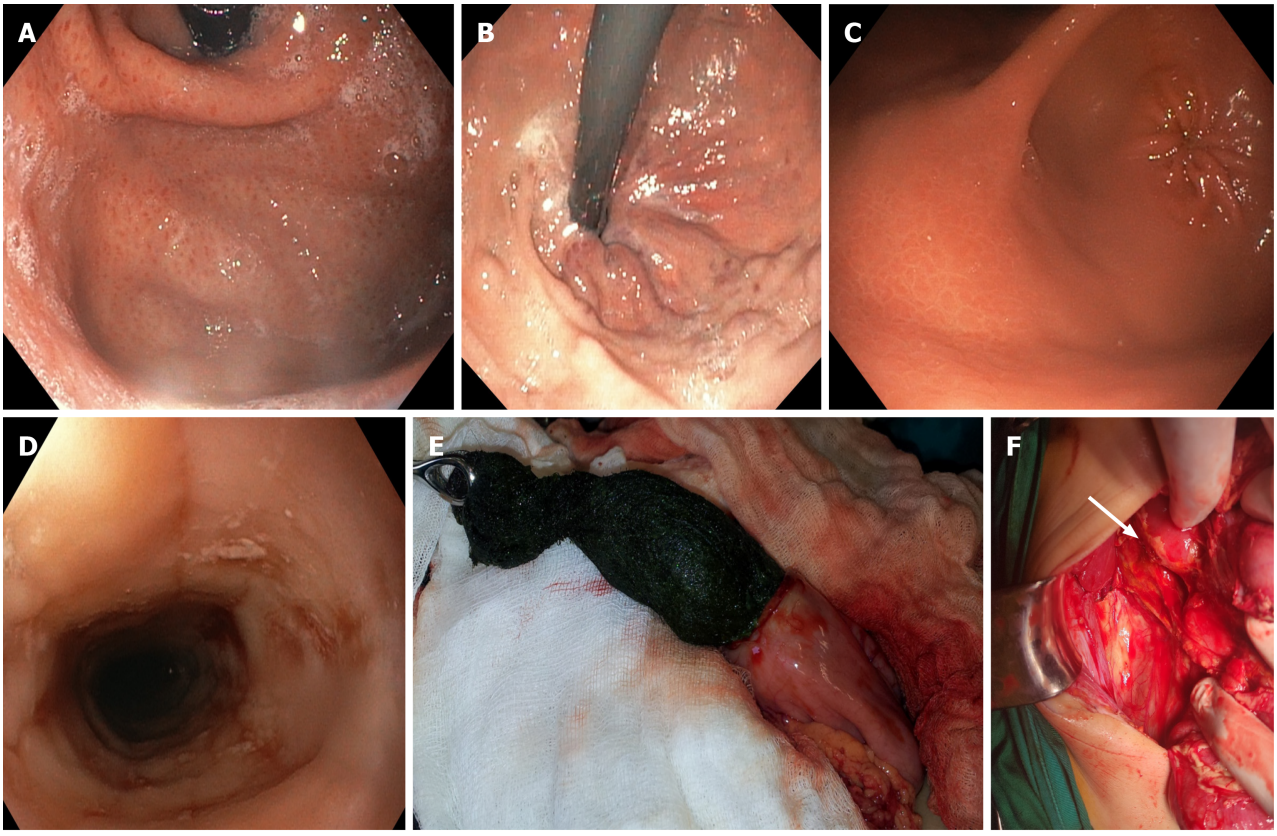

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Figure 3 Causes of upper gastrointestinal bleeding in children older than 3-years-old. A: Erosive gastritis in a 14-year-old girl with cerebral palsy; B: Gastroesophageal varices type 2 in a 6-year-old girl with chronic liver disease due to extrahepatic portal vein obstruction; C: Macronodular gastritis in a 16-year-old girl due to *Helicobacter pylori* infection; D: Eosinophilic esophagitis in a 16-year-old boy; E: Gastric trichobezoar in a 9-year-old boy; F: Traumatic perforation of the duodenum as a consequence of a handlebar injury in a 6-year-old boy. The patient was referred to the hospital two days after injury and the surgery was performed on the day of admission.

