Original Article

Causes of bloody stools in neonates: a case series report

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Background: Bloody stools in a neonate may stand for a spectrum of conditions ranging from benign to life-threatening. It is critical to detect the cases that have significant underlying pathology, especially those which require urgent surgical intervention. Previous studies always focused on one particular disease related to bloody stools in neonates, or the study only involved a small number of cases. This study aimed to investigate the common causes of bloody stools in neonates.

Methods: This retrospective cohort study included the neonates admitted to our institution due to "bloody stools" over a 5-year period. We compared the differences among patients' characteristics, feeding choice, underlying diseases, and operation rate between preterm and term neonates.

Results: A total of 300 patients were included, accounting for 1.1% of the total neonatal admissions. The overall rate of exclusive breastfeeding was 28.0%. The most common underlying causes for bloody stools were: cow's milk protein allergy (CMPA, 53.3%), swallowed blood syndrome (10.0%), viral enteritis (9.7%), necrotizing enterocolitis (NEC) > stage II (8.3%), non-specific enteritis (7.3%), and anal fissure (5.0%). The median [interquartile range (IQR)] onset age for bloody stools for all infants was 12 [3–22] days after birth. Preterm neonates had a lower rate of exclusive breastfeeding (P=0.844), higher incidence of NEC > stage II (P=0.014), later bloody stools onset age (P<0.001), and longer length of hospital stay than term neonates (P<0.001). For neonates with NEC, those with bottle-fed had an earlier onset age for bloody stools than those with breast-fed (P=0.027). Only 1.7% (n=5) required surgery (2 stage III NEC, 1 post-NEC stricture, and 2 volvuli). Survival at hospital discharge was 100%.

Conclusions: Bloody stools in neonates is generally a benign, self-limiting disorder, not related to surgical conditions. The overall operation rate among neonates with bloody stools was only 1.7%. CMPA and NEC were the most common underlying non-surgical and surgical diseases, respectively, for neonates with bloody stools. Feeding choice is related to bloody stools in neonates, policies and strategies to support breastfeeding should be strengthened in the future.

Keywords: Bloody stools; neonate; cow's milk protein allergy (CMPA); necrotizing enterocolitis (NEC)

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Introduction

Bloody stools have become the main alarming sign in 0.3% of the infants admitted to intensive care units (1,2). The underlying cause of bloody stools in neonates could be benign, such as swallowed maternal blood and anal fissure, but it also could be gastrointestinal bleeding due to a variety of reasons including digestive tract disorders and comorbidities of some critical illnesses, such as necrotizing enterocolitis (NEC), intestinal malrotation with volvulus, Hirschsprung disease, infectious colitis, and systemic coagulopathy (3-7). Bloody stools secondary to NEC is a surgical emergency, and the late diagnosis may lead to detrimental results. NEC is among the most common and devastating diseases in neonates. The estimated rate of death associated with NEC was about 20–30% in very low birth weight (BW) infants, with the highest rate among infants who require surgery (8). Neonates with NEC usually require a long duration of intravenous nutrition and length of hospital stay. In addition, neonates recovering from NEC have substantially increased risk of central nervous system injury and neurodevelopmental delays (9).

Bloody stools in a neonate may stand for a spectrum of conditions from benign to life-threatening, so it is critical to detect the cases that have serious underlying pathology, especially the patients require an emergent surgical intervention. However, there is still no consensus in the management of neonates with bloody stools, as a result, neonates presenting with bloody stools usually undergo blood tests and abdominal radiographs, have enteral feeding stopped and are administered antibiotics, aiming at decreasing the risk of deterioration.

Given previous studies usually focused on one particular disease related to bloody stools, or the study only involved a small number of cases (1,5), this study aimed to analyze the common underlying diseases of bloody stools in neonates over a 5-year period in one of the largest neonatal intensive care units (NICUs) in China. We present the following article in accordance with the STROBE reporting checklist (available at https://tp.amegroups.com/article/view/10.21037/tp-22-166/rc).

