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The role of endoscopy in pediatric gastrointestinal bleeding

Authors Markus Franke[1], Andrea Geiß[1], Peter Greiner[2], Ulrich Wellner[3], Hans-Jürgen Richter-Schrag[4], Dirk Bausch[3], *, Andreas Fischer[4], *

Institutions Institutions are listed at the end of article.

Corresponding author
Andreas Fischer, MD
University Hospital Freiburg
Interdisciplinary
Gastrointestinal Endoscopy
Department of Medicine II
Hugstetter Str. 55
Freiburg 79106
Germany
Fax: +4976127025411
andreas.fischer@uniklinik-
freiburg.de

Background and study aims: Gastrointestinal bleeding in children and adolescents accounts for up to 20 % of referrals to gastroenterologists. Detailed management guidelines exist for gastrointestinal bleeding in adults, but they do not encompass children and adolescents. The aim of this study was to assess gastrointestinal bleeding in pediatric patients and to determine an investigative management algorithm accounting for the specifics of children and adolescents.
Patients and methods: Pediatric patients with gastrointestinal bleeding admitted to our endoscopy unit from 2001 to 2009 (n = 154) were identified. Retrospective statistical and neural network analysis was used to assess outcome and to determine an investigative management algorithm.
Results: The source of bleeding could be identified in 81 % (n = 124/154). Gastrointestinal bleeding was predominantly lower gastrointestinal bleeding (66 %, n = 101); upper gastrointestinal bleeding was much less common (14 %, n = 21). Hematochezia was observed in 94 % of the patients with lower gastrointestinal bleeding (n = 95 of 101). Hematemesis (67 %, n = 14 of 21) and melena (48 %, n = 10 of 21) were associated with upper gastrointestinal bleeding. The sensitivity and specificity of a neural network to predict lower gastrointestinal bleeding were 98 % and 63.6 %, respectively and to predict upper gastrointestinal bleeding were 75 % and 96 % respectively. The sensitivity and specificity of hematochezia alone to predict lower gastrointestinal bleeding were 94.2 % and 85.7 %, respectively. The sensitivity and specificity for hematemesis and melena to predict upper gastrointestinal bleeding were 82.6 % and 94 %, respectively. We then developed an investigative management algorithm based on the presence of hematochezia and hematemesis or melena.
Conclusions: Hematochezia should prompt colonoscopy and hematemesis or melena should prompt esophagogastroduodenoscopy. If no source of bleeding is found, additional procedures are often non-diagnostic.

Introduction
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Gastrointestinal bleeding (gastrointestinal bleeding) during infancy and childhood is common and accounts for up to 20 % of referrals to pediatric gastroenterologists [1 – 3]. Despite its often dramatic clinical presentation, the mortality of gastrointestinal bleeding in children is low, which contrasts sharply with the significant mortality observed in elderly patients [4].
Gastrointestinal bleeding is commonly classified as upper or lower gastrointestinal bleeding. Lower gastrointestinal bleeding is defined as bleeding originating from parts of the intestine distal to the ligament of Treitz, whereas upper gastrointestinal bleeding originates proximal to the duodenojejunal junction. Lower gastrointestinal bleeding is

further classified as middle gastrointestinal bleeding from the ligament of Treitz to the ileocecal valve and lower gastrointestinal bleeding from the ileocecal valve to the anus [1].
The most common causes of lower gastrointestinal bleeding in adult patients are diverticular bleeding, ischemic colitis, angioectasia, hemorrhoids and colorectal neoplasia [5]. In contrast, inflammatory bowel disease, colorectal polyps and infectious conditions are the most common causes of lower gastrointestinal bleeding in pediatric patients. Lower gastrointestinal bleeding in children may also originate from age-related conditions, such as necrotizing enterocolitis [1, 6, 7]. In adult patients, the most common etiologies of upper gastrointestinal bleeding are peptic ulcer disease, gastroduodenal erosions, esophagitis and varices [8], which are also the most common conditions observed in pediatric patients [1, 6, 7].

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* These authors contributed equally.

According to current guidelines from the American Society of Gastrointestinal Endoscopy (ASGE), upper or lower gastrointestinal bleeding is a clear indication for endoscopy in adults [5,8]. Depending on the severity of the bleeding, the guidelines recommend sigmoidoscopy or colonoscopy in the presence of hematochezia and occult bleeding [5,9]. Esophagogastroduodenoscopy (EGD) is recommended in the presence of melena and hematemesis [8]. However, these guidelines do not encompass children and adolescents. Despite routine use of EGD, colonoscopy, and sigmoidoscopy in pediatric gastrointestinal bleeding, there are no large series on gastrointestinal bleeding in children.

