

# Causes of hematochezia and hemorrhagic antibiotic-associated colitis in children and adolescents

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## Abstract

Diseases causing hematochezia range from benign to potentially life-threatening. Systematic pediatric data on the causes of hematochezia are scarce. We studied the underlying causes and long-term outcome of hematochezia in children. We further investigated the relevance of antibiotic-associated hemorrhagic colitis in children, especially if caused by *Klebsiella oxytoca*.

Infants, children, and adolescents with hematochezia were recruited prospectively. Patients were grouped according to age (<1 year, 1–5 years, 6–13 years, >14 years). In addition to routine diagnostics, *K oxytoca* stool culture and toxin analysis was performed. We collected data on history, laboratory findings, microbiological diagnostic, imaging, final diagnosis, and long-term outcome.

We included 221 patients (female 46%; age 0–19 years). In 98 (44%), hematochezia was caused by infectious diseases. Endoscopy was performed in 30 patients (13.6%). No patient died due to the underlying cause of hematochezia. The most common diagnoses according to age were food protein-induced proctocolitis in infants, bacterial colitis in young children, and inflammatory bowel disease in children and adolescents. Seventeen (7.7%) had a positive stool culture for *K oxytoca*. Antibiotic-associated colitis was diagnosed in 12 (5%) patients: 2 caused by *K oxytoca* and 2 by *Clostridium difficile*; in the remaining 8 patients, no known pathobiont was identified.

Infections were the most common cause of hematochezia in this study. In most patients, invasive diagnostic procedures were not necessary. Antibiotic-associated hemorrhagic colitis caused by *K oxytoca* was an uncommon diagnosis in our cohort. Antibiotic-associated colitis with hematochezia might be caused by pathobionts other than *C difficile* or *K oxytoca*.

**Abbreviations:** AAC = antibiotic-associated colitis, AACU = antibiotic-associated colitis of unknown origin, AAHC = antibiotic-associated hemorrhagic colitis, CDI = *Clostridium difficile* infection, FPIP = food protein-induced proctocolitis, GI = gastrointestinal, IBD = inflammatory bowel disease, NEC = necrotizing enterocolitis, UC = ulcerative colitis.

**Keywords:** antibiotic-associated colitis, children, hematochezia, *Klebsiella oxytoca*, proctocolitis

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## 1. Introduction

Hematochezia in children and adolescents is a troubling sign for parents, and also for physicians. The spectrum of underlying diseases is diverse and ranges from benign to potentially life-threatening.<sup>[1,2]</sup> However, its epidemiologic properties have not been studied adequately in children. Only few larger series about causes of hematochezia in pediatric patients exist.<sup>[3–10]</sup> This prospective study aimed at elucidating the range of disorders causing hematochezia in pediatric patients across all age groups.

A second aim was to investigate the frequency of antibiotic-associated colitis (AAC) presenting with hematochezia in the pediatric population. Antibiotic treatment alters the ecology of the normal intestinal microbiome, which might result in AAC (*Clostridium difficile* infection [CDI]).<sup>[11,12]</sup> Extensive antibiotic-associated growth of the bacterium *C difficile* is widely known as a cause of AAC.<sup>[13]</sup> Recently *Klebsiella oxytoca* has been discussed as a novel enteric pathobiont causing a distinct form of AAC, termed antibiotic-associated hemorrhagic colitis (AAHC).<sup>[11,14]</sup> Our study group was able to identify a toxin produced by *K oxytoca* as the low-molecular-weight compound tilivalline, which is a unique enterotoxin only found in *K oxytoca*.<sup>[14]</sup> In contrast to colitis induced by *C difficile*, AAHC is usually segmental and predominately located in the right colon, characterized by bloody diarrhea and acute abdominal pain.<sup>[11]</sup> In children, only few case reports about AAHC caused by *K oxytoca* exist.<sup>[15,16]</sup> Currently, no studies about preconditions, incidence, and age pattern of AAHC in pediatric population are available.

## 2. Material and methods

### 2.1. Patient cohort and inclusion criteria

From May 2011 to December 2012, pediatric patients aged 0 to 19 years with bloody stool were prospectively recruited at 5 Austrian (nonsurgical) pediatric hospitals. Each hospital had at least 1 pediatric gastroenterologist in charge of patient ascertainment. Patient ascertainment was supported by continuous dissemination of study information among hospital staff, direct referral of children with hematochezia to pediatric gastroenterologists, and by daily clinical staff meetings. Hematochezia (blood per rectum, in or separate from stool) was confirmed by hospital staff (visual stool inspection). A guaiac test (Haemocult, Beckman Coulter, Germany) was mandatory when hematochezia could not be reliably confirmed by visual inspection.