Unusual UGIB causes affecting the esophagus

UGIB is reported as a very rare clinical presentation in patients with alimentary tract duplications, including in newborns, infants, and older children[56-58]. The esophagus is, after the ileum, the second most common spot of occurrence of these congenital anomalies[56,59]. Alimentary tract duplications are usually diagnosed in infancy and childhood, with 60% of patients presenting at ages younger than 2 years[60]. The majority of esophageal duplications are related to the right side of the esophagus and do not communicate with its lumen[61]. However, they may sometimes contain gastric epithelium

which can provoke peptic ulceration, intra-cystic hemorrhage, and fistulation into the esophagus, presenting with hematemesis or melena[62].

Furthermore, it is not uncommon for eosinophilic gastrointestinal diseases (EGIDs) to initially present with GI bleeding [63]. Eosinophilic esophagitis (EoE) (Figure 3D), with an estimated prevalence of 10 to 57 per 100000, is the most common type of EGIDs, a group of chronic GI disorders, characterized by GI symptoms and pathological eosinophilic infiltration of various parts of the GI tract, without secondary causes of tissue eosinophilia[64]. Ozdogan *et al*[63] reported on 3 patients aged 8, 10, and 12 years who had hematemesis as the initial sign of EoE.

Unusual UGIB causes affecting the stomach

Gastric duplications (GDs) comprise only 7% of all GI duplications[59]. These congenital anomalies are commonly located in the region of the greater curvature. The cystic type comprises around 80% of GDs and they do not communicate with the gastric lumen, unlike the remaining 20% representing tubular GDs which are contiguous with the stomach and usually communicate with the gastric lumen. According to the study by Li *et al*[65] which included 319 patients with GD, vomiting and abdominal pain were the most common manifestations of these anomalies. GI hemorrhage was shown to be the third most common symptom, occurring in 16.3% of children.

Eosinophilic gastritis is even rarer than EoE, with a prevalence estimated at 6.6 per 100000[66]. Ozdogan *et al*[63] reported on 2 patients aged 7 and 14 years with eosinophilic gastritis who initially presented with hematemesis.

Some gastric tumors may also lead to GI bleeding. Gastrointestinal stromal tumors (GISTs) are an extremely rare cause of UGIB, described in several case series and reports[67]. They are most commonly located in the stomach and the median age at diagnosis is reported to be between 60 years and 69 years[68]. Patients 16-years-old or younger represent only 1.4%, and those less than 21-years-old represent 2.5% of all gastric GIST patients[67,69]. Authors from the United States have reported on a case of an 11-year-old girl who presented with anemia and guaiac-positive stool 1 mo after tonsillectomy. Because her anemia was thought to be secondary to blood loss from her tonsillectomy, iron therapy was started. Since 2 wk thereafter her hemoglobin decreased again, esophagogastroduodenoscopy was performed and demonstrated 7-8 large submucosal masses in the antrum and distal body of the stomach, with deep ulceration in one of the masses. Endoscopic ultrasound-guided fine needle aspiration confirmed the diagnosis of epithelioid GIST[69].

Furthermore, there are scarcely reported cases of primary gastric lymphomas in children. Authors from Korea reported on a case of a 10-year-old patient with a family history of gastric adenocarcinoma, who presented with recurrent hematemesis and melena. Esophagogastroduodenoscopy revealed diffuse antral ulcers, while a tissue biopsy showed a diffuse large B cell non-Hodgkin lymphoma[70]. Other rare gastric tumors such as Schwannoma causing GI bleeding have been reported anecdotally in toddlers and adolescents[71,72]. Moreover, Corasaniti *et al*[73] reported on a case of a young infant who presented with bilious vomiting, melena, and anemia due to a giant gastric polyp, histologically proven to be focal foveolar hyperplasia.