In addition, most studies are well over 10 years old or limited by the evaluation of specialized settings [2,3,10], such as acute upper gastrointestinal bleeding [11].

Consequently, no clear management guidelines exist to date that encompass both acute and chronic upper and lower gastrointestinal bleeding. Available guidelines deduct most of their recommendations from observations made in adults [12].

The aim of this study, therefore, was to identify an investigative management algorithm for acute and chronic upper and lower gastrointestinal bleeding that accounts for specifics in children and adolescents. The aim was not to determine when and how endoscopic hemostatic treatments should be performed [11]. We retrospectively assessed 1481 endoscopies performed in 966 pediatric patients who were admitted to our endoscopy unit from 2001 to 2009.

Patients and methods
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Definitions and endpoints

The study group was defined as children and adolescents (aged <18 years) with signs of gastrointestinal bleeding who had received at least 1 endoscopic procedure to localize the source of bleeding. Acute gastrointestinal bleeding was defined as melena or oral or rectal loss of fresh blood or its degradation products. Chronic gastrointestinal bleeding was defined as anemia or occult blood in the stool. All patients with prior surgical intervention or trauma potentially associated with gastrointestinal bleeding were excluded from the study.

Identification of study subjects

For identification of patients with gastrointestinal bleeding, we searched the endoscopy database of all patients treated at our institution, a tertiary care university medical center, for children and adolescents who underwent endoscopy from February 2001 to June 2009 for gastrointestinal bleeding. Institutional review board approval was granted for evaluation of patients with gastrointestinal bleeding in a retrospective manner from a prospective database. Declaration of consent from the legal guardian was obtained at least 24 hours before endoscopic procedures were performed. In cases of emergency endoscopy due to acute gastrointestinal bleeding, informed consent was obtained immediately prior to the endoscopic examination.

Data management and statistics

Data collection was retrospective. Statistical analysis and testing were performed with MedCalc (MedCalc Software bvba, Ostend, Belgium, www.medcalc.org). Rational and ordinal/nominal variables were represented as median/range and number/percent, respectively. Statistical testing was performed with the tests as indicated at a 2-sided significance level of $P=0.05$.

Artificial neural network (ANN) simulation was performed with Java Neural Network Simulator Version 1.1 (JavaNNS, University of Stuttgart and Tübingen, Germany), http://www.ra.cs.uni-tuebingen.de/software/JavaNNS/). Predictor variables with a Spearman rank correlation coefficient of +/– 0.30 or greater was selected for ANN prediction. A 3-layered neural network with the following parameters was used for prediction: feed-forward connections without shortcuts, number of input and hidden neurons equal to the number of predictor variables, 2 binary output neurons representing the predicted variables, Act_Logistic and Out_Identity functions for input and hidden neurons, and Out_Threshold05 function for output neurons. The dataset was split into a training and a test dataset each containing 50% of the cases. The network was trained with 1,000 backpropagation learning cycles on the training dataset and tested on the test dataset. Predictive values were calculated from the results in the test dataset with MedCalc.

Procedures

All children and adolescents underwent flexible endoscopy performed by an experienced endoscopist under general anesthesia. The decision to perform esophagogastroduodenoscopy (EGD) or colonoscopy was made by the attending physician after clinical assessment of the patient. If endoscopy did not identify the source of the gastrointestinal bleeding, additional diagnostic procedures, such as repeat endoscopy, scintigraphy, capsule endoscopy, contrast enema or magnetic resonance angiography were performed.

Results
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From February 2001 to June 2009, 1481 endoscopic procedures were performed on 966 children and adolescents. One hundred fifty-four patients with signs of gastrointestinal bleeding presented to our endoscopy unit, 97 boys and 57 girls. The median age at the time of the initial endoscopy was 7.55 years (range: 2 days – 17.57 years). Bleeding episodes lasted a median of 21 days (range 0 days – 728 days) prior to endoscopy. Hospital admission was predominantly for gastrointestinal bleeding (n=134; 87%), only 20 children (13%) had a bleeding episode during hospitalization for other reasons (❍ Table 1). Comorbidities predisposing to gastrointestinal bleeding were present in 23% of the patients (n=35; ❍ Table 1).

