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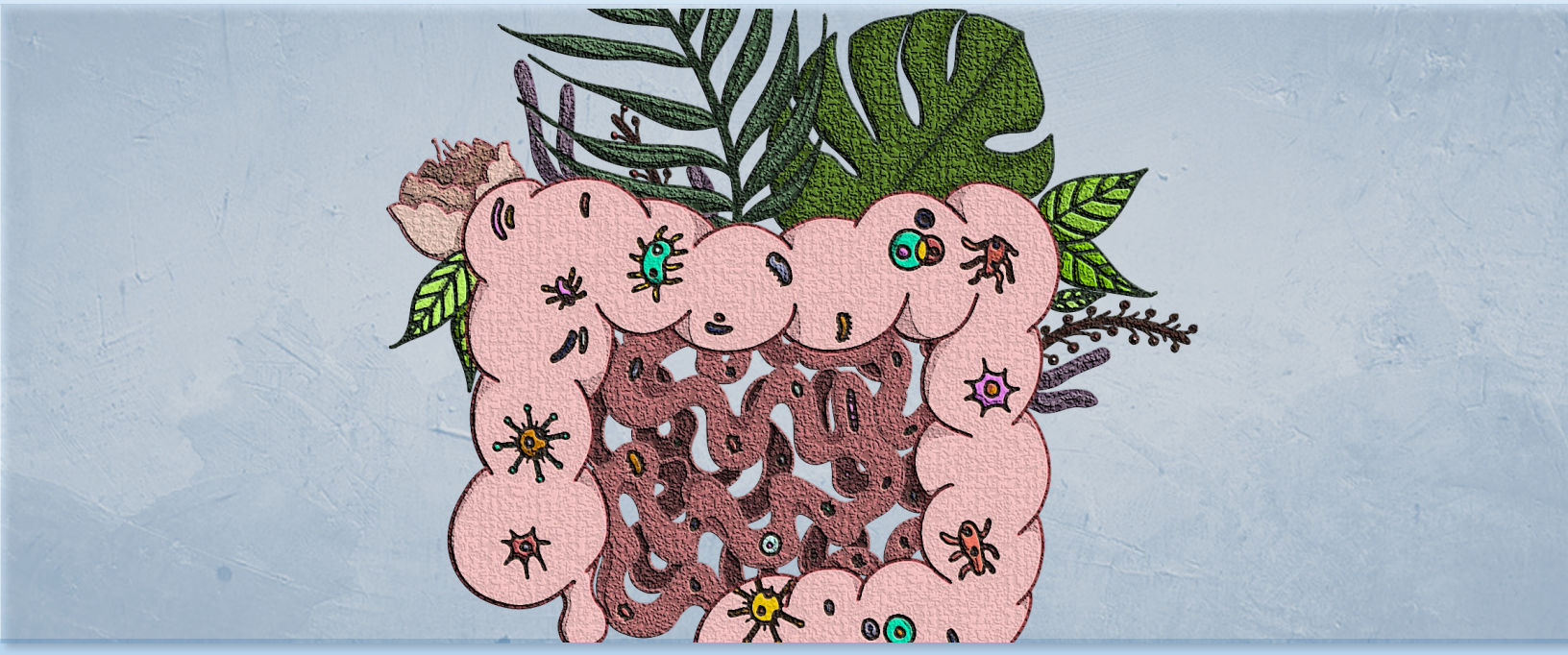

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Archives of Pediatric Gastroenterology, Hepatology, and Nutrition

Original Article

Demographic Characteristics of Children with Biliary Atresia in dr. Kariadi General Hospital, Semarang

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Abstract:

Background: Biliary atresia (BA) is a progressive fibrosing obstructive cholangiopathy involving both the intrahepatic and extrahepatic biliary system; resulting in obstruction of bile flow and neonatal jaundice. Early diagnosis of biliary atresia and Kasai procedure improves patients outcome. Data form several studies revealed that BA is the most common cause of neonatal cholestasis (25%) and the leading cause of end-stage liver disease in pediatric population. The aim of this study is to determine the outcome and characteristics of children with biliary atresia in dr. Kariadi General Hospital, Semarang.

Methods: In this study, a retrospective database analysis of 80 infants diagnosed with biliary atresia was conducted. Patient's demographic data including age, sex, age at disease onset, were collected from year 2018 to 2022; including all comorbidities and complications. Data regarding procedure performed for each patient and their outcome were included in this study.

Results: Eighty children were included in this study. The mean age of children referred with biliary atresia was 1.89 month, while the mean age at diagnosis was 2.5 month. Most of the patients were girls. The incidence of cytomegalovirus infection comorbidity in patients with biliary atresia is quite high, which were reported at 82%. Children diagnosed with biliary atresia and cytomegalovirus infection resulted in worse prognosis than those without.

Conclusion: Our study support the theories that biliary atresia may be caused by the exposure of external environment during perinatal period such as viral infection. The prognosis of patients with cytomegalovirus comorbidity is worse than that without.

Keywords: biliary atresia, characteristics, pediatric patients, demographic, cytomegalovirus

Introduction

Biliary atresia (BA) is a progressive fibrosing obstructive cholangiopathy involving both the intrahepatic and extrahepatic biliary system; resulting in obstruction of bile flow and neonatal jaundice.[1] Several studies have reported that biliary atresia is the

most common cause of neonatal cholestasis (25%) and the leading cause of end-stage liver disease in pediatric population.[2] Hence, early diagnosis of biliary atresia and Kasai procedure are exceedingly important to improve patients outcome. If left untreated, the survival rate is less than 10% at 3 years of age.

Clinical manifestations of biliary atresia often emerged during neonatal period with persistent jaundice, clay-coloured stools, and hepatomegaly. Theories suggest that genetic and environmental factors are the main contributing factors, since approximately 3-20% of children with biliary atresia had been associated with other syndromes or other congenital abnormalities. Evidence of CMV infection has been reported in 10-38% of infants with biliary atresia.[2] Biliary atresia is more common in certain geographic areas, suggesting that several genetic components may play an important role in pathogenesis of the disease.

Currently, there is limited data regarding biliary atresia patients in Indonesia, especially in Semarang. Thus, this study is conducted to demonstrate the current data of biliary atresia which includes epidemiology, clinical characteristic and outcome in Indonesian population.

Methods

Retrospective database analysis of 80 infants diagnosed with biliary atresia was conducted in dr. Kariadi General Hospital, Semarang, Indonesia from 2018-2022. Cases of cholestasis with clinical, biochemical data and surgical findings that consistent with biliary atresia, were included in this study. Patient's demographic including age, sex, age at disease onset, and any co-infections were recorded; including complications and outcome.

Result

Eighty medical record of children that consistent with biliary atresia were included in this study. The mean age of children referred with biliary atresia was 1.89 months, while the mean age at diagnosis was 2.5 months and at death was 20.1 months. Children diagnosed with biliary atresia had high average bilirubin levels (total bilirubin 18.32, direct bilirubin 11.82, indirect bilirubin 2.96) as well as levels of liver damage parameters (SGOT, SGPT, alkaline phosphatase, gamma GT) as shown on **Table 1**.

Table 1. Data of age and laboratory parameters of children with biliary atresia

Parameter	Mean (SD)
Age	
Age at referral (month)	1.89 (4.711)
Age at diagnosis (month)	2.5 (2.677)
Age at death (month)	20.1 (15.39)
Laboratory Parameters	

Total bilirubin	18.32 (56.25)
Direct bilirubin	11.82 (22.89)
Indirect bilirubin	2.96 (10.45)
SGOT	249.58 (2256.4)
SGPT	142.23 (540.6)
Alkaline phosphatase	532.06 (1525.3)
Gamma GT	596.168 (3514.9)

Most of the subjects in this study were girls (53.75%). Most children with biliary atresia was born with low birth weight, and had poor nutritional status, ranging from moderate to severe malnutrition. Abdominal ultrasonography was performed on children with suspicion of biliary atresia and only 56.25% of the results show a triangular cord sign. Children with biliary atresia have a high survival rate with 51.25% of patients underwent IOC. About 82% of patients also recorded to have comorbidities of congenital CMV infection (**Table 2**).