As a second inclusion criterion and in addition to routine stool diagnostics, a stool culture for *K oxytoca* was performed. Pediatric patients from oncology wards were not included in our study. After inclusion decisions regarding evaluation and treatment of patients were not influenced by the study. For all patients in this study long-term outcome was documented either by chart review, and if chart review did not give conclusive information, by telephone interview. The time from initial diagnosis to determination of long-term outcome was documented. In all, 237 patients with hematochezia were invited to participate; 15 patients were excluded because hematochezia could not be confirmed, and in 1 case no stool culture for *K oxytoca* was performed. None of the patients refused to participate in the study. As a control group for infants with suspected food protein-induced proctocolitis (FPIP) we screened 33 otherwise healthy infants (aged 1–6 months) hospitalized for nongastrointestinal (GI) diseases for *K oxytoca*. The local ethics committee of the Medical University Graz approved our study

(23–270 ex 10/11). The study was registered in an international clinical study registry (UMIN clinical trial registry; R000008499).

### 2.2. Clinical data analysis

Medical history, clinical course, and final diagnosis were documented for all patients. The following clinical and laboratory parameters were assessed: age at onset of symptoms; sex; history; signs and symptoms; medication history; laboratory results (white blood cell count, C-reactive protein [CRP]); stool diagnostics (*Campylobacter*, *Salmonella*, *Shigella*, *Yersinia*, *K oxytoca*, *C difficile*, *Adenovirus*, *Norovirus*, and *Rotavirus*); the need for blood transfusions; imaging studies (ultrasound, colonoscopy).

### 2.3. Definitions

Patients were grouped into the following groups: infants (<1 year), young children (1–5 years), children (6–13 years), and adolescents (14–19 years).<sup>[17]</sup>

Antibiotic-associated colitis was diagnosed in patients with bloody diarrhea during or up to 14 days after completion of antibiotic therapy. Patients positive for *C difficile* toxin and with positive *C difficile* stool culture were diagnosed with CDI. A positive *K oxytoca* stool culture, a positive toxin assay and toxin PCR,<sup>[11]</sup> and the documentation of colitis by sonography were required for the diagnosis of AAHC. Depending on history, clinical symptoms, microbiological findings, imaging results, and the clinical course, we arbitrarily defined the causal association of a given diagnosis and a positive stool culture for *K oxytoca* as likely, possible, and unlikely.

Infants not appearing sick (aged 1–6 months) with blood-streaked stools and cessation of hematochezia after change of nutrition to either extensively hydrolyzed formula or a cow-milk protein-free nutrition of the infant's mother were diagnosed with suspected FPIP.<sup>[18]</sup>

The diagnosis “hematochezia with signs of GI infection, infectious work-up negative” was made in patients with obvious signs of a GI infection (fever, abdominal pain, diarrhea, and/or vomiting), an uneventful clinical course and full recovery, but no pathogen detection. The diagnosis “hematochezia without GI infection” was made in patients without clinical signs of GI infection, whose clinical and infectiological work-up was unremarkable and in whom hematochezia ceased spontaneously. As a surrogate for long-term outcome we documented the time from initial inclusion to the final chart review (including follow-up visits of inpatient or outpatient visits, related or unrelated to hematochezia).

### 2.4. Microbiological diagnostics and analysis of *K oxytoca* strains

Stool culture was performed for *Salmonella*, *Shigella*, *Yersinia*, *Campylobacter*, *EHEC* (Shiga toxin PCR, in case of a positive test result conventional culture for *EHEC*), and additionally for *K oxytoca*. To detect *C difficile*, a combination of GDH and Toxin A/B EIA test (Innsbruck, Wels, Leoben, Oberwart; Alere C. Diff Quik Chek Complete, Alere, Austria; ImmunoCard, Szabo Scandic, Austria) or a Toxin A/B PCR (Graz) was followed by toxigenic culture if positive. *Rota*, *Adeno*, and *Norovirus* were detected by enzyme-linked immunosorbent assay (ELISA). *K oxytoca* species were identified using the API 20E or VITEK test (bioMérieux, Marcy l'Etoile, France).