Methods

This is a retrospective cohort study. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). It was approved by the Ethical Review Board of Children's Hospital of Fudan University [No. (2021) 289] and individual consent for this retrospective analysis was waived. We included neonates admitted to the NICU due to "bloody stools" with red blood cells in the stool or a positive fecal occult blood test (4) between January 1, 2016 and December 31, 2020. We excluded term infants with an admission age >28 days, preterm infants with an admission age >44 weeks post-menstrual age, and those with missing gestational age (GA) or BW. Data were collected retrospectively from the clinical records. The modified Bell's staging criteria was used to classify NEC according to clinical and radiographic presentations (10,11). Cow's milk protein allergy (CMPA) was diagnosed based on medical history, clinical features, recovery from symptoms by removing causal allergens, with or without an oral food challenge test (12). We used the term "non-specific enteritis" to refer to cases that lacked specific causes for bloody stools. Definition of preterm and term neonates were based on GA and expressed according to the 11th revision of international classification of diseases (ICD-11, WHO) (13).

Statistical analysis

The data were analyzed using SPSS software (v. 22.0, SPSS Inc., Chicago, IL, USA). The main statistical analyses are descriptive. Continuous variables were presented as median and interquartile range (IQR) and categorical data were expressed as number and percentage (%). Chi square or Fisher's exact test were used for categorical variables, and Mann-Whitney for continuous variables to compare the differences among patients' characteristics, feeding choice, underlying diseases, and operation rate between preterm and term neonates. A two-sided P value less than 0.05 was considered as statistically significant.

Results

Patient demographics

A total of 300 cases were included, accounting for 1.2% (300/26,082) of the total neonatal admissions from 2016 to 2020. The ratio of male to female was 1.2:1. The median [IQR] GA was 38.7 [36.8–39.6] weeks, in which 27.0% (n=81) had a GA <37 weeks and 5.3% (n=16) were small for GA. The median [IQR] BW was 3,200 [2,664–3,550] g with 20.0% (n=60) of BW <2,500 g, and 2.7% (n=8) of BW <1,500 g. For neonates with bloody stools secondary to NEC, those with BW <1,500 g accounted for 12.0%. There

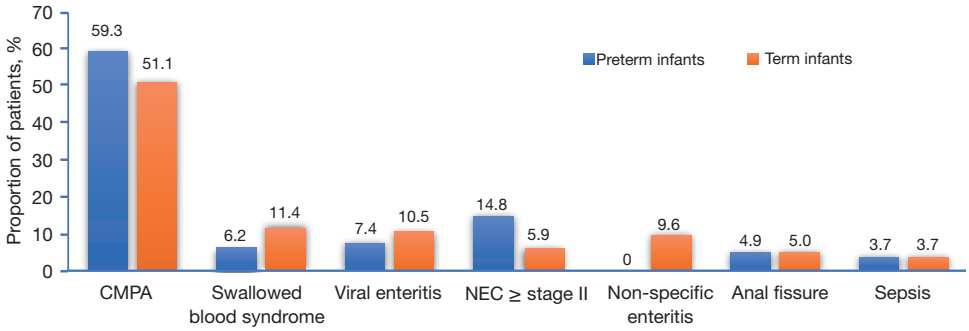

Figure 1 Causes of bloody stools in preterm and term infants. CMPA, cow's milk protein allergy; NEC, necrotizing enterocolitis.

Table 1 Preterm and term infants with bloody stools: clinical characteristics and outcomes

Characteristic	Preterm infants	Term infants	P
Number of patients	81 (27.0)	219 (83.0)	–
Male	42 (51.9)	123 (56.2)	0.505
BW, g	2,130 [1,808–2,668]	3,400 [3,120–3,650]	<0.001
GA, weeks	34.6 [32.7–36.9]	39.0 [38.4–39.8]	<0.001
Exclusive breastfeeding	22 (27.2)	62 (28.3)	0.844
Bloody stool onset age, days	20 [10–29]	9 [3–19]	<0.001
Bloody stool onset age >7 days	67 (82.7)	120 (54.8)	<0.001
CMPA	48 (59.3)	112 (51.1)	0.211
NEC ≥ stage II	12 (14.8)	13 (5.9)	0.014
Hospital stay length, days	9 [8–15]	7 [5–9]	<0.001
Need for surgery	2 (2.5)	3 (1.4)	0.614

Comparisons of categorical variables were performed with Chi square test or Fisher's exact test. Mann-Whitney test was applied for comparisons of continuous variables. Values are given in n (%), or median and interquartile range [IQR]. BW, birth weight; GA, gestational age; CMPA, cow's milk protein allergy; NEC, necrotizing enterocolitis; IQR, interquartile range.

were only 9 (3.0%) neonates with congenital heart diseases, including 5 cases of ventricular septal defects, 3 of atrial septal defects, and 1 of Ebstein's anomaly.