Bezoars (including trichobezoars, phytobezoars, pharmacobezoars, lactobezoars, *etc*.) are indigestible conglomerations trapped in the GI tract[74]. They are most commonly located in the stomach, although they may be observed in the esophagus, duodenum, and other segments of the bowel[75]. Trichobezoars (Figure 3E) are associated with trichotillomania and trichophagia in psychiatric patients. Bhatia *et al*[76] reported on 24 cases of trichotillomania attending the psychiatry outpatient department and found that the majority of cases (54.2%) belonged to the age group of 6-years-old to 10-years-old. In 2021, LaGrandeur *et al*[77] reported on a case of a seemingly healthy school-aged girl who presented with recidivant hematemesis, in whom a gastric trichobezoar was revealed during endoscopy.

Unusual UGIB causes affecting the duodenum

Duplications of duodenum contain gastric mucosa in up to 20% of cases. This could lead to intracystic hemorrhage or perforation of the cyst with subsequent GI bleeding and peritonitis[56]. Diagnostics of the alimentary tract duplication rely on ultrasonography, GI contrast study, computed tomography, and magnetic resonance imaging. Additional testing including scintigraphy may be useful in detecting ectopic gastric mucosa[61].

Varices in the duodenum are rarely present as a cause of UGIB, in comparison to varices located in the esophagus and stomach which are well-known complications of portal hypertension. Duodenal varices are mostly reported in adult patients. Hiçsönmez *et al*[78] reported on a curious case of a 12-year-old girl with severe bleeding from duodenal varices secondary to EHPVO and subsequent cavernous transformation of the portal vein.

Duodenal trauma (Figure 3F) in the pediatric population is infrequent, comprising 2%-10% of blunt abdominal trauma cases and only 0.14%-0.16% of all injured children per year[79,80]. Bicycle accidents are the most frequent cause of blunt trauma, representing between 5% and 14% of total closed abdominal injuries. A case study from Spain in 2019 described an adolescent boy with duodenal perforation after being injured by a bicycle handlebar, presenting with hematemesis, abdominal pain, and swelling and tenderness in the upper right abdominal quadrant and epigastrium. An exploratory laparotomy revealed perforation in the posterior wall of the third part of the duodenum and the patient was treated with the resection of the third portion of the duodenum and Roux-en-Y duodenojejunostomy[81].

Some unexpected, potentially dangerous foreign bodies used in everyday life may lead to severe GI damage. Nguyen *et al*[82] reported on a case of a 6-year-old girl who presented with abdominal pain, coffee-ground emesis, and melena due to uncooked pasta lodged in the duodenum and creating an erosion.

Hemobilia is a rare cause of UGIB both in adults and children. The bleeding from and into the biliary tract usually follows trauma to the hepatobiliary-pancreatic system[83]. Some of the rare causes of hemobilia reported in the pediatric population are parasitic infestation with Ascaris lumbricoides, liver abscess (occurring predominately in African and Asian regions), GD, pancreatitis, choledochal cyst, gall bladder polyps, and Von Willebrand disease[83,84].

Unusual UGIB causes affecting distinct locations

Dieulafoy's lesions are vascular malformations comprising abnormally enlarged arteries with the potential for massive GI bleeding. These anomalies, which are thought to be congenital, account for 1%-5.8% of all cases of acute UGIB and are most commonly located at the lesser curvature of the stomach[85-87]. However, they were shown to be extragastric in 33% of cases, affecting the duodenum, colon, esophagus, rectum, or jejuno-ileum[86]. Dieulafoy's lesions are more common in males than females (2:1 ratio), and the mean age at presentation is within the 5th decade of life (range: 50-70 years)[88]. This disorder may be underdiagnosed in any age group, and there are only several sporadic cases and case series available in the literature, comprising children of ages from preterm neonates to 18-years-old[89-92]. The signs and symptoms are related to blood loss, either due to intermittent or massive acute GI hemorrhage. Melena is the most common form of presentation, followed by hematemesis, hemoptysis, hematochezia, and iron deficiency anemia. In most severe cases, bleeding from Dieulafoy's lesions may lead to hemodynamic instability[93]. Since these lesions have a major potential for life-threatening hemorrhage, they should be included in the differential diagnosis of massive UGIB in all age groups.