## 2.5. *K oxytoca* toxin analysis (classical assay/PCR)

We have previously shown that *K oxytoca* strains causing AAHC produce a cytotoxin (tilivalline).<sup>[11,19]</sup> The toxin-producing *K oxytoca* strains possess a pathogenicity island (PAI) encoding genes necessary for tilivalline production.<sup>[14]</sup> Analysis of toxin production was performed using classical cell culture toxin assay and PCR as previously described (detailed description see Schneditz et al).<sup>[14,19,20]</sup>

## 2.6. Statistics

For statistical analysis we used IBM SPSS Statistics 21 (V 21.000, SPSS Inc., Chicago, IL). The Fisher exact test was used to analyze associations between groups. A *P* value <0.01 was considered statistically significant.

## 3. Results

### 3.1. Patient characteristics/clinical features

In all, 221 pediatric patients (female, *n*=102, 46%) were included in this study (Table 1). All included patients were inpatients at study inclusion. Hematochezia was confirmed by visual inspection only in 143 patients (64,7%), and by visual inspection and positive guaiac test in 78 patients (35,3%). In 2 patients hematochezia can be interpreted as an incidental finding by an underlying coagulation disorder (1 disseminated intravascular coagulation, 1 immune thrombocytopenia). Furthermore, in 7 patients an underlying GI condition potentially causing hematochezia was already present at time of study inclusion (1 necrotizing enterocolitis [NEC], 6 inflammatory bowel disease [IBD]). Thirty patients (13.6%) had a pre-existing chronic condition (10 patients with a chronic GI disease, 20 patients with a chronic non-GI disease). Long-term outcome (related or unrelated to hematochezia) was documented in all patients (mean 24 months, SD±7.5 months). In 4 patients (1.8%) a packed red blood cell transfusion was administered (Table 1). Colonoscopy was performed in 30 (14.0%) patients. In 17 of these 30 patients endoscopy led to a diagnosis, in 11/30 colonoscopy and histology remained inconclusive, and in 2/30 the diagnosis was already known (repeated ileocolonoscopy in 2

ulcerative colitis [UC] patients). Twenty-seven (90.0%) of the colonoscopies were performed in children and adolescents, 3 in infants and young children (1 infant: signs of GI infection, infectious work-up negative; 1 infant: hematochezia without definitive diagnosis; 1 young child: connective tissue disease/vasculitis). Twenty-two patients (10%) had a positive history of ongoing antibiotic therapy or termination of antibiotic therapy within 14 days of onset of bloody diarrhea. AAC as the underlying cause of hematochezia was determined in 12 of these patients. In the remainder hematochezia was caused by other underlying diseases or pathogens (eg, IBD, *Campylobacter*, NEC, esophageal varices, disseminated intravascular coagulation).

### 3.2. Frequency of underlying diagnoses in pediatric patients presenting with hematochezia

Infectious diseases were a common cause of hematochezia in all age groups (Fig. 1, Table 2). *Campylobacter* enterocolitis was the most frequent diagnosis (*n*=48, 21.8%) followed by signs of GI infection, infectious work-up negative (*n*=31, 14.0%), and *Salmonella* enterocolitis (*n*=29, 13.1%). IBD (*n*=21, 9.5%; 13 ulcerative colitis, 8 Crohn disease), hematochezia without definite diagnosis (*n*=20, 9.0%), and suspected FPIP (*n*=19, 8.6%) occurred with comparable frequency. *Norovirus* enterocolitis-associated hematochezia was found in 10 patients (5.4%). Anal fissure (*n*=5, 2.3%) and intussusception (*n*=5, 2.3%) were uncommon diagnoses in our patient cohort. IBD was not diagnosed in infants and young children, intussusception (*n*=5, 2.3%) was only diagnosed in these 2 age groups. Diseases diagnosed only twice or once in our patient cohort are listed in Table 3.