Table 2. Demographic characteristics of children with biliary atresia

Characteristics	**n (%)**
Gender	
Male	37 (46.25)
Female	43 (53.75)
Birthweight	
Normal birth weight	18 (22.5)
Low birth weight	38 (47.5)
Very low birth weight	18 (22.5)
Extremely low birth weight	6 (7.50)
Nutrition Status	
Normal	16 (20)
Moderate malnutrition	40 (50)
Severe malnutrition	24 (30)
Abdominal Ultrasonographic (Presence of Triangular Cord Sign)	
Yes	45 (56.25)
No	35 (43.75)
IOC	
Yes	41 (51.25)
No	39 (48.75)
Death	
Yes	15 (18.75)

No	65 (81.25)
CMV Infection	
Yes	66 (82.5)
No	14 (17.5)

Notes: IOC: intraoperative cholangiography; CMV: Cytomegalovirus

Only half of children (53.33%) who died of biliary atresia had CMV. Even so, most of these children had high levels of bilirubin profile and liver damage parameters, as well as poor nutritional conditions. IOC may provide higher life expectancy in children with biliary atresia (**Table 3**).

Table 3. Characteristics and laboratory parameters of children who died of biliary atresia

Parameter	n (%)
Total Bilirubin (mg/dL)	
>5	11 (73.33)
1-5	4 (26.67)
Indirect Bilirubin (mg/dL)	
>5	9 (60)
1-5	6 (40)
Direct Bilirubin	
>5	10 (66.67)
1-5	5 (33.33)
Nutritional Status	
Normal	1 (6.67)
Moderate Malnutrition	8 (53.3)
Severe Malnutrition	6 (40)
IOC	
Yes	4 (26.67)
No	11 (73.3)
CMV Infection	
Yes	8 (53.33)
No	7 (46.67)

Discussion

Biliary atresia is a progressive, inflammatory liver disease characterized by obstructive cholangiopathy and disrupted bile flow in early infancy. The incidence of biliary atresia ranges from 4.2 to 32 per 100,000 live births, with the highest incidence reported in French Polynesian and East Asian countries. Although the exact pathogenesis of

biliary atresia remains unknown, recent research suggests that multifactorial immunologic responses, triggered by various factors (e.g. ethnicity, infections, genetic and environmental factors), play important roles.[1]

The etiology of biliary atresia is unknown. Theories suggest a multitude of etiological and causative factors that are both genetic and acquired. Since about 3% to 20% of children with biliary atresia are associated with other syndrome or congenital abnormality, and as biliary atresia is more common in certain geographic regions, it is likely that some genetic component is present in the pathogenesis of the disease, although no single etiology has been found so far. Only a few familial cases are described and no increase in the incidence has been noted in the case of twins.[2,3]

The extrahepatic bile ducts first become visible as an out-pouching of the foregut at 20 days of gestation, and the intrahepatic bile ducts become visible at 45 days, which was formed from the primitive hepatocytes. The porta-hepatis is the place of the interface between the extra and intrahepatic bile ducts, and the successful union is crucial for the development of the patent biliary system. The non-syndromic isolated type of biliary atresia might result from faulty remodelling in fetal life at the hepatic hilum. This is supported by the fact that there are similarities in the cytokeratin staining of the bile ducts in patients with biliary atresia and first-trimester fetal bile ducts strengthening the possibility that biliary atresia could occur due to the failure of the bile duct remodelling at the hepatic hilum with the persistence of fetal bile ducts.[4]

Other theories favor a possible acquired, inflammatory, and infectious cause for the pathogenesis of the disease. Rotavirus and reovirus type 3 are specifically mentioned, as perinatal animal models infected by those viruses produced biliary atresia; however, these results have not been consistently seen in humans.[5,6] There have also been studies that show immune-related damage to the ductules of patients with biliary atresia due to an increase in the expression of intercellular adhesion molecule (ICAM)-1 in the bile ductules.[7]

In this study, cases of biliary atresia were more common in female infants than male infants. The study by Bellomo-Brandao et al. found that from 165 infants, intrahepatic cholestasis was found in 62.64% male infants, while extrahepatic cholestasis was found in 55.25% female infants with p-value = 0.026. This finding was similar to this study; despite no significant differences were found, this study showed that BA or extrahepatic cholestasis was commonly found in female infants.[8,9]
The data in this study were children who were enrolled at an average age of 1.89 month where they were only diagnosed as BA when they were 2.5 month old. these findings indicate an early detection of cases. Data also showed that the patient was referred

before the age of 8 weeks. The diagnosis can be made before the end of 12 weeks or 100 days.

The diagnosis of BA was based on clinical manifestations (yellowing of the eyes and whole body, a cholic stool) and anatomical pathology examination (histopathological features such as bile plug, ductular proliferation, and portal edema with and/or fibrosis of liver biopsy tissue). Biopsy samples were taken and extracted from liver tissue.[10] Cytomegalovirus infection is initially more common in intrahepatic cholestasis (without BA); however, several studies have shown that CMV infection can be found in extrahepatic cholestasis (BA). The study found that viruses including CMV can be a trigger leading to dysregulation of immune mechanisms with genetic influences and eventually causes BA. Cytomegalovirus infection has the ability to replicate both in hepatocytes and cholangiocytes. This virus can directly induce damage to the liver and biliary duct system and induce damage to the immune system in infected cells, leading to the formation of inclusion of bodies in hepatocyte and vascular cells of epithelial cells, especially along with 21 biliary duct epithelial cells.[10]

In the past, most patients with biliary atresia died before the age of 3 years; however, the 5-year survival rate has increased sharply, from 30% to 75%, since the introduction of Kasai portoenterostomy in 1968. Although timely Kasai procedure is a primary surgical option for early survival, liver transplantation is also required as a curative option because the 4-year survival rate after Kasai is as low as 42%. This research show that children with biliary atresia were less likely to die and death often resulted from sepsis. Twenty three-percent underwent IOC with Kasai and other procedures. Ascending cholangitis is the most common complication after Kasai, and is a causative factor of liver damage. Bacterial cholangitis occurs at a rate of 70%-90% and recurs in most cases. [11,12] In this study, 51.25% of infants underwent IOC, continued with Kasai procedure. While the infant mortality rate is 81.25% in infants with biliary atresia, while infants who survive are 18.75%.

Conclusion

Biliary atresia is a congenital disorder in the form of progressive fibrosing obstructive cholangiopathy involving both the intrahepatic and extrahepatic biliary system; resulting in obstruction of bile flow and neonatal jaundice. Data obtained from biliary atresia in children at dr. Kariadi Hospital Semarang found that the mean age of children who came with biliary atresia was 1.89 months, while the age at diagnosis was 2.5 months. Children with biliary atresia are more likely to die from postoperative sepsis. Almost half of the patients underwent IOC with the Kasai Procedure and other procedures. Our study is in accordance to the theories that biliary atresia may cause by exposure form the external environmental factors during the perinatal period such

as viral infection. The prognosis of patients with cytomegalovirus co-infection is worse than that in the absence of the co-infection.

Conflict of Interest

None declared.