ZES is an extremely rare condition caused by gastrin-producing tumors (gastrinomas), with an overall incidence of 0.1-3 per 1000000. Only 2% of gastrinoma cases occur in the pediatric population[94]. These tumors are usually located in the duodenal wall or in the pancreas. Hypergastrinemia causes non-healing or recurrent ulcers in 85% of cases localized in the duodenum. However, these ulcers may also appear in the stomach, jejunum, or multiple locations[95]. Authors from India reported on a case of a 12-year-old boy with a refractory peptic ulcer caused by gastrinoma in the pancreatic head. Upper GI endoscopy displayed multiple linear ulcers both in the mid and lower parts of the esophagus involving the gastroesophageal junction, as well as multiple superficial ulcers in the antrum and three parts of the duodenum[94]. Also, Zaatar *et al*[96] reported on a 7-year-old boy who presented with mild to moderate iron deficiency anemia, with fasting hypergastrinemia (serum gastrin of 200-500 pg/mL). Investigation revealed a positive stool guaiac test and elevated gastric acid secretion, while endoscopy showed multiple small gastric fundal ulcerations and severe gastritis. However, the investigation towards ZES produced negative findings.

Peutz-Jeghers syndrome is an autosomal dominant inherited disorder, occurring with an incidence of 1 to 50000-200000, characterized by GI hamartomas and mucocutaneous pigmentations due to melanin deposition[97,98]. This rare disorder usually presents with painless rectal bleeding. Nevertheless, authors from Indonesia reported in 2022 on the case of a 5-year-old patient who presented with abdominal pain, dark-red bloody stools, and anemia due to bleeding from scar ulcers in the duodenal region and erosive inflammation of the upper and lower GI tract along with multiple polyps. The patient had multiple black spots on the lips and mucous membranes (conjunctiva and buccal mucosa) and a family history of similar symptoms, which led to the diagnosis of Peutz-Jeghers syndrome[98].

The inflammation in CD may affect any part of the GI tract. Whilst in lower GI it commonly manifests as hematochezia, CD is rarely associated with UGIB. Though it has been rarely reported, when found on endoscopy, the source of UGIB bleeding in patients with CD is commonly a secondary deep ulcer or multiple ulcers[46,99].

HSP is considered the most common type of vasculitis in children, affecting 9-22 children per 100000 annually[100]. Although over two-thirds of patients with HSP have GI symptoms during acute illness, these symptoms are usually transient. Most patients (90%) with HSP are children younger than 10 years, with a peak incidence in the 6th year of life [101]. However, it can be also diagnosed in infants, adolescents, and adults[100,102]. HSP has been shown to present with a milder course in infants and children younger than 2 years[102,103]. Authors from Taiwan retrospectively analyzed 158 children with HSP from 1987 to 1998. A total of 104 boys and 54 girls (male:female = 1.9:1; ranging in age from 2-13 years) were enrolled in that study. The main GI manifestations included abdominal pain (88%), GI bleeding (75%), and vomiting (25%). Hematemesis, leukocytosis (> 20000/cm^3), high C-reactive protein (> 50 mg/L), and hemorrhagic erosive duodenitis were found to correlate with prolonged hospitalization[104]. A retrospective study conducted in China from 2017 to 2019, analyzed 99 children who had GI bleeding as a complication of HSP. The age at onset ranged from 2-16 years, and the majority (72%) of patients were males. Among all patients with HSP and GI bleeding, 37 had hematemesis, 71 had hematochezia, and 9 had both symptoms. No significant difference was found in sex and age distributions between those who had mild and those who had severe bleeding (P > 0.05)[105]. Furthermore, authors from Italy conducted a retrospective study 1998-2002, which included 95 boys and 55 girls diagnosed with HSP, and concluded that males were affected more often than females (male:female = 1.8:1)[101]. The age and sex distributions showed that most patients (91%) were less than 10-years-old, which is in concordance with previous reports. Out of 77 (51%) children who had GI involvement, GI bleeding was present in 27 children (18%). Among these patients, GI bleeding was revealed by fecal occult blood test and/or melena in 23 (15%), while 3 (2%) had melena alone and 1 had hematemesis.