EGD as a single initial procedure was performed in 14% (n=21), colonoscopy in 43 patients (27.9%). Combined upper and lower endoscopies were performed in 90 patients (58.4%; ❍ Table 1).

The source of bleeding could be identified in 81% of these patients (n=124). The first endoscopic procedure was diagnostic in 68% of the patients (n=105). In 12% of the cases (n=19), additional procedures or repeat endoscopy were needed to reveal the source of bleeding (❍ Table 1). In the 124 cases in which a diagnosis was obtained, gastrointestinal bleeding was predominantly lower gastrointestinal bleeding (66%, n=101), upper gastrointestinal bleeding was much less common (14%, n=21) and upper and lower gastrointestinal bleeding together were exceedingly rare (1%, n=2). The most common causes of lower gastrointestinal bleeding were colorectal polyps (20%, n=31) and inflammatory bowel disease (20%, n=31), followed by colitis (8%. n=13). Colitis was classified as eosinophilic colitis (n=5), infectious colitis (n=3) and non-specific colitis (n=5). The most common causes of upper gastrointestinal bleeding were gastritis (5%,

Table 1 Patients and diagnosis.

	All n = 154
Age, years, median (range)	7.55 (0.01 – 17.57)
Sex (male : female)	97 : 57
Days from onset of symptoms to first procedure, median (range)	21 (0 – 728)
Hospital admission for bleeding	134
History of	35 (23 %)
Hematologic disease	8 (5 %)
Malignancy	4 (3 %)
Hepatobiliary disease	10 (6 %)
Renal disease	4 (3 %)
Cardiac disease	9 (6 %)
Initial procedure	
EGD	21 (14 %)
Colonoscopy	43 (28 %)
EGD + Colonoscopy	90 (58 %)
Diagnosis obtained	124 (81 %)
after first endoscopy	105 (68 %)
after additional procedures	19 (12 %)
Cause of bleeding	
Upper gastrointestinal bleeding	21 (14 %)
Gastritis	8 (5 %)
Esophageal/gastric ulcer	4 (3 %)
Esophagitis	3 (2 %)
Esophageal varices	2 (1 %)
Other	4 (3 %)
Lower gastrointestinal bleeding	101 (66 %)
Inflammatory bowel disease	31 (20 %)
Colorectal polyp	31 (20 %)
Colitis	13 (8 %)
Anal fissure	9 (6 %)
Angiodysplasia	2 (1 %)
Meckel's diverticulum	2 (1 %)
Other	13 (8 %)
Upper and lower gastrointestinal bleeding	2 (1 %)
Unknown	30 (19 %)

Table 2 Symptoms.

	All n = 154	Lower gastro-intestinal bleeding n = 101	Upper gastro-intestinal bleeding n = 21
Abdominal pain	58	34	9
Anemia	62	35	18
Hematemesis	22	1	14
Hematochezia	119	95	3
Melena	21	5	10
Occult bleeding	7	4	2
Vomiting	28	7	12

ing with upper and lower gastrointestinal bleeding were then used to construct an ANN for the prediction of the source of bleeding. ANN implicitly detects complex nonlinear relationships between dependent and independent variables and may detect all possible interactions between predictor variables. Depending on the predictor variables, these properties of ANN result in almost ideal sensitivity and specificity [13]. After training the network with a training dataset of 63 patients, its quality to predict upper and lower gastrointestinal bleeding was assessed using a test dataset of 63 patients (○ Table 4). Using the neural network to predict lower gastrointestinal bleeding, its sensitivity was 98 % (95 % confidence interval: 90 % – 100 %) and its specificity was 63.6 % (95 % confidence interval: 31 % – 89 %). Sensitivity and specificity for upper gastrointestinal bleeding were 75 % (95 % confidence interval: 43 % – 95 %) and 96 % (95 % confidence interval: 86 % – 100 %) respectively.

However, ANN are often perceived as black boxes and of limited clinical usefulness. We therefore sought to determine if a similar prediction of the bleeding site was attainable using clinical signs and symptoms alone. The symptoms that correlated most strongly with lower gastrointestinal bleeding (hematochezia) and upper gastrointestinal bleeding (hematemesis and melena; ○ Table 3) were therefore selected and assessed for their sensitivity and specificity to predict upper and lower gastrointestinal bleeding. The sensitivity and specificity of hematochezia alone for prediction of lower gastrointestinal bleeding were 94.2 % (95 % confidence interval: 88 % – 98 %) and 85.7 % (95 % confidence interval: 64 % – 97 %), respectively. Sensitivity and specificity for hematemesis and melena in prediction of upper gastrointestinal bleeding were 82.6 % (95 % confidence interval: 61 % – 95 %) and 94 % (95 % confidence interval: 88 % – 98 %), respectively.