Causes of bloody stools

The most common diagnosis of bloody stools was CMPA (53.3%), followed by swallowed blood syndrome (10.0%), viral enteritis (9.7%), NEC ≥ stage II (8.3%), non-specific enteritis (7.3%), anal fissure (5.0%), sepsis (3.7%), coagulation disorders (1.0%), malrotation/volvulus (0.7%), idiopathic thrombocytopenic purpura (0.3%), Kasabach-Merritt syndrome (0.3%) and lactose intolerance (0.3%). Causes of bloody stools for preterm and term infants are presented in *Figure 1*. Preterm infants had a higher incidence of NEC than term infants (14.8% *vs.* 5.9%, P=0.014) (*Table 1*).

Causes depending on the age at onset

The median [IQR] bloody stools onset age of all patients was 12 [3–22] days after birth. There were 10.7%, 17.0%, 10.0%, 18.7% and 43.7% cases with bloody stools onset age <1, 1–3, 4–7, 8–14, and >14 days after birth, respectively. The 2 cases of volvulus were term infants with bloody stools onset age at 2 days of life. About 96.7% of neonates with swallowed blood syndrome had bloody stools onset age in the first 3 days of life. About 72.5%, 82.8% and 72.0%

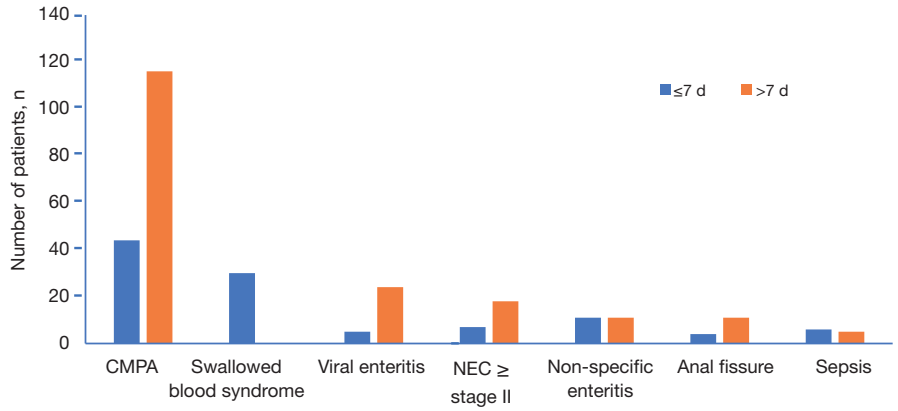

Figure 2 Bloody stool onset age ≤7 *vs.* >7 days in different diagnoses. CMPA, cow's milk protein allergy; NEC, necrotizing enterocolitis.

neonates with CMPA, viral enteritis and NEC had bloody stools onset age >7 days after birth (*Figure 2*). Preterm infants had a later bloody stools onset age than term ones (20 *vs.* 9 days, P<0.001).

Causes depending on feeding choice

The rate of exclusive breastfeeding was only 28.0% for all infants, and it was 28.1% and 24.0% in neonates with CMPA and NEC respectively. There was no significant difference in the rate of exclusive breastfeeding between preterm and term infants (27.2% *vs.* 28.3%, P=0.844). For neonates with CMPA, there were no significant differences in bloody stools onset age (P=0.856) and length of hospital stay (LOS) (P=0.757) in neonates with exclusive breastfeeding, bottle feeding, and mixed feeding. For neonates with NEC, those who were exclusively breastfed had the latest bloody stools onset age, and those who were bottle-fed had the earliest bloody stools onset age (24 *vs.* 7 days, P=0.027), but there was no significant difference in LOS in the three groups (P=0.762).

LOS and outcome

The median [IQR] LOS for all infants was 8 [5–10] days, and 88% had a LOS <14 days. Preterm infants had longer LOS than term ones (9 *vs.* 7 days, P<0.001). Compared to other diagnoses, neonates with NEC had a longer LOS (16 *vs.* 7 days, P<0.001). Only 1.7% (n=5) required an operation (2 stage III NEC, 1 post-NEC stricture, and 2 volvuli). Survival at hospital discharge was 100%.

Discussion

The current report presents our experience with 300 neonates who presented with bloody stools over a 5-year-period in one of the largest NICUs in China. Bloody stools in neonates were not rare, as its prevalence in our cohort was 1.1%, which was much higher than previous studies reported (1,2).