Obscure GI bleeding

Obscure GI bleeding is a type of bleeding that persists or recurs without an obvious etiology despite upper endoscopy and colonoscopy evaluation[24]. Since it is usually caused by small bowel lesions, it does not represent UGIB. Small bowel capsule endoscopy has a high diagnostic yield and safety in the investigation of obscure GI bleeding and it has been strongly recommended by the European Society of Gastrointestinal Endoscopy as the first-line investigation[106]. Nevertheless, some authors suggest that it may be appropriate to consider an endoscopic second look before performing a capsule endoscopy[107].

CONCLUSION

In the pediatric population, the etiology of UGIB is diverse and mostly age-related. Since there is a significant etiologic

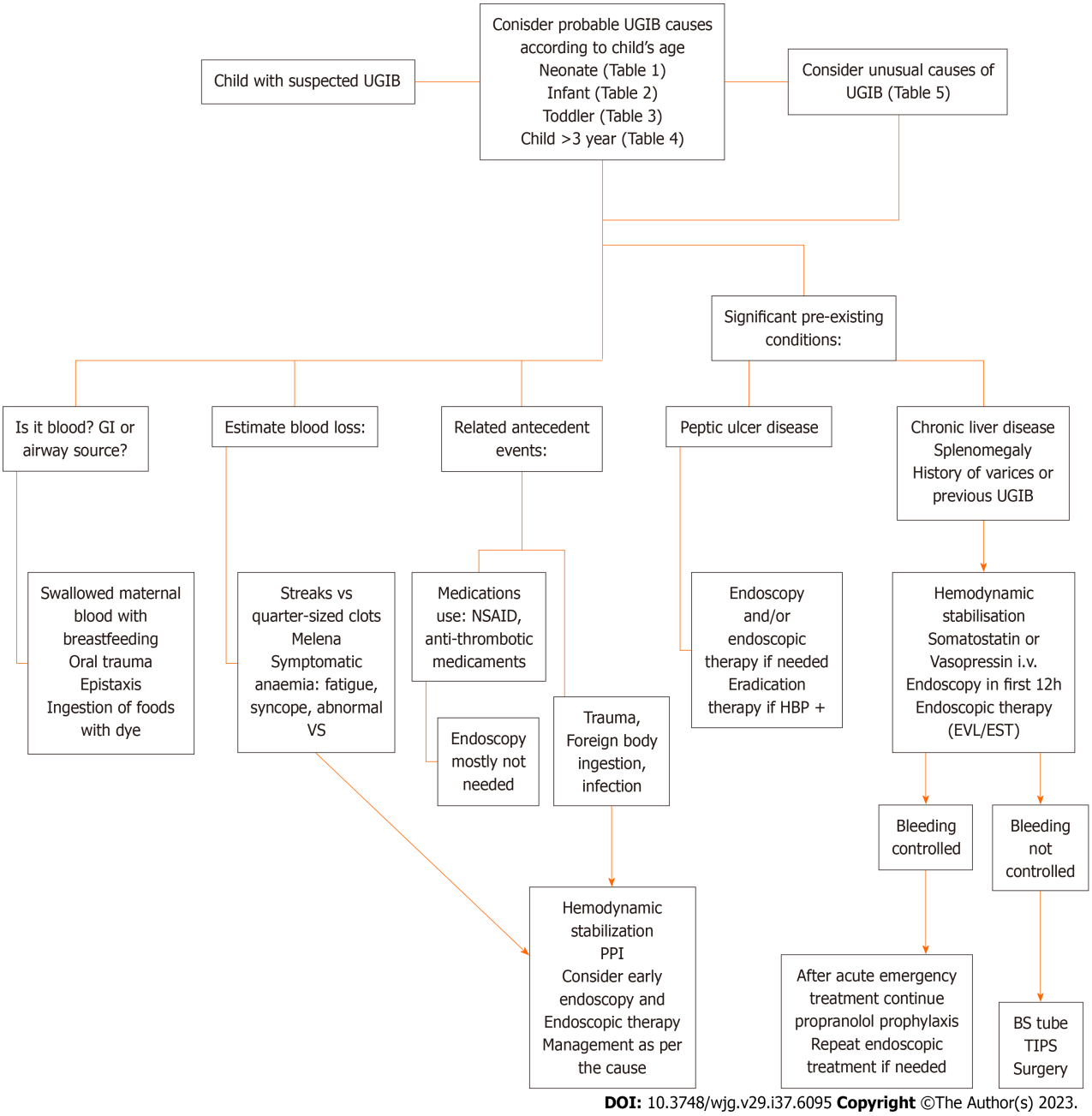

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Figure 4 Clinical approach to children with upper gastrointestinal bleeding. BS: Blakemore-Sengstaken; EST: Endoscopic sclerotherapy; EVL: Esophageal varices ligation; GI: Gastrointestinal; PPI: Proton pump inhibitor; TIPS: Transjugular intrahepatic portosystemic shunt; UGIB: Upper gastrointestinal bleeding; VS: Vital signs; NSAIDs: Non-steroidal anti-inflammatory drugs.

overlap between the age groups, the differential diagnosis must take into account a wide variety of conditions, including rare causes. Even if the hemorrhage is non-life threatening, UGIB is distressing for children and their families. Therefore, all cases of GI bleeding require prompt and thorough investigation based on the use of existing diagnostic algorithms with the utmost goal being discernment of the origin of hemorrhage. Clinically significant UGIB is commonly caused by variceal bleeding in low- and middle-income countries, whereas non-variceal etiology is more common in high-income countries.