Funding

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References

1. Santos JL, Carvalho E, Bezerra JA. Advances in biliary atresia: From patient care to research. Braz J Med Biol Res. 2010;43(6): 522-7.
2. Bassett MD, Murray KF. Biliary atresia: Recent progress. J Clin Gastroenterol, 2008;42(6):720-9.
3. Moreira RK, Cabral R, Cowles RA, Lobritto SJ. Biliary atresia: A multi disciplinary approach to diagnosis and management. Arch Pathol Lab Med. 2012;136(7):746-60.
4. Sira MM, Salem TAH, Sira AM. Biliary atresia: A challenging diagnosis. World J Gastroenterol, 2013;1:24-35.
5. Oliveira NL, Kanawaty FR, Costa SC, Hessel G. Infection by Cytomegalovirus in patients with neonatal cholestasis. Arq Gastroentero. 2002;39(2):132-6.
6. Buonsenso D, Serranti D, Gargiullo L, Ceccarelli M, Ranno O, Valentini P. Congenital Cytomegalovirus infection: Current strategies and future perspectives. Eur Rev Med Pharmacol Sci. 2012;16(17):919-35.
7. Caliendo AM, Schuurman R, Yen-Lieberman B, Spector SA, Andersen J, Manjiry R, et al. Comparison of quantitative and qualitative PCR assays for Cytomegalovirus DNA in plasma. J Clin Microbiol. 2001;39(4):1334-8.
8. Mack CL, RJ Sokol. Unraveling the pathogenesis and etiology of biliary atresia. Pediatr Res. 2005;57:87-94.
9. XuY, YuJ, ZhangR, Yin Y, Ye J, et al. The perinatal infection of Cytomegalovirus is an important etiology for biliary atresia in China. Clin Pediatr (Phila). 2012;51(2):109-13.
10. Rauschenfels S, Krassmann M, Al-Masri AN, Verhagen W, Leonhardt J, Kuebler JF, et al. Incidence of hepatotropic viruses in biliary atresia. Eur J Pediatr. 2009;168(4):469-76.
11. Rashed YK, Saber MA, Tawfik M, Mourad WS. Histopathological features and accuracy for diagnosing biliary atresia by prelaparotomy liver biopsy in Egypt. Gaz Egypt Paediatr Assoc. 2013;61:42-5.
12. Rastogi AN, Krishnani K, Yachha V, Khanna U, Poddar, Lal R. Histopathological features and accuracy for diagnosing biliary atresia by prelaparotomy liver biopsy in developing countries. J Gastroenterol Hepatol. 2009;24(1):97-102.

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Original Article

Characteristics of Pediatric Patients with Diarrhea in Indonesia: A Laboratory-based Report

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Abstract:

Background: Diarrhea is still a common health problem in Indonesia, with high morbidity and mortality rate. The severity of diarrhea is associated with age, nutritional status, and cause of diarrhea. This study aims to describe the characteristics and laboratory findings, particularly stool analysis, in pediatric patients with diarrhea.

Methods: A retrospective study was conducted using data from patients aged 0 to 18 with diarrhea who underwent stool analysis in Cipto Mangunkusumo Hospital between 2012 and 2016.

Results: The average age of children with diarrhea was 45 months, with most patients (55,6%) being under two years old children. More than half of the patients were boys (58.8%). Two-thirds of the patients (67%) presented with watery stool diarrhea. The interpretation of stool analysis indicated that nearly half of the patients (48%) experienced diarrhea due to bacterial infection, followed by fat malabsorption (20.8%). Similar results were also seen in the stool analysis of children aged 0-24 months, with the prevalence of bacterial infection (35.2%) and fat malabsorption (30.2%) being the most commonly identified etiology of diarrhea.

Conclusion: In Indonesia, children under two and male gender were more frequently reported to experience diarrhea. The primary manifestation of pediatric diarrhea was watery stools, while the most common etiology was bacterial infections.

Keywords: diarrhea, stool analysis, pediatric patients

Introduction

The high morbidity and mortality rates of diarrhea remain a major concern in developing countries, including Indonesia. Diarrhea is the recurrent passage of watery stools that occurs at least three times in 24 hours. The disease is further classified as acute diarrhea, which occurs for less than seven days; prolonged diarrhea, occurring for 7-14 days; and persistent diarrhea that last for more than 14 days.[1]

The severity of diarrhea is associated with the age of the patient, nutritional status, and the underlying cause of diarrhea.[1] According to RISKESDAS 2013, infant is the main age group that suffered from diarrhea. In addition, diarrhea in this particular age group primarily occurred at the age of 12-23 months (7.6%), majorly in the male gender (5.5%), and commonly in patients who lived in the countryside (6.2%).[2]

A cross-sectional study conducted by Hendrawati et al. reported that more than 25% of children with diarrhea also suffered from malabsorption syndrome, with the prevalence of lactose and fat malabsorption were 11% and 51%, respectively. Furthermore, this study found that 19% of 3480 stool specimens of pediatric patients show signs of maldigestion. Food allergy may also lead to malabsorption. In addition, previous study found that the prevalence of cow's milk allergy in patients with diarrhea in Indonesia was 3%.[3,4]

The purpose of this study was to identify the characteristics and laboratory findings of pediatric patients based on their stool analysis profile treated in Cipto Mangunkusumo Hospital.

Methods

This research was a retrospective, cross-sectional study conducted in Cipto Mangunkusumo Hospital, Jakarta, Indonesia. Patients aged 0 to 18 years old who suffered from diarrhea and underwent stool examination in the Laboratory of Gastrohepatology Division, Department of Child Health, Cipto Mangunkusumo Hospital were included in this study. Meanwhile, subjects with incomplete medical records were excluded. Stool analysis and other supporting data were obtained from the medical records documented in 2012 – 2016. Other supporting data include age, gender, history of bacterial infection, fungal infection, food maldigestion, carbohydrate maldigestion, protein maldigestion, lactose malabsorption, fat malabsorption, and suspected cow milk allergy.

Bacterial infection was considered positive if the stool leucocyte count was higher than +2 or 10-20 leucocytes per high magnification field.[3] Meanwhile, the diagnosis of fungal infection was noted in samples with positive appearance of fungal. Food maldigestion was indicated by the presence of meat or vegetable fibers in the stool, while carbohydrate maldigestion was considered positive in the existence of amylum.[3,5] The presence of the protein molecule indicated protein maldigestion.[5] Furthermore, the diagnosis of lactose malabsorption was established in samples with fecal pH less than 6, or if the fecal reducing substance results read as 0, trace (1/4% glucose), + (1/2% glucose), ++ (3/4% glucose), +++ (1% glucose), and ++++ (2% glucose).[6,7] Fat malabsorption was confirmed if the amount of fat exhibited positive 2 (++) in the microscopic examination.[3] Lastly, cow's milk allergies were suspected in patients with

erythrocyte counts in stool > 5. The data collected were then quantified using SPSS version 21.

All data, including other personal information provided and gathered, was kept confidential. This research had received ethical permission no. 964/UN2.F1.D1/KBK/PDP.01/2016.

Result

Subjects Demographics

From 2012 until 2016, stool analysis was performed on 1031 pediatric patients with diarrhea in Cipto Mangunkusumo Hospital. The age ranged between 0 to 18 years old, with the average age of 45 months. Most of the patients were children under two years old (55.6%). Furthermore, more than half of the patients (58.8%) were male.

Table 1. Characteristics of study subjects

Characteristics	n (%)
Gender	
Male	606 (58.8)
Female	423 (41)
Age	
<24 months	573 (55.6)
24-59 months	191 (18.5)
>60 months	262 (25.4)

Consistency of the Stool

The stool analysis results demonstrated various stool characteristics such as consistency, and laboratory findings. Among the 857 patients, 67% of the patients presented with watery stool diarrhea.

Table 2. Consistency of stool analysis in this study

Consistency	n (%)
Normal	155 (15)
Solid	11 (1.1)
Liquid	691 (67)

Laboratory Findings and Interpretation

Various laboratory examinations of the stool samples were performed to determine the cause of diarrhea. Each etiology presented distinct characteristics, which were mentioned in the methodology. One patient might have more than one significant laboratory findings and hence was diagnosed with more than one causes of diarrhea.