Typical clinical signs and symptoms therefore are likely equivalent and may even be superior compared to the neural network analysis in prediction of the site of bleeding. Based on these findings, we developed an investigative management algorithm for gastrointestinal bleeding in children and adolescents based on the presence of hematochezia and hematemesis or melena (○ Fig. 1): (1) Colonoscopy should be performed in the presence of hematochezia, but usually requires some form of bowel preparation; (2) EGD should primarily be performed in the presence of hematemesis or melena and can be used immediately; (3) In the case of non-diagnostic endoscopy, severe or ongoing bleeding warrants repeat endoscopy or other diagnostic tests. However, if the initial endoscopy is negative, additional diagnostic procedures are negative in 65 % of the cases after initial colonoscopy and in 79 % of the cases after initial EGD.

n = 8) and gastric or esophageal ulcers (3 %, n = 4; ○ Table 1). Other and age-related causes of upper and lower gastrointestinal bleeding, such as esophageal varices, Meckel's diverticula or angiodysplasia of the colon were exceedingly rare (○ Table 1).

Follow-up of 21 of the 30 patients with an unidentified source of bleeding revealed that 13 patients had no further bleeding episodes and bleeding had stopped spontaneously in another 6 patients. Bleeding only continued in 2 patients as obscure bleeding. The majority of patients presented with clinical symptoms typically associated with upper or lower gastrointestinal bleeding. Hematochezia was observed in 94 % of the patients with lower gastrointestinal bleeding (n = 95 of 101), whereas other symptoms were less common in lower gastrointestinal bleeding. Hematemesis (67 %, n = 14 of 21) and melena (48 %, n = 10 of 21) were both associated with upper gastrointestinal bleeding (○ Table 2).

To develop an investigative management algorithm for gastrointestinal bleeding in children, the afore mentioned clinical symptoms and other signs of gastrointestinal bleeding were first assessed for their correlation with upper and lower gastrointestinal bleeding in all patients with a definitely identified bleeding site (○ Table 3). The signs and symptoms most strongly correlat-

	Upper gastrointestinal bleeding			Lower gastrointestinal bleeding		
Parameter	CC	*P*	n	CC	*P*	n
Hematemesis	**0.75**	**0.000**	**124**	**− 0.72**	**0.000**	**124**
Hepatobiliary comorbidity	**0.47**	**0.000**	**124**	**− 0.41**	**0.000**	**124**
Melena	**0.46**	**0.000**	**124**	**− 0.49**	**0.000**	**124**
Cardiac comorbidity	**0.36**	**0.000**	**124**	**− 0.38**	**0.000**	**123**
Renal comorbidity	**0.33**	**0.000**	**124**	**− 0.35**	**0.000**	**124**
Anemia on admission	0.27	0.007	96	− 0.23	0.027	96
Peritonism	0.24	0.013	106	0.04	0.698	106
Malignancy	0.20	0.030	124	− 0.21	0.020	124
Abdominal pain	0.19	0.047	110	− 0.16	0.090	110
Hematologic comorbidity	0.3	0.156	124	0.03	0.732	124
Occult bleeding	0.09	0.344	124	− 0.10	0.276	124
Abdominal tenderness	0.06	0.533	109	− 0.01	0.939	109
Age	0.05	0.567	124	0.00	0.982	124
Sex	− 0.01	0.919	124	− 0.01	0.955	124
Severe anemia on admission	− 0.02	0.922	44	0.02	0.895	44
Obstipation	− 0.11	0.255	106	0.11	0.255	106
Failure to thrive	− 0.13	0.183	111	0.13	0.183	111
Diarrhea	**− 0.16**	**0.088**	**113**	**0.20**	**0.034**	**113**
Hb on admission	**− 0.23**	**0.025**	**96**	**0.20**	**0.052**	**96**
Week of bleeding	**− 0.42**	**0.000**	**124**	**0.40**	**0.000**	**124**
Hematochezia	**− 0.71**	**0.000**	**124**	**0.76**	**0.000**	**124**

Table 3 Correlation of symptoms with bleeding source.