We emphasize that a properly taken anamnesis is very important for differentiating the true cause of bleeding from conditions mimicking hematemesis and melena. The information about dietary habits, medicaments use, other underlying diseases, and the possibility of foreign body ingestion are crucial leads to the right diagnosis. The identification of unusual causes of UGIB prevents delay in the diagnosis of rare and potentially treatable conditions. Finally, exact and timely recognition of the cause of UGIB in the pediatric population may significantly preclude morbidity and mortality. Therefore, we have created a comprehensive diagnostic-therapeutic flow-chart that, combined with the information provided in the Tables of this article, may help clinicians in the initial management of the child with UGIB (Figure 4).

Table 5 Unusual causes of upper gastrointestinal bleeding in children, based on age

Cause	Age of onset	Bleeding source location
Esophageal duplications[60,62]	All ages	Esophagus
Eosinophilic esophagitis[63]	Children ≥ 3 yr	Esophagus
Gastric duplications[65]	All ages	Stomach
Eosinophilic gastritis	Children ≥ 3 yr	Stomach
Gastric GIST[69]	Children ≥ 3 yr	Stomach
Lymphoma[70]	Children ≥ 3 yr	Stomach
Schwannomas[71,72]	Toddlers, children ≥ 3 yr	Stomach
Focal foveolar hyperplasia[73]	Infants	Stomach
Bezoar[77]	Children ≥ 3 yr	Stomach
Duplications of duodenum[56,60]	All ages	Duodenum
Duodenal varices[78]	Children ≥ 3 yr	Duodenum
Blunt duodenal trauma[81]	Children ≥ 3 yr	Duodenum
Food as a foreign body	Children ≥ 3 yr	Duodenum
Hemobilia[83,84]	All ages	Biliary tract
Dieulafoy's lesions[89-92]	All ages	Distinct locations
Peptic ulcers in ZES[94]	Children ≥ 3 yr	Distinct locations
Peutz-Jeghers syndrome[98]	Children ≥ 3 yr	Distinct locations
Crohn's disease[99]	Children ≥ 3 yr	Distinct locations
HSP[101,104,105]	Toddlers, children ≥ 3 yr	Distinct locations

GIST: Gastrointestinal stromal tumor; HSP: Henoch-Schönlein purpura; ZES: Zollinger-Ellison syndrome.

FOOTNOTES

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