Most of the samples demonstrated the presence of leucocytes, erythrocytes, and fat. Positive results with a low number of these components in stool can be considered normal. However, excessive amounts may indicate various conditions such as bacterial infection, dysentery, or fat malabsorption.

Table 3. Stool analysis profile of the study subjects

Laboratory Findings*	**n (%)**
Mucus	536 (52)
Blood	25 (2.4)
Leucocyte	
+1	273 (26.5)
+2	395 (38.3)
+3	198 (19.2)
Erythrocyte	
+1	471 (45.7)
+2	200 (19.4)
+3	82 (8.0)
Fat	
+1	347 (33.7)
+2	188 (18.2)
+3	63 (6.1)
Amylum	129 (12.5)
Plant fibers	192 (18.6)
Muscle fibers	34 (3.3)
Occult blood	337 (32.7)
pH	
6 or more	951 (92.2)
Less than 6	80 (7.8)
Glucose	
0.25%	22 (2.1)
0.50%	36 (3.5)
0.75%	8 (0.8)
1%	16 (1.6)
2%	3 (0.3)
Parasites	6 (0.6)
Fungi	216 (21)

*One participant might present with more than 1 significant findings

The laboratory findings of each participant were then interpreted to determine the etiology of diarrhea. The most common interpretation indicated that most patients suffered from diarrhea caused by bacterial infection (48%).

Table 4. Interpretation of stool analysis profile in patients aged 0-18 years

Diagnosis*	**n (%)**
Bacterial infection	503 (48.8)
Fungal infection	80 (7.8)
Carbohydrate maldigestion	130 (12.6)
Food maldigestion	187 (18.1)
Protein maldigestion	29 (2.8)
Fat malabsorption	214 (20.8)
Lactose malabsorption	76 (7.4)
Suspected cow's milk allergy	45 (4.4)
Dysentery/Infective colitis	143 (13.4)

*One participant might have more than 1 interpretation

Table 5. Interpretation of stool analysis profile in patients aged 0-59 months

Diagnosis*	**n (%)**
Bacterial infection	269 (35.2)
Fungal infection	49 (6.5)
Carbohydrate maldigestion	72 (9.5)
Food maldigestion	81 (10.7)
Protein maldigestion	9 (1.2)
Fat malabsorption	228 (30.2)
Lactose malabsorption	76 (10.1)
Suspected cow's milk allergy	42 (5.6)
Dysentery/Infective colitis	94 (12.4)

*One participant might have more than 1 interpretation

Discussion

The relationship between diarrhea and nutrition has been discussed widely. Many factors contributed in the effect of diarrhea towards nutritional status. Increased

nutrients loss, malabsorption, maldigestion, and the impact of inflammatory responses are some of the factors involved in diarrhea with malnutrition. In this study, diarrhea mainly occurred in children aged 0-24 months (55.6%). This result was similar to other research in Indonesia, which stated that diarrhea mainly occurred in children aged less than 24 months with the prevalence of 56.68%.[8]

This study demonstrated that the prevalence of diarrhea in children, especially boys, was higher than in girls. It is similar to a study done in a hospital located in Yogyakarta, Indonesia.[9] Another study in Munimbili National hospital also revealed that 60% of diarrhea patients were boys aged 7-12 months old.[10]

The characteristics of stool analysis varied among patients. The most prevalent consistency among the samples in our study was liquid / watery stool (67%). Diarrhea can cause malabsorption when the fluid volume in the colon is higher than the absorption capacity. Damage in the intestine due to diarrhea decreases absorption and increases secretion, generating the liquid consistency of the stool.[1]

Leukocytes in stools are produced as a response to the inflammatory process in the mucosa of the colon. The presence of leukocytes in the feces indicates the existence of invasive bacteria or bacteria-produced cytotoxin, which may cause tissue damage. Furthermore, higher numbers of leukocytes increase the likelihood of invasive pathogens infection. Fecal leukocyte stain was considered to have better accuracy and diagnostic value in determining the etiology of diarrhea.[11, 12] In our study, the number of samples with leukocyte counts of +2 was higher than patients with leukocytes count of +3, which accounted for 38.3% and 19.2% respectively.

The erythrocyte counts in our study were accounted for 19.4% (+2) and 8% (+3), respectively. Although there was still no consensus in interpreting the erythrocytes count in stool analysis, a study in Bangladesh had reported the benefit of direct microscopical stool examination to quantify the leukocytes and erythrocytes in making an early diagnosis of Shigella infection.[13]

Diarrhea is commonly related to motility dysfunction. Changes in motility can affect absorption and lead to diarrhea. The reduction in motility promotes faster growth of bacteria, as the pathogen can invade the intestine and disrupt the immunity of the mucosal intestine, leading to the disruption of nutrient absorption.[14]

Based on the interpretation of stool analysis, bacterial infections were the most frequently identified etiology of diarrhea in our study. It contradicts other findings, which stated that viral infection was more likely to cause diarrhea in children.[15] However, our study did not perform any viral examination and stool culture.

Therefore, the presence of viral infection and the type of bacteria causing diarrhea could not be determined.

Diarrhea can cause maldigestion and malabsorption, which decreases nutrient absorption. The main types of maldigestion and malabsorption that frequently occurred in this study were fat malabsorption (20.8%), food maldigestion (18.1%), and carbohydrate maldigestion (12.6%). Despite the lack of information on the prevalence of food maldigestion, a study by Hendrawati et al. stated that the prevalence of fat malabsorption and carbohydrate maldigestion were 51% and 19%, respectively. These findings were higher compared to our study.[3] The lower prevalence in our study could be caused by the absence of data in some medical records. In addition, Hendrawati et al. found that the peak incidence of carbohydrate maldigestion occurred at the age of 12-59 months.[3] Carbohydrate is a component of diet with the highest percentage of consumption in children at this particular age (12-59 months old). Furthermore, diarrhea caused by Enterotoxigenic E.coli (ETEC) was found to occur more frequently in children aged 12-59 months old. Diarrhea caused by ETEC is classified as secretory diarrhea, in which the increase in intestinal motility and decrease in transit time were observed. This will cause rapid contact between digestive enzymes and carbohydrates, leading to inadequate digestion of carbohydrates, which results in the occurrence of carbohydrate maldigestion.[16]

Conclusion

Diarrhea in children mainly occurs before two years old, particularly in boys than girls. Watery diarrhea was the most frequent type of diarrhea, and bacterial was found to be the primary etiology.

Conflict of Interest

None declared.

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References

1. Juffrie M, Soenarto, Sri SY, Oswari H, Arief S, Rosalina I. Buku ajar gastroenterologi-hepatologi. Jakarta: Badan Penerbit IDAI; 2012.
2. Badan Penelitian dan Pengembangan Kesehatan. Riset kesehatan dasar Jakarta [Internet]. 2013 [cited 2022 August 6]. Available from: www.litbang.depkes.go.id.
3. Hendrawati LD, Firmansyah A, Darwis D. Macronutrient malabsorption in acute diarrhea: Prevalence and affecting factors. Paediatr Indones. 2005;45(5):207-10.
4. Marzuki N, Akib A, Boediman I. Cow's milk allergy in patients with diarrhea. Paediatr Indones. 2016;44(6):239-42.
5. Mundt LA, Shanahan K. Graff's textbook of urinalysis and body fluids. 2nd Edition. Philadelphia: Lippincott Williams & Wilkins; 2011.
6. Davidson AGF, Mullinger M. Reducing substances in neonatal stools detected by clinitest. Pediatrics. 1970;46(4):632-5.
7. Joneja JV. Lactose intolerance. Dealing with food allergies in babies and children. Boulder, Colorado: Bull Publishing Company; 2007.
8. Yusuf S. Profil diare di ruang rawat inap anak. Sari Pediatri. 2016;13(4):265-70.
9. Palupi A, Hadi H, Soenarto SS. Status gizi dan hubungannya dengan kejadian diare pada anak diare akut di ruang rawat inap RSUP Dr. Sardjito Yogyakarta. Jurnal Gizi Klinik Indonesia. 2009;6(1):1-7.
10. John S, Nuru P. Admission patterns and outcomes of paediatric patients admitted at the diarrhea unit of Muhimbili National Hospital (MNH). Dar Es Salaam Medical Students' Journal. 2008;15(1):9-12.
11. Savola KL, Baron EJ, Tompkins LS, Passaro DJ. Fecal leukocyte stain has diagnostic value for outpatients but not inpatients. J Clin Microbiol. 2001;39(1):266-9.
12. Manalip D, Warouw SM, Manoppo JIC. Hubungan antara patogen usus dengan kadar laktoferin tinja pada anak dengan diare akut. Sari Pediatri. 2016;17(2):124-8.
13. Khan AI, Huq S, Malek MA, Hossain MI, Talukder KA, Faruque A, et al. Analysis of fecal leukocytes and erythrocytes in Shigella infections in urban Bangladesh. Southeast Asian J Trop Med Public Health. 2006;37(4):747.
14. Subagyo B, NB S. Diare akut. Buku ajar gastroenterologi-hepatologi. 1st Edition. Jakarta: Badan Penerbit IDAI. 2010.
15. Widowati T, Mulyani NS, Nirwati H, Soenarto Y. Diare Rotavirus pada anak usia balita. Sari Pediatri. 2016;13(5):340-5.
16. Bouchier IAD. Gastroenterology: Clinical science and practice: Saunders; 1993.