Bold: parameters selected for the neural network analysis; CC: correlation coefficient, CC>0: correlation with upper gastrointestinal bleeding, CC<0: correlation with lower gastrointestinal bleeding.

Table 4 Training and test dataset for the neuronal network analysis.

	Training n = 63	Test n = 63
Upper gastrointestinal bleeding	11 (18 %)	12 (19 %)
Lower gastrointestinal bleeding	52 (84 %)	51 (82 %)
Hematochezia	49 (79 %)	51 (82 %)
Hematemesis	6 (10 %)	10 (16 %)
Melena	9 (15 %)	6 (10 %)
Hepatobiliary disease	4 (6 %)	4 (6 %)
Renal disease	3 (5 %)	0 (0 %)
Cardiac disease	4 (6 %)	5 (8 %)
Week of bleeding – median (range)	2 (0 – 104)	3 (0 – 78)

Discussion
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In this study we identified 154 children with gastrointestinal bleeding in a series of 966 children and adolescents who underwent 1461 endoscopic procedures. Despite its retrospective and single-center nature, the large dataset allowed us to evaluate an investigative management algorithm for both upper and lower gastrointestinal bleeding in children and adolescents accounting for the specific underlying conditions in these patients. However, the data were not suitable for determining which patients do not require endoscopy despite gastrointestinal bleeding. Using neural network analysis and correlation analysis, hematochezia and hematemesis or melena were identified as sensitive and specific markers for lower and upper gastrointestinal bleeding. However, 95 % confidence intervals were relatively large for both sensitivity and specificity in neural network analysis. Inferential uncertainty could thus be relatively high. However, ANN and correlation analysis results are remarkably similar, thus making a large inferential uncertainty unlikely.

According to the ASGE Guidelines, hematemesis and melena are considered typical indications for EGD [5]. Hematochezia, melena and anemia of unclear genesis are typical indications for colonoscopy [5]. These recommendations are also reasonable if children and adolescents are affected. In our series, only 2.5 % (3/119) of children with hematochezia had upper gastrointestinal bleeding and only 4.5 % (1/22) with hematemesis suffered from lower gastrointestinal bleeding. Melena was more frequent in upper gastrointestinal bleeding (47.6 %, 10/21) than in lower gastrointestinal bleeding (23.8 %, 5/21). Therefore, the relatively high proportion of patients with comorbidities predisposing to gastrointestinal bleeding (23 %) in our dataset did not seem to introduce a relevant selection bias.

In children and adolescents in contrast to adults, endoscopy is almost exclusively performed under general anesthesia. Therefore, performing both EGD and colonoscopy while these young patients are anesthetized also seems warranted, especially if bleeding is severe. In case of hematemesis or melena, EGD can and should be performed immediately after admission because the bleeding site will be found in the upper gastrointestinal tract with a probability of 76 % (positive predictive value). In case of hematochezia, colonoscopy should be performed because lower gastrointestinal bleeding is highly probable (97 % positive predictive value). Unlike with suspected upper gastrointestinal bleeding, in the presence of hematochezia, emergency endoscopy is not feasible due to the bowel preparation needed prior to colonoscopy. Careful assessment of hemodynamic stability thus is necessary to determine if bowel preparation can be performed in the presence of hematochezia. In the rare case of peracute bleeding and hemodynamic instability, other diagnostic tools such as angiography or surgical exploration seem warranted.