### 3.3. Infants (<1 year)

Suspected FPIP was diagnosed in 19 infants (33.3%). In 9 (47.7%) of the patients diagnosed with suspected FPIP, the stool culture for *K oxytoca* was positive. When comparing these 19 infants with suspected FPIP with 33 healthy control infants (17 breastfeeding difficulties, 10 mother-child interaction problems, 6 inconsolable crying under observation), only 4 (12%) had a positive stool culture for *K oxytoca* (*P*<.01). Other frequent

**Table 1**  
Patient characteristics categorized by age group.

	Total	Infants (<1 y)	Young children (1–5 y)	Children (6–13 y)	Adolescents (14–19 y)
<i>n</i>	221	57	64	46	54
Age, y	6.9±6.4	0.3±0.3	3.0±1.4	9.5±2.4	16.2±1.2
Female	102 (46.2)	28 (49.1)	26 (40.6)	20 (43.5)	28 (51.9)
Accompanying symptoms	187 (84.6)	36 (63.6)	61 (95.3)	41 (89.1)	49 (90.7)
Positive stool culture for <i>Klebsiella oxytoca</i>	17 (7.7)	15 (26.3)	1 (1.6)	0 (0)	1 (1.9)
Pre-existing gastrointestinal disease predisposing to hematochezia*	7 (3.2)	0 (0)	0 (0)	2 (4.4)	4 (7.4)
Packed red blood cell transfusion†	4 (1.8)	1 (1.8)	1 (1.6)	0 (0)	2 (3.7)
Colonoscopy‡	30 (13.6)	2 (3.5)	1 (3.3)	11 (23.9)	15 (27.8)
Antibiotic therapy ≤14 d§	22 (10)	6 (10.5)	9 (14.1)	3 (6.5)	4 (7.4)

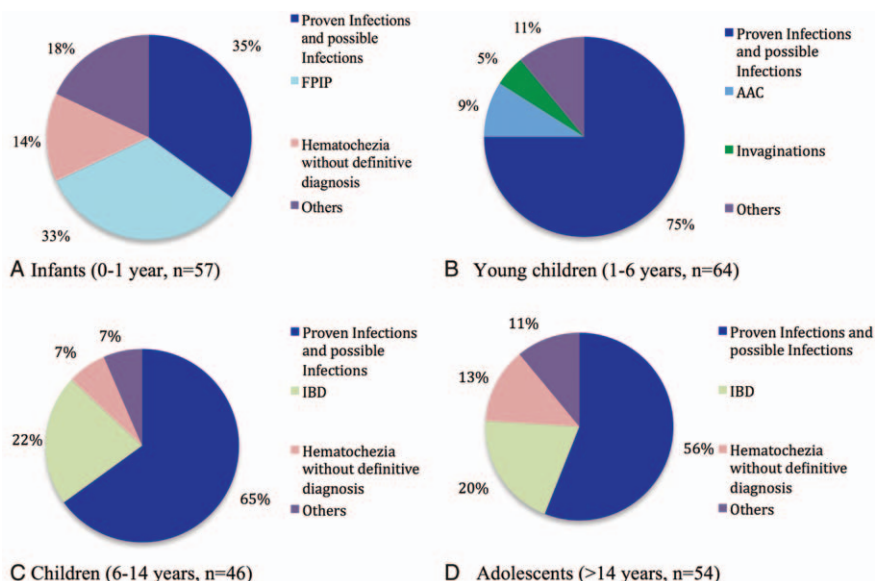
Patients aged 0 to 19 years were categorized into age groups and accordingly grouped into infants (0–1 years), young children (1–6 years), children (6–14 years), and adolescents (≥14 years). The average age is given in mean ± standard deviation. The table shows the proportion of female sex, of patients with accompanying symptoms like fever, abdominal pain, or diarrhea, of patients with a positive stool culture for *Klebsiella oxytoca*, of patients with pre-existing gastrointestinal disease, and of those who received a blood transfusion. Also shown are patients in whom an endoscopy was performed and those who received antibiotic therapy before hematochezia. Data are shown in number (%).

\* Ulcerative colitis 4, Crohn disease 2, NEC 1.

† Diagnoses: ulcerative colitis (2×), esophageal varices, necrotizing enterocolitis.

‡ In 17 patients (7.7%), the endoscopy led to a diagnosis, in 9 patients (4.1%), no diagnosis could be made by endoscopy, and in 4 patients (1.8%), inflammatory bowel disease was diagnosed earlier.

§ Occurrence of hematochezia during or up to 14 days after completion of antibiotic therapy.



**Figure 1.** The 3 most common diagnoses versus less common diagnoses (Others, diseases diagnosed twice or once in the respective age group) in infants, young children, children, and adolescents with the leading symptom of hematochezia. Patients with infectious causes were pooled together (infectious diseases listed in order of frequency: *Campylobacter*; signs of GI infection, infectious work-up negative; *Salmonella*; norovirus; AAHC; CDI; *Shigella*; adenovirus; rotavirus; EHEC; hantavirus). AAC=antibiotic-associated colitis, AAHC=antibiotic-associated hemorrhagic colitis, CDI=*Clostridium difficile* infection, EHEC=entero-hemorrhagic *Escherichia coli*, FPIP=food protein-induced proctocolitis, IBD=inflammatory bowel disease.