APGHN Archives of Pediatric Gastroenterology, Hepatology, and Nutrition

Case Report

Hypergastrinemia in Children : A Case Report

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Abstract:
Gastrin is an important hormone in the gastrointestinal system that promotes gastric acid secretion. Gastrin hormone is produced by the G-cells in the antrum of the stomach. Besides stimulating gastric acid secretion, gastrin also induces the proliferation of the gut epithelial cells, tissue remodelling, and angiogenesis. Gastrin levels higher than 100-150 pg/ml are known as hypergastrinemia. Hypergastrinemia may cause the hypersecretion of stomach acid, which, if not treated properly, may leads to refractory peptic ulcer, severe gastroesophageal reflux disease (GERD), diarrhea, or death due to complications of refractory peptic ulcer. This case presented a 12 years old boy with a chief complaint of severe epigastric pain in the past month, accompanied by nausea, especially during supine position. The patient had a previous history of esophagitis. He showed no significant changes upon empirical PPI treatment. However, slight improvements were observed after the administration of Helicobacter pylori treatment. The gastrin level in this patient was 198 pg/mL. Upon discharge, the patient was still given PPI treatment. During the follow-up visitation, patient complaints had improved significantly, and the patient was planned to undergo routine evaluations of gastrin.

Keywords: hypergastinemia, children, stomach acid

Introduction

Gastrin is an essential hormone in the gastrointestinal system, particularly in promoting gastric acid secretion. The hormone is produced by G-cells located in the gastric antrum. The presence of gastrin helps stimulate the secretion of gastric acid, induce the proliferation of the epithelial cells, as well as promote tissue remodelling and angiogenesis. Hypergastrinemia is a condition in which the level of gastrin exceeds 100-150 pg/ml.[1] Gastrin functioned to stimulate pepsin and parietal cells, increases the blood flow in the gastric mucosa, and exerts trophic effects on gastric, duodenum, and colon mucosa.[1,2]

Gastrin is initially synthesized as pro-gastrin or pro-hormone, which binds to other gastrin molecules in varying lengths. The hormone is then secreted to the vascular system with different affinity toward the gastrin receptors. There are two types of gastrin receptors, Cholecystokinin-A (CCK A) and Cholecystokinin-B (CCK B).

Circulating gastrin will activate CCK B on the parietal cells, leading to gastric acid secretion. Gastrin is produced as a response to food. Protein and amino acids were one of the major stimulators of gastrin secretion.[1] Hypergastrinemia is frequently found in several conditions, such as Zollinger-Ellison syndrome, Helicobacter pylori (H. pylori) infection, or the use of proton pump inhibitor (PPI).[3] This study depicted the management of pediatric hypergastrinemia with atypical manifestation.

Case Report

A twelve-year-old boy came with a chief complaint of severe epigastric pain for the past month, accompanied by nausea, particularly when lying down. The patient had previous history of esophagitis and appendicitis. During the endoscopy examination, the mucosa in the proximal and middle part of esophagus was within normal limits; however, the distal part of esophageal mucosa was severely hyperemic, with the mucosal break in 70% of the circumference, partially confluence between the folds. One inflamed polyp was also found during the endoscopy. Furthermore, the gastric mucosa was severely hyperemic, especially in the cardia, fundus, corpus, and pylorus. Erosion was found in the corpus and fundus part of the gaster. The pyloric gap was found, while bile reflux was not found. The mucosa of duodenal bulb and descending part of duodenal were mildly hyperemic. Patients were then given PPI, prokinetic therapy, rebamipide, and sucralfate.

However, upon the follow-up examination, the patient still complained of severe epigastric pain with no significant improvement. The results of both the abdominal CT-scan using contrast and abdominal ultrasound were within normal limits, including the pancreas. Meanwhile, the H. pylori examination through biopsy displayed negative result. Patient did not undergo urea-breath test examination due to financial limitations. Despite being given the maximum treatment according to the one-month test results, the patient still exhibited no improvement. Thus, after careful consideration, the patient was given H. pylori treatment. The treatment includes a combination of PPI, clarithromycin, and amoxicillin.

Significant improvement was seen after the initiation of therapy. Gastrin hormone examination was conducted to rule out the possibility of Zollinger-Ellison syndrome. The result showed a high level of gastrin (198 pg/ml; normal value : < 65 pg/mL). As patient responded to the H. pylori treatment, the treatment was continued until completion, along with the PPI treatment. After six weeks of PPI treatment, patient symptoms improved significantly, and on the eighth week, all complaints were completely resolved.

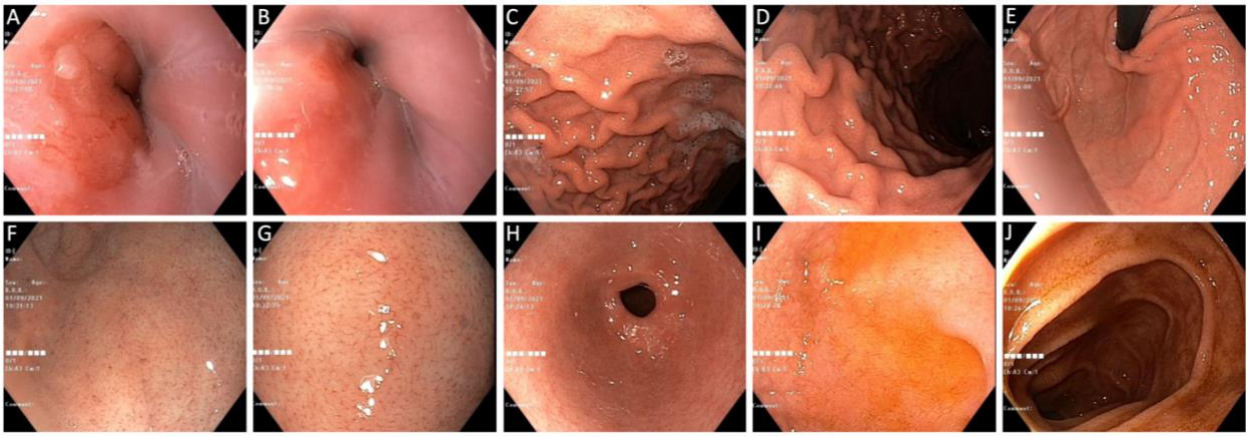

Figure 1. Endoscopic result. (a) and (b) showed severe hyperemia in distal esophageal mucosa with mucosal break and partial confluence between folds; (c) and (d) showed severe hyperemia and erosion in the corpus; (e) showed severe hyperemia and erosion in cardia and fundus; (f) and (g) showed severe hyperemia in antral; (h) showed severe hyperemia in pylorus; (i) and (j) showed mild hyperemia in duodenal bulb and descending part of duodenal.