Bloody stools in a neonate are an alarming sign, which may stand for a spectrum of benign to life-threatening conditions. Benign etiologies include swallowed maternal blood (from delivery or due to maternal nipple abrasions), anal fissures, and CMPA in the older infant (14,15). More severe conditions include infections such as bacterial or viral sepsis, infectious colitis, gastrointestinal malformations, and NEC (16,17). It is critical to detect the cases with significant underlying pathology, especially those that require an emergent surgical intervention. Next, we would like to highlight some of our study findings.

First, we found that the most common underlying surgical condition among neonates with bloody stools was NEC. Bloody stools secondary to NEC in a neonate is a surgical emergency, as its late diagnosis may lead to detrimental outcomes. NEC was most commonly seen among preterm infants. The prevalence of NEC is about 7% in very low BW infants, and the estimated rate of death associated with NEC ranges between 20% and 30%, with the highest rate among infants requiring surgery (18-21). NEC was thought to be a single, homogeneous entity, whereas it is currently clear that it comprises different conditions or endotypes (22). In addition to the "Classic" NEC of preterm neonate, other diseases commonly diagnosed as

NEC include spontaneous intestinal perforation, ischemic intestinal necrosis, food protein intolerance enterocolitis syndrome (FPIES), and congenital anomalies of the bowel that mimic NEC (23). Our study showed that preterm neonates had a higher incidence of NEC, but NEC in neonates with BW <1,500 g in our study only accounted for a small part and about one half infants with NEC were full term neonates. One possible reason was that we focused on the infants admitted to NICU due to "bloody stools", and we didn't include neonates who presented bloody stools after admission, while extremely preterm neonates or those with BW <1,500 g usually presented with bloody stools during hospitalization. Another possible reason was that in term neonates, NEC may be secondary to other diseases, such as FPIES (24), as the rate of breastfeeding was very low in our study. Unfortunately, biomarkers to differentiate FPIES from NEC are not yet available, and a recent study suggest that FPIES may be underreported in neonates (25).

Second, we found that most neonates with bloody stools were not related to surgical diseases, and nearly one half of them were CMPA. CMPA is the most common allergy in the first year of life and it is due to infant formula or breast milk of mothers who drink or eat cow's milk or its products. The prevalence of CMPA in infants is approximately 2% to 3% (12,26,27), and it has been on a steady rise over the last years (28). Our findings were in line with previous studies suggesting that most infants with allergic colitis are symptomatic in the first month, and bloody stools were one of the most common manifestations of CMPA in infants at the time of onset (2,29-31). Exclusive breastfeeding and avoiding the use of regular cow's milk formula as supplementary feed for breastfed infants in the first 6 months of life has been known to reduce and prevent CMPA (32-35), and the lack of breast milk has been significantly associated with bloody stools (1,5,36). However, the rate of breastfeeding was very low in our study. Although the World Health Organization recommends exclusive breastfeeding for the first 6 months, followed by breastfeeding along with appropriate complementary foods up to 2 years of age or beyond, exclusive breastfeeding rates at 6 months were only between 0.50% and 33.45% in China in the past decade, and the common reasons given for ceasing breastfeeding or exclusive breastfeeding before 6 months included perceived breast milk insufficiency, mother returning to work, maternal or child illnesses, and concern about nutrition or available formula milk (37). Policies and strategies to support breastfeeding would be helpful for reducing and preventing CMPA and should be strengthened in the future.

Our study is limited to its retrospective single-institution design. Furthermore, we didn't include infants who presented with bloody stools during hospitalization. Further multicenter studies are required to investigate the causes of bloody stools in all neonates.

Conclusions

Bloody stools in neonates are generally a benign, self-limiting disorder, not related to surgical diseases in most cases. The overall operation rate among neonates with bloody stools was only 1.7%. CMPA and NEC were the most common underlying non-surgical and surgical diseases, respectively, for neonates with bloody stools. Feeding choice is related to bloody stools in neonates, and policies and strategies to support breastfeeding should be strengthened in the future.

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Footnote

Reporting Checklist: The authors have completed the STROBE reporting checklist. Available at https://tp.amegroups.com/article/view/10.21037/tp-22-166/rc

Data Sharing Statement: Available at https://tp.amegroups.com/article/view/10.21037/tp-22-166/dss

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://tp.amegroups.com/article/view/10.21037/tp-22-166/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013) and was approved by the Ethical

Review Board of Children's Hospital of Fudan University [No. (2021) 289]. Individual consent for this retrospective analysis was waived.

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