**Table 2**

**Relative frequency of different diagnoses in children and adolescents (0–19 years) with the leading symptom of hematochezia.**

	Total	Infants (<1 y)	Young children (1–5 y)	Children (6–13 y)	Adolescents (14–19 y)
	n=221	n=57	n=64	n=46	n=54
<i>Campylobacter</i> enterocolitis	48 (21.8)	3 (5.3)	25 (39.1)	10 (21.7)	10 (18.5)
Signs of GI infection, infectious work-up negative*	31 (14.0)	7 (12.3)	7 (11.0)	10 (21.7)	7 (13.0)
<i>Salmonella</i> enterocolitis	29 (13.1)	5 (8.8)	9 (14.1)	8 (17.4)	7 (13.0)
Inflammatory bowel disease (IBD)	21 (9.5)	0 (0)	0 (0)	10 (21.7)	11 (20.4)
Hematochezia without definitive diagnosis	20 (9.0)	8 (14.0)	2 (3.1)	3 (6.5)	7 (13.0)
Food protein-induced proctocolitis (FPIP)	19 (8.6)	19 (33.3)	0 (0)	0 (0)	0 (0)
Antibiotic-associated colitis (AAC)	12 (5.4)	2 (3.5)	8 (12.5)	0 (0)	2 (3.7)
Norovirus enterocolitis	10 (4.5)	3 (5.3)	3 (4.7)	2 (4.3)	2 (3.7)
Anal fissure	5 (2.3)	2 (3.5)	1 (1.6)	1 (2.2)	1 (1.9)
Intussusception	5 (2.3)	2 (3.5)	3 (4.7)	0 (0)	0 (0)
Others†	21 (9.5)	6 (10.5)	6 (9.4)	2 (4.3)	7 (13.0)

Diagnoses are arranged in descending order according to the frequency for total patient sample (n = 221). Patients are further divided in infants (<1 years), young children (1–5 years), children (6–13 years), and adolescents (14–19 years). The data are given in number (%).

\* No detection of *Campylobacter*, *Salmonella*, *Shigella*, *Yersinia*, *Escherichia coli*, *Klebsiella oxytoca*, *Clostridium difficile*, norovirus, rotavirus.

† Patients with diseases that were only diagnosed once or twice in our patient cohort (see Table 3).

**Table 3**

**Other diseases in our patient cohort with leading symptom of hematochezia.**

<i>Clostridium difficile</i> enterocolitis (without antibiotic trigger)	Disseminated intravascular coagulation
Necrotizing enterocolitis (2)	Amanita poisoning
<i>Shigella</i> enterocolitis (2)	Esophageal varices grade II
Colorectal polyp	Adenovirus enterocolitis
Schönlein-Henoch purpura	Rotavirus enterocolitis
Rectal lymphonodular hyperplasia	Adenovirus and rotavirus enterocolitis
Connective tissue disease (vasculitis)	Idiopathic thrombocytopenic purpura
Hantavirus infection	Familial adenomatous polyposis
Hemorrhoids	Meckel diverticulum
Entero-hemorrhagic <i>Escherichia coli</i> , Hemolytic-uremic syndrome	

diagnoses in infants were hematochezia without GI infection (n = 8, 14%) and hematochezia with signs of GI infection, infectious work-up negative (n = 7, 12.3%). *Salmonella* enterocolitis (n = 5, 8.8%) and *Campylobacter* enterocolitis (n = 3, 5.3%) were less frequent in infants compared with other age groups. NEC (n = 2, 3.5%) and AAHC (n = 2, 3.5%) were diagnosed in infants only.

**3.4. Young children (1–5 years)**

The most frequent cause of hematochezia in patients aged between 1 and 5 years was *Campylobacter* enterocolitis (n = 25, 39.1%), followed by *Salmonella* enterocolitis (n = 9, 14.1%), AAC (n = 8, 12.5%), and hematochezia with signs of GI infection (infectious work-up negative) (n = 7, 11.0%). In other age groups AAC was an uncommon diagnosis (n ≤ 2).