Discussion

Hypergastrinemia was defined as serum gastrin level higher than 100-150 pg/mL.[1] The elevation of gastrin may occur in two conditions: during the decrease of gastric acid level (appropriate hypergastrinemia) and in the normal or high level of gastric acid (inappropriate hypergastrinemia). The increase of gastrin due to the low number of gastric acids was typically considered a normal body response in restoring the amount of gastric acid. Two of the most frequent causes of this situation include H. pylori infection and prolonged use of PPI or histamine H2 blocker. Meanwhile, the rise of gastrin despite the normal or high level of gastric acid is most likely pathological. The conditions that might cause hypergastrinemia despite the normal level of gastric acid are anatomical disturbances such as tumors, particularly Zollinger Ellison Syndrome (ZES).[1,2,4]

ZES is a neuroendocrine tumor that secretes gastrin and causes symptoms such as diarrhea and peptic ulcer.[4] The syndrome is rarely found in pediatric patients, accounting for only 1% of all ZES cases.[5] The tumor is frequently located in the duodenum or pancreas and causes ectopic secretion of gastrin. The diagnosis criteria for ZES are increased gastrin level > 10 times the normal value (> 65 pg/ml) or, in the other literature, increased level of gastrin > 1000 pg/mL.[6,7] Meanwhile, the radiological examination was considered less reliable in the case of ZES, as more than 60% of small tumors in the duodenum were not detected.[4] Based on previous studies, CT-scan and MRI could only detect tumors bigger than 2-3 cm.[6,8] In patients with ZES, the prescription of PPI was seen to be beneficial in controlling acid secretion

and improving the symptoms experienced by the patient.[4] In our case, the gastrin level of the patient was increased; however, it did not exceed > 10 times the normal value. Furthermore, despite the low diagnostic ability, the radiology examination results were within normal limits. This result decreased the possibility of ZES and eliminated other anatomical disturbances that might cause hypergastrinemia. Patient also did not exhibit any improvement after the administration of PPI during the follow-up examination. Based on these findings, we concluded that the diagnosis of ZES could be ruled out.

H. pylori infection disturbs the antral part of the somatostatin cells and causes the decreased production of somatostatin, an essential hormone inhibiting antral G cell secretion. This leads to the reduction of gastric acid secretion, which resulting in hypergastrinemia. In general, H. pylori infection only induces a subtle increase in gastrin level; however, the moderate elevation is deemed essential in causing the increase of gastric acidity and, ultimately, the risk of duodenal ulcer.[3] Furthermore, severe colonization of the pathogen in the gastric corpus may cause atrophic gastritis, which may further induce hypergastrinemia as it disrupts the function of somatostatin in inhibiting gastrin secretion.[1,7,9] Upon the initiation of H. pylori treatment, the hypergastrinemia typically resolved.[9]

In our case, the gastrin level in our patient was only moderately increased, and the number did not exceed more than ten times the normal value. Furthermore, upon treatment initiation for H. pylori, the patient showed clinical improvements. However, the H. pylori examination demonstrated a negative result. Interestingly, the positive result of H. pylori from biopsy examination were rarely observed in Indonesian children. The low accuracy of biopsy for H. pylori infection in Indonesian children could be caused by several factors. Study had shown that despite its high specificity, biopsy demonstrated varied number of sensitivity (85-95%).[10] Furthermore, the accuracy of biopsy is affected by several factors such as prior use of PPI, H2 antagonist, or antibiotic, gastritis, low number of pathogens, and poor specimen handle.[10] Based on a study by Shirin et al., the negative test might be induced by using PPI prior to the H. pylori examination, which might cause the misinterpretation as the PPI interferes with the pathogens' viability, morphology, and ability to produce urease.[11] Thus, the diagnosis of H. pylori was considered in this patient, and the initiation of treatment should be justified, especially in patients who exhibit no improvement with prior treatments.

The use of PPI was also one of the most frequently identified causes of hypergastrinemia. PPI inhibits gastric acid secretion, which subsequently induces the rise of serum gastrin level as the body tries to restore the amount of gastric acid. The increased gastrin level typically occurred only in the first four months after using PPI

and was constant in the following period. PPI was seen to only induce a moderate increase of gastrin level, at around 200-400 pg/mL. The gastrin level was commonly returned to normal after 5-7 days of PPI discontinuation.[1] Interestingly, studies have shown that the use of PPI may obscure not only hypergastrinemia due to H. pylori but also hypergastrinemia that ZES causes as it decreases the level of gastrin, leading to the misdiagnosis.[4] The patient in our case was known to consume PPI during the course of treatment. However, the knowledge of prior usage of PPI before the chief complaint was unknown. According to Ito et al., to confirm the etiology of hypergastrinemia, the administration of PPI must be discontinued first to prevent misdiagnosis.[4] Hence, upon managing other hypergastrinemia cases, we recommended terminating any PPI treatment with extensive observations of patient symptoms and manifestation prior to re-evaluating the gastrin level to reduce the risk of misdiagnosis.

The patient in our case, exhibited symptoms improvement after the initiation of H. pylori treatment along with the administration of PPI. A follow-up study by Sokic-Milutinovic et al. has demonstrated that the plasma gastrin level will declined to its normal level within six months in patients with successful eradication of H. pylori.[12] Furthermore, re-evaluating the gastrin level post-PPI discontinuation may be useful for our patient to further confirm the elimination of diagnosis related to PPI and inappropriate hypergastrinemia.[1,4] In addition, hypergastrinemia has been frequently associated with the occurrence of malignancy, particularly carcinoids.[1] Chronic hypergastrinemia has been associated with carcinogenesis and was seen to induce the proliferation of several types of cells, especially the gastric Enterochromaffin-like (ECL) cell.[1,9] Although the incidence was rare, the occurrence of carcinoid due to hypergastrinemia has been reported by several studies.[13-16] Fortunately, all of the reported cases were primarily among adult patients. Despite the lack of information on the occurrence of carcinoid in pediatric hypergastrinemia, the evidence of the increased risk of malignancy in patients with hypergastrinemia should be of concern. Thus, further evaluation of gastrin hormone was recommended in our case to confirm the diagnosis, monitor the therapy's effect, and further evaluate the level of gastrin hormone post-therapy.

Conclusion

Hypergastrinemia is a condition that may happen due to appropriate hypergastrinemia, often found in PPI or H2 Blocker therapy and H. pylori infection, or inappropriate hypergastrinemia, such as in ZES. Based on the examinations, we concluded that the patient did not suffer from ZES or any significant anatomical disturbances in the stomach. However, the evaluation of gastrin hormone level is still needed to confirm the diagnosis, therapy evaluation, and assessment for the risk of complications.

Conflict of Interest

None declared.