Despite the wide variety of potential bleeding sources in pediatric patients [1, 6, 7], in our series, colorectal polyps and inflammatory bowel disease were the most common causes of gastrointestinal bleeding. They accounted for 40 % of the identified condi-
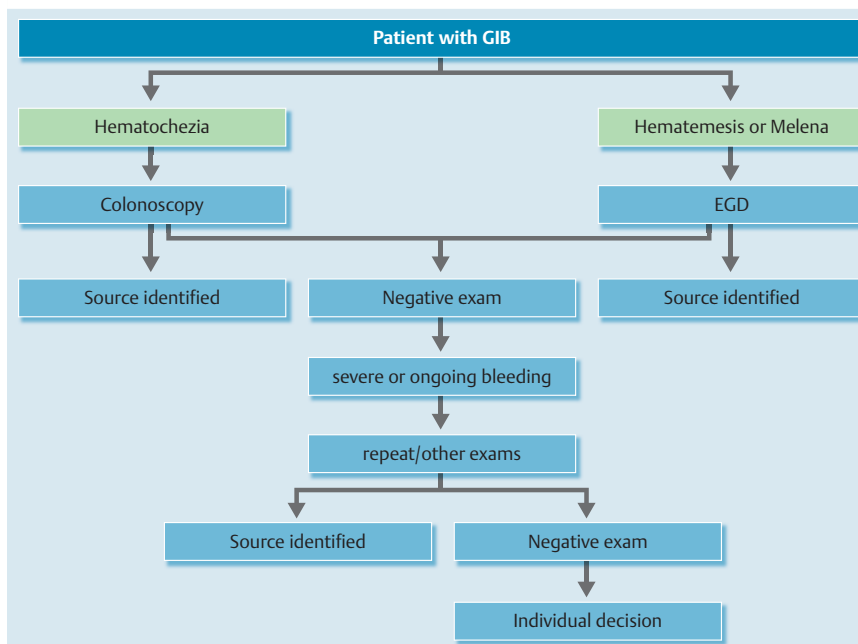
Fig. 1 Suggested investigative management algorithm for patients with upper and lower gastrointestinal bleeding based on the statistical analysis and neural network analysis. Hematochezia is a sensitive and specific marker for lower gastrointestinal bleeding and should prompt colonoscopy. Hematemesis or melena are indicative of upper gastrointestinal bleeding and should be followed up by EGD. If the patient requires general anesthesia, both EGD and colonoscopy should be performed. In the rare case of peracute bleeding and hemodynamic instability, other diagnostic tools such as angiography or surgical exploration seem warranted. If no source of bleeding is found during the first endoscopic procedure, additional procedures are often non-diagnostic. Further diagnostic workup should therefore only be considered in case of ongoing gastrointestinal bleeding requiring blood transfusions.

tions for gastrointestinal bleeding. Age-specific causes of gastrointestinal bleeding, such as necrotizing enterocolitis, were rare. If initial endoscopy was non-diagnostic, further diagnostic workup was often futile. A diagnosis could only be obtained in 39% of the 49 patients with non-diagnostic initial endoscopy. However, in our study, repeat endoscopy and other diagnostic modalities, such as cross-sectional abdominal imaging, were equally effective in these cases. Given the relatively small number of these cases in our series, no diagnostic algorithm could be established for occult bleeding. A case-by-case decision may be required in these patients based on their clinical symptoms. Given the similarity of the algorithm formulated for upper and lower gastrointestinal bleeding (○ **Fig. 1**) to the ASGE guidelines [5,8], it may be reasonable to adhere to the ASGE guidelines for obscure gastrointestinal bleeding in these cases [9].

Repeated endoscopy can be considered if a finding may have been overlooked in the initial endoscopy. In our pediatric collective, in contrast to adult patients, capsule endoscopy plays a subordinate role. However, considering that gastrointestinal bleeding in children may also be self-limiting in many cases, watchful waiting should also be considered in non-acute gastrointestinal bleeding.

Endoscopy is a very useful first-step diagnostic tool in the localization of gastrointestinal bleeding in pediatric patients. Hematochezia is a sensitive and specific marker for lower gastrointestinal bleeding and should prompt colonoscopy. Hematemesis or melena are indicative of upper gastrointestinal bleeding and should be followed up by EGD. If the patient requires general anesthesia, both EGD and colonoscopy should be considered. However, in the rare case of peracute bleeding and hemodynamic instability, other diagnostic tools such as angiography or surgical exploration seem warranted.

If no source of bleeding is found during the first endoscopic procedure, additional procedures are often non-diagnostic. Further diagnostic workup should therefore only be considered in case of ongoing gastrointestinal bleeding requiring blood transfusions.

Despite the relatively large number of cases, the study is limited by its retrospective and single-center nature. Therefore, prospective validation of the aforementioned investigative management algorithm is needed.

Competing interests: None

Institutions
[1] University Hospital Freiburg, Department of General and Digestive Surgery – University of Freiburg, Faculty of Medicine, Freiburg, Germany.
[2] University Hospital Freiburg, Department of Pediatric and Adolescent Medicine – University of Freiburg, Faculty of Medicine, Freiburg, Germany.
[3] Department of Surgery, University Medical Center Schleswig-Holstein, Campus Luebeck, Germany
[4] University Hospital Freiburg, Department of Medicine II – University of Freiburg, Faculty of Medicine, Freiburg, Germany.

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