### 3.5. Children (6–13 years)

*Campylobacter* enterocolitis, hematochezia with signs GI infection (infectious work-up negative), IBD (each n=10, 21.7%), and *Salmonella* enterocolitis (n=8, 17.4%) were the most frequent diagnoses in children between 6 and 13 years of age. No patient of this age group was diagnosed with AAC.

### 3.6. Adolescents (14–19 years)

Inflammatory bowel disease (n=11, 20.4%) (UC n=7, 12.7% or Crohn disease n=4, 7.4%) and *Campylobacter* enterocolitis (n=10, 18.5%) were the most frequent diagnoses in patients >14 years, followed by hematochezia with signs of GI infection (infectious work-up negative), *Salmonella* enterocolitis, and hematochezia without GI infection (each n=7, 13%). Within our patient cohort, only 1 adolescent was diagnosed with hemorrhoids.

### 3.7. Patients with AAC

The diagnosis of AAC was made in 12 patients (5.4%, male-to-female ratio 2:1; 2 infants, 8 young children, 2 adolescents) (Supplemental Digital Content [SDC] 1: Table 4, <http://links.lww.com/MD/B831>). Two infants fulfilled the criteria for AAHC including a positive stool culture for *K oxytoca* and toxin detection (<1% of total patient cohort with hematochezia; 16.7% of AAC patients). Two young children (16.7% of AAC patients) were diagnosed with CDI. In 8/12 patients (66.7%) with the clinical diagnosis of AAC, neither *C difficile* nor *K oxytoca* could be detected (6 young children, 2 adolescents). Differences in symptoms between patients with AAHC and CDI could not be detected. In 9/12 (75%) patients, hematochezia had started during antibiotic therapy. The duration of initial antibiotic intake until start of bloody stools averaged 6.6 days. The triggering antibiotic treatments was heterogeneous; however, all patients had been treated with beta-lactam antibiotics. In addition to hematochezia, diarrhea, abdominal pain, vomiting, and fever were common symptoms. After termination or change of antibiotic therapy hematochezia resolved in all cases. In none of the patients diagnosed with AAC colonoscopy was performed.

### 3.8. Patients with positive *K oxytoca* stool culture

In 17 (7.7%) of all patients with hematochezia (female n=6, 35.3%; male n=11, 64.7%), the stool culture for *K oxytoca* was positive (SDC 2: Table 5, <http://links.lww.com/MD/B832>). Of these patients, 15 (88.2%) were infants. Among patients with a positive stool culture for *K oxytoca*, 9 (52.9%) were diagnosed with suspected FPIP, 2 (11.8%) with AAHC, and the remaining 6 (29.4%) with diseases diagnosed only once in our patient cohort (SDC 2: numbers 13–17). In 1 case, due to a complex history and postoperative course after heart surgery, a definitive diagnosis as the cause of hematochezia could not be made (SDC 2: number 12). Seven (41.2%) patients with positive *K oxytoca* stool culture had received antibiotic therapy before the onset of hematochezia. *K oxytoca* strains could be retained for further analysis in 15 (88.2%) cases. In 11 of these 15 *K oxytoca* strains, toxin production was demonstrated by classical toxin assay and PCR assay. In view of patient history, clinical course, and *K oxytoca* toxin result, a possible causal association of *K oxytoca* and hematochezia was defined as likely in both cases of AAHC, as possible in all patients with suspected FPIP, and also in patient

number 12 and 13 because of medical history, and as unlikely in the remaining patients.

## 4. Discussion

Although hematochezia is a sign frequently encountered in clinical practice, there are only a few prospective studies about the frequency, age distribution, and differential diagnoses causing bloody stools in pediatric patients.<sup>[3–10,21]</sup> Our study includes 221 pediatric patients (0–19 years), which were recruited in a (nonsurgical) pediatric setting. An even distribution of patients across age groups in our cohort allows comparison of the frequency of diagnoses according to age. Surprisingly, there are only few prospective studies investigating causes of hematochezia in the pediatric population with a comparable number of patients.<sup>[3,5,8–10]</sup> Most reports used very different definitions for pediatric age groups, differed in the way patients were recruited, in how clinical diagnoses were defined, or in how clinical data were acquired and documented. Furthermore, most studies have an uneven distribution of patients according to pediatric age groups. Taken together, these facts make comparisons between these series, including our own, difficult, if not impossible.