References

1. Dacha S, Razvi M, Massaad J, Cai Q, Wehbi M. Hypergastrinemia. Gastroenterol Rep (Oxf). 2015;3(3):201-8.
2. Metz DC, Cadiot G, Poitras P, Ito T, Jensen RT. Diagnosis of Zollinger-Ellison syndrome in the era of PPIs, faulty gastrin assays, sensitive imaging and limited access to acid secretory testing. Int J Endocr Oncol. 2017;4(4):167-85.
3. Rehfeld JF. Gastrin and the Moderate Hypergastrinemias. Int J Mol Sci. 2021;22(13).
4. Ito T, Cadiot G, Jensen RT. Diagnosis of Zollinger-Ellison syndrome: increasingly difficult. World J Gastroenterol. 2012;18(39):5495-503.
5. Massaro SA, Emre SH. Metastatic gastrinoma in a pediatric patient with Zollinger-Ellison syndrome. J Pediatr Hematol Oncol. 2014;36(1):e13-5.
6. Epelboym I, Mazeh H. Zollinger-Ellison syndrome: classical considerations and current controversies. Oncologist. 2014;19(1):44-50.
7. Phan J, Benhammou JN, Pisegna JR. Gastric Hypersecretory States: Investigation and Management. Curr Treat Options Gastroenterol. 2015;13(4):386-97.
8. Norton JA, Fraker DL, Alexander HR, Gibril F, Liewehr DJ, Venzon DJ, et al. Surgery increases survival in patients with gastrinoma. Ann Surg. 2006;244(3):410-9.
9. Burkitt MD, Varro A, Pritchard DM. Importance of gastrin in the pathogenesis and treatment of gastric tumors. World J Gastroenterol. 2009;15(1):1-16.
10. Wang YK, Kuo FC, Liu CJ, Wu MC, Shih HY, Wang SS, et al. Diagnosis of Helicobacter pylori infection: Current options and developments. World J Gastroenterol. 2015;21(40):11221-35.
11. Shirin D, Matalon S, Avidan B, Broide E, Shirin H. Real-world Helicobacter pylori diagnosis in patients referred for esophagoduodenoscopy: The gap between guidelines and clinical practice. United European Gastroenterol J. 2016;4(6):762-9.
12. Sokic-Milutinovic A, Todorovic V, Milosavljevic T, Micev M, Drndarevic N, Mitrovic O. Gastrin and antral G cells in course of Helicobacter pylori eradication: six months follow up study. World J Gastroenterol. 2005;11(27):4140-7.
13. Attila T, Santharam R, Blom D, Komorowski R, Koch TR. Multifocal gastric carcinoid tumor in a patient with pernicious anemia receiving lansoprazole. Dig Dis Sci. 2005;50(3):509-13.
14. Furumoto K, Kojima H, Okuno M, Fuji H, Mizuno R, Mori T, et al. Gastric carcinoid with hypergastrinemia: report of three cases. Case Rep Med. 2010;2010.
15. Jianu CS, Fossmark R, Viset T, Qvigstad G, Sordal O, Marvik R, et al. Gastric carcinoids after long-term use of a proton pump inhibitor. Aliment Pharmacol Ther. 2012;36(7):644-9.
16. Nandy N, Hanson JA, Strickland RG, McCarthy DM. Solitary Gastric Carcinoid Tumor Associated with Long-Term Use of Omeprazole: A Case Report and Review of the Literature. Dig Dis Sci. 2016;61(3):708-12.

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Case Report

Intussusception in Five Months Old Infant, A Rare Cause Colocolica without Pathologic Lead Point: A Case Report

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Abstract:
Intussusception is a common cause in gastrointestinal obstruction and one of condition in which early treatment is critical. Given the risk of acute bowel ischemia, intussusception represents an abdominal emergency in the pediatric population. The symptoms are generally related to intestinal obstruction, as intussusception accounts for up to 50% of pediatric small bowel obstructions in some series. Colocolica intussusception is an uncommon type of intussusception in children that is usually associated with a pathological lead point. This report depicts a five-months-old female baby with a chief complaint of bloody stool 7 hours before admission, accompanied with non-bilious vomit. Patient exhibited the classic triad of intussusception and upon the radiologic examination, a colocolica was noted. Patient then underwent urgent exploratory laparotomy, and the colocolica was reduced through manual reduction (milking technique).

Keywords: infant, colocolica, intussusception

Introduction

Intussusception is one of the major causes of pediatric gastrointestinal obstruction and acute abdominal pain. Global incident rates of intussusception were estimated at around 15 to 34 cases per 100000 children.[1] Approximately 50% of cases were reported in infants, with peak incidences ranging from 4 to 9 months. Furthermore, the cases were twice as prevalent in males.[1,2]

Intussusception is developed due to bowel invagination into the adjacent segment, and was reported to affect small bowel in half of the pediatric cases.[3] In most cases, the etiology was idiopathic. However, about 10% of cases were presented with predisposing condition such as congenital abnormalities, infection, vascular

malformation, neoplasm, bleeding disorder, and associated systemic diseases.[4] These factors are thought to be a key pathological lead point resulting in bowel movement interference that leads to invagination.[5] In intussusception, the invaginate segment is known as intussusceptum. Meanwhile, the recipient segment is termed as intussuscipient.[5]

The intestinal junctions between the movable and fixed retroperitoneal parts are primarily susceptible to intussusception.[5] Accordingly, about 95% of intussusception cases were ileocolic, in which distal ileum invaginates into the colon.[6] However, colon to colon invagination called colicolic intussusception may occur in sporadic cases.[6] Previous report has documented a rare case of colocolic intussusception and intestinal malrotation with the presence of pathological lead point in a seven-year-old child.[7] In contrast, intussusception in infants without pathological lead point was rarely reported in literature. Hence, through this report, we aimed to elaborate the clinical presentation of idiopathic colocolic intussusception and management in infants.

Case

A five-month-old female baby came to the emergency department with a chief complaint of bloody stool 7 hours before admission, accompanied by non-bilious vomit. The patient exhibited the same complaints one month ago; however, the symptoms resolved spontaneously. The patient had history of switching formula milk at two months old and one week ago. The patient parents also reported two previous episodes of active bloody stool with no history of fever, vomit, dyspnea, or seizure. Any underlying disease was not present. The patient was born full term through section caesarian due to cephalopelvic disproportion with a birth weight of 3400 gr.

On examination, the patient was lethargic, pale, and irritable. The vital signs showed blood pressure of 80/50 mmHg, heart rate of 135 times/min, respiratory rate of 30 times/min, and body temperature of 37,5°C. The nutritional status was within normal limits, with body weight and length of 6,6 kgs and 65 cm, respectively. The abdomen was distended without abnormal bowel sound. A sausage-shaped mass was found during palpation at the right hypochondrium, and unoccupied spaces in the right iliac fossa were noted. Moreover, a bloody jelly stool was found during the rectal examination. The laboratory result was within normal limits. Abdominal ultrasonography (**Figure 1**) revealed suggestive intussusception in the left region (colocolic).

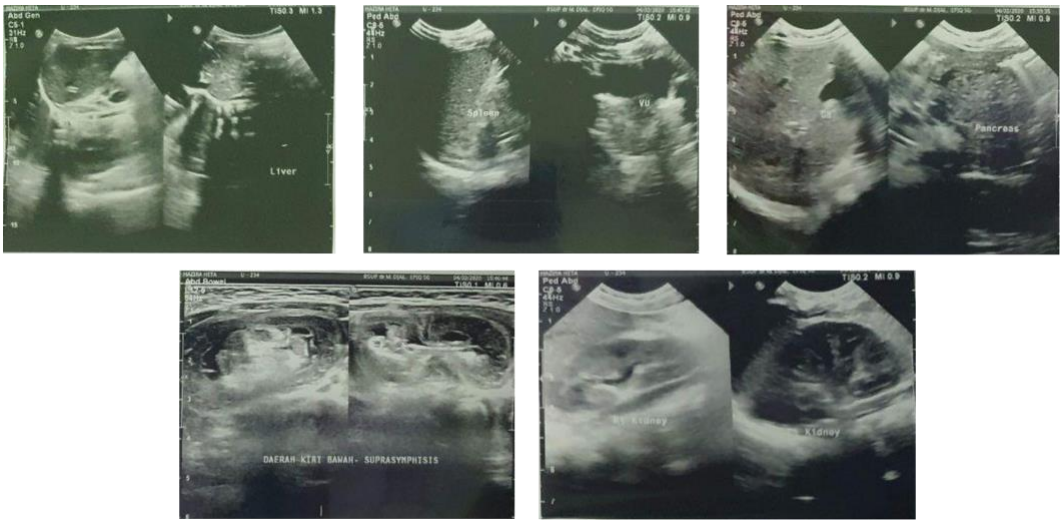
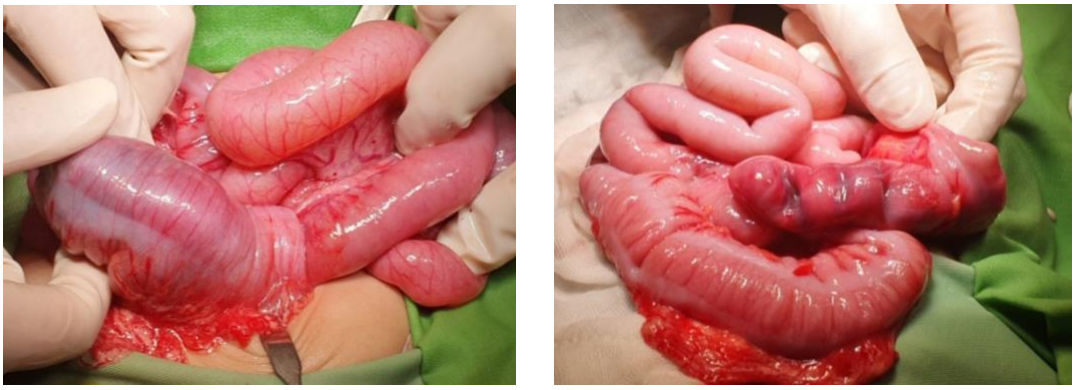