In our patient cohort, GI infection was the most common cause of hematochezia across all age groups. Cucchiara et al,<sup>[7]</sup> Yachha et al,<sup>[4]</sup> and Teach and Fleisher<sup>[6]</sup> described infectious colitis as 1 of the most common causes of hematochezia. Spencer,<sup>[5]</sup> Uno et al,<sup>[21]</sup> and Moravej<sup>[9]</sup> did not mention this illness, although some of these studies recruited patients in a nonsurgical setting. Some diagnoses causing hematochezia (eg, suspected FPIP, IBD) are correlated to certain age groups, which is reflected in our results. In our cohort, suspected FPIP was 1 of the most common diagnoses in infants (33.3%). Teach et al,<sup>[6]</sup> Cucchiara et al,<sup>[7]</sup> and Yachha et al<sup>[4]</sup> diagnosed suspected FPIP in between 2.2% and 16.4% of their pediatric patient cohort. Studies that recruited in a pediatric surgical setting did not mention this diagnosis.<sup>[3,5,21,22]</sup> In contrast, IBD was a frequent diagnosis in children and adolescents. Apart from de Ridder et al, none of the other studies about causes of hematochezia mentioned IBD in a comparable number of patients.<sup>[3,4,6,7,9,10,21]</sup> This might be explained by younger patient cohorts<sup>[3,4,7,10,21]</sup> and/or high proportions of infants and young children in these studies.<sup>[3,4,6,7,9,10,21]</sup> Two studies from a surgical department observed intussusception as 1 of the most common diagnoses.<sup>[6,21]</sup> Studies from pediatric departments (ie, nonsurgical setting), in accordance to our results, did not mention this condition.<sup>[4,7–10]</sup> These examples underline the need for exact definitions of clinical settings (eg, nonsurgical vs surgical), patient cohort, age groups, and diagnoses for future studies in pediatric patients with hematochezia. Our observations and attempts to compare with existing literature raise the question if current reviews on the causes of hematochezia in children need to be revised according to patient cohort and age.<sup>[23–27]</sup>

Life-threatening diseases such as intussusception, NEC, or esophageal varices were uncommon diagnoses within our study cohort. None of our patients died due to the underlying cause of hematochezia. In general, our observations suggest that hematochezia in nonsurgical pediatric patients is not a life-threatening symptom in the majority of cases. It is currently unclear whether and when invasive diagnostic procedures (eg, endoscopy) are necessary in pediatric patients with hematochezia. Several studies using endoscopy in pediatric patients with hematochezia identified polyps as 1 of the most frequent diagnoses.<sup>[3,7,8,10,28,29]</sup> In our pediatric internistic patient cohort, polyps were identified

as the cause of hematochezia only twice. It is unlikely that our restrictive use of endoscopy led to underdiagnosing polyps, because hematochezia does not spontaneously resolve in these patients. GI infection, the most frequent cause of hematochezia in our cohort, and suspected FPIP, the most common diagnosis in infants, do not require acute invasive diagnostic.<sup>[30,31]</sup> It might therefore be concluded that in a nonsurgical pediatric setting, endoscopy should be used restrictively in patients with hematochezia, especially in infants and young children.

Antibiotic-associated diarrhea constitutes 1 of the most frequent side effects of antimicrobial therapy with variable clinical presentation, ranging from mild self-limiting diarrhea to severe AAC.<sup>[32–34]</sup> AAC was assumed to be mainly caused by infection with toxin-producing *C difficile* strains.<sup>[35]</sup> Previously, our study group has shown that AAHC, a distinct form of AAC where *C difficile* is absent, is caused by *K oxytoca*.<sup>[11]</sup> Whereas AAC due to *C difficile* goes along with bloody diarrhea in only 14% of patients,<sup>[36]</sup> hematochezia is a main feature in all patients with *K oxytoca*-associated AAHC.<sup>[20]</sup> In our cohort, AAC with bloody diarrhea was diagnosed in 5.4% of patients; most of these patients were young children. AAHC caused by *K oxytoca* in pediatric patients is largely unexplored. Currently, only 3 case reports are available in the literature.<sup>[15,16]</sup> Within our study cohort, only 2 infants fulfilled the clinical presentation of AAHC (bloody diarrhea, acute abdominal pain after antibiotic treatment, detection of toxin-producing *K oxytoca*). We conclude that AAHC caused by *K oxytoca* in pediatric patients is an uncommon diagnosis, comparable with the frequency of Shigellosis or EHEC infection in northern Europe.<sup>[37,38]</sup> Nonetheless, AAHC should be considered as a differential diagnosis in pediatric patients with hematochezia and a history of antibiotic treatment. Thus, by including *K oxytoca* into routine stool diagnostics, unnecessary invasive diagnostics and/or drug treatment could be avoided in children.

A surprising observation was the presence of AAC in the absence of known bacterial or viral enteropathogens (including *K oxytoca* and *C difficile*) in 8 children accounting for 67% of all AAC cases. Although the occurrence of AAC in the absence of established enteropathogens has been observed in previous studies with adults<sup>[11]</sup> and children,<sup>[32,39]</sup> this finding is usually not discussed by the authors. We therefore want to point out that apart from AAC due to *K oxytoca* or *C difficile*, there is a syndrome of colitis due to antibiotics not caused by these pathogens.<sup>[40,41]</sup> This entity, which we term AAC of unknown origin (AACU), needs to be investigated in future studies because neither pathogenesis nor clinical, endoscopic, and histologic features have been described in detail so far. Alterations in the intestinal microbiome by antibiotics leading to dysbiosis and overgrowth of pathobionts,<sup>[40,42]</sup> which in return results in colitis, seems to be an attractive hypothesis for the pathogenesis of AACU. This hypothesis has to be evaluated in larger patient cohort with AAC in children and also in adults.

Most of our patients with a positive stool culture of *K oxytoca* were infants. In our study, more than 25% of all infants with hematochezia were positive for *K oxytoca*. In the other age groups, stool positivity for *K oxytoca* was uncommon or not present. Currently, there are no published data about the presence of *K oxytoca* in stool of healthy children. In our study, *K oxytoca* was found in 12% of healthy infants. Högenauer et al<sup>[11]</sup> tested stool samples from healthy adults for *K oxytoca*: only 1.6% were positive. Similar to reports of high colonization rates of *C difficile* in infants,<sup>[43]</sup> our results suggest that colonization rates of *K oxytoca* might be higher in infants compared with

other age groups. Further investigations with larger pediatric cohorts including all age groups are necessary to make an assertion about the natural enteric colonization with *K oxytoca* in the pediatric population. Most of the infants in our cohort of patients positive for *K oxytoca* were suspected to have FPIP. Our data on *K oxytoca* positivity in healthy infants make this observation statistically significant. The relevance of this observation has to be further investigated.

Our study has several limitations: First, we termed a large patient group “hematochezia with signs of GI infection, infectious work-up negative” (refer “Definitions” subsection above). Whereas from a clinical point of view, these patients were interpreted as having acute GI infection, routine infectious work-up was negative. We cannot rule out that these patients had rare infectious diseases that we did not test for (eg, non-STE *C Escherichia coli* pathotypes, rare enteric viruses) or even noninfectious diseases (eg, toxic exposure). Second, at study initiation, due to our previous experience with AAHC and *K oxytoca* in children and also in adults, we decided not to include oncology ward patients. Therefore, this patient group and their possible causes of hematochezia (eg, typhlitis, graft-vs-host disease) are not represented in our study. Third, we did not routinely test for *Entamoeba histolytica* in our patients, a disease that often causes hematochezia. This disease is very uncommon in Austria. Since we did not interfere with clinical decision-making, it was optional for clinicians to order testing for *E histolytica*, given, for example, a travel history or contact with an index patient. However, in our study cohort, no test for *E histolytica* was ordered. Given these points to consider, we argue that it is unlikely that *E histolytica* infection was common in our cohort or would significantly change our results. Fourth, there is no clear definition of the time frame for a causal relationship of a previous antibiotic therapy with the occurrence of AAC. The risk for CDI is highest after 1 month, but is still increased even 3 months after antibiotic therapy<sup>[44]</sup>. As we assessed previous antibiotic therapy only within 14 days before the occurrence of hematochezia, it is possible that we underestimated cases of antibiotic-associated colitis in our study. Finally, since we only report on children in Austria, our data have to be interpreted with caution in other geographic regions.

## 5. Conclusions

In conclusion, our large nonsurgical pediatric cohort provides important information about the frequency of different diseases causing hematochezia across pediatric age groups. The frequency of AAHC caused by *K oxytoca*, at least for the northern European regions, is comparable with rare GI infections such as Shigellosis or EHEC infection. Our data support the conclusion that AAC presenting with hematochezia, apart from *C difficile* and *K oxytoca*, might be caused by other yet unidentified pathobionts.

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