Figure 1. Abdominal ultrasonography results

Urgent exploratory laparotomy was performed, and the colocolic intussusception in the colon was recorded (**Figure 2**). The bowel was manually reduced by milking technique. Venous congestion was discovered; however, it spontaneously resolved after a short period of observation.



(a) (b)

Figure 2. (a) Intraoperative intussusception. (b) Intestinal reduction through milking technique

After the procedure, the patient was transferred to the intensive care and was given total parenteral nutrition for the next two days. The patient was discharged on the seventh-day post-operation after exhibiting good tolerance to the breast milk diet. During the follow-up visit two weeks post-discharge, the patient continued to tolerate the regular diet and exhibited normal bowel movements with no evidence of recurrent obstruction.

Discussion

Our case presented colocolica intussusception occurring in a five-month-old female baby. Literature from Hasan Sadikin Hospital showed that intussusception incidence peaked before the first year of live, specifically at eight months old.[8] Similarly, several studies stated that intussusceptions cases occurred most commonly in children under one year old. The prevalence of intussusception in children under one year old were expected around 60%, while 80% of the cases occurred before the age of 24 months old. [9] This indicates that our patient was within the age range with a higher risk of intussusception.

The typical presentation of intussusception, known as the classic triad, consists of abdominal pain, red currant jelly stool, and the presence of palpable abdominal mass with history of viral prodrome; however, not all infants exhibit these manifestations. A study by Bruce et al. demonstrated that the presence of all triad symptoms, including crampy abdominal pain, vomiting, and bloody stool, were only observed in 21% of patients, while the presence of two out of three manifestations was seen in 70% of cases.[4] Furthermore, Schollin et al. showed that this classical manifestation only present in less than 25% of cases in children under three.[10] Pain and vomiting may appear in almost 80% of cases and around 65% of cases experienced palpable abdominal mass.[11] In our case, the patient exhibit all of the classic triad manifestations, which highly indicating of intussusception.

Children, particularly infants, were typically healthy prior to the initial symptom, although some of the patient experienced history of antecedent gastrointestinal infection. Patients commonly experienced sudden onset of abdominal pain, presented as crying, and as the intussusception progressed, the obstruction prolonged and vomiting became prominent to reduce pressure and pain.[4,12] Majority of the cases (90%) was idiopathic with no apparent trigger. However, a variety of pathological conditions associated with intussusception had been observed in neonates or older children, such as small bowel lymphoma, Meckel diverticulum, duplication cysts, polyps, vascular malformations, inverted appendiceal stumps, parasites (e.g., Ascaris lumbricoides), Henoch-Schönlein purpura, and cystic fibrosis.[4] Most cases of intussusception were ileocolic (95%); however, ileocolocolic intussusception in infant without a pathological lead point is very rare. Furthermore, the occurrence of colocolic intussusception in children was also uncommon.[6]

Radiologic imaging was thought to be beneficial in establishing the diagnosis. Plain abdominal X-rays demonstrated relatively low sensitivity (29-50%) towards intussusception; thus, this modality was not the primary option in such perforation cases.[13] In contrast, abdominal ultrasonography exhibited better sensitivity (98-100%) and specificity (88-100%), allowing it to be the main modality in diagnosing

intussusception.[13] Ultrasound is not only subtle and specific in diagnostic; the non-ionizing radiation properties may benefit pediatric patients.[12] Furthermore, pathological lead foci can be identified using ultrasound. The intussusceptum and intussuscipient have different intestinal characteristics with distinct mucosal and serosal layer interfaces in ultrasound.[14] Longitudinal view of the affected bowel segment may demonstrate a crescent-like-shaped hyperechoic rim resembling a kidney, known as pseudokidney.[13] Additionally, color doppler could be performed to identify bowel ischemia and bowel necrosis.[15] This modality may detect the alteration of blood flow, which is essential in considering the appropriate management.[15] Despite the excellent resolution of CT scan in diagnosing intussusceptions, it is hardly utilized due to higher radiation dosage and anesthesia requirements.[15]

Some invagination cases were spontaneously self-resolved. For uncomplicated cases, hydrostatic or pneumatic enema reduction could be the treatment of choice.[15] However, the surgical approach is preferable in patients with certain conditions, such as unstable patients with evidence of peritonitis or perforation, healthcare centers with inadequate radiologic modality, and most commonly, unsuccessful douche reduction.[15] Untreatable intussusception will lead to complications such as intestinal bleeding, necrotic, perforation with peritonitis, shock, sepsis, repetitive invagination, and death.[16] In our case, the pathological lead point was not found during laparotomy, and no bowel resection was done. Prophylaxis antimicrobial treatment was given to anticipate septicemia. The patient was discharged after seven days of hospitalization in stable condition. Any gastrointestinal complaints during the follow-up visit were not reported.

Conclusion

Intussusception is one of the most common emergencies in pediatric patients. A complete investigation of the clinical history, physical examination, laboratory analysis, and abdominal ultrasonography is essential in diagnosing intussusception. Abdominal ultrasonography, in particular, is a useful modality because of its sensitivity and specificity. Explorative laparotomy followed by milking and manual reduction can be chosen as a treatment option in infants with colocolica intussusception without a pathological lead point. Early determination and intervention are exceedingly important to attain better results and prevent death.

Abbreviation

PICU : Pediatric Intensive Care Unit

References

1. Jiang J, Jiang B, Parashar U, Nguyen T, Bines J, Patel MM. Childhood intussusception: a literature review. PLoS One. 2013;8(7):e68482.
2. Edwards EA, Pigg N, Courtier J, Zapala MA, MacKenzie JD, Phelps AS. Intussusception: past, present and future. Pediatr Radiol. 2017;47(9):1101-8.
3. Fialkowski EW, BW. Intestinal Obstructions. Walker's pediatric gastrointestinal disease: physiology, diagnosis, management. 6th Edition. North Carolina: PMPH USA, Ltd; 2018. p. 1424–30.
4. Bruce J, Huh YS, Cooney DR, Karp MP, Allen JE, Jewett Jr TC. Intussusception: evolution of current management. Journal of pediatric gastroenterology and nutrition. 1987;6(5):663-74.
5. Marsicovetere P, Ivatury SJ, White B, Holubar SD. Intestinal intussusception: etiology, diagnosis, and treatment. Clinics in colon and rectal surgery. 2017;30(01):030-9.
6. Kennedy M, Liacouras C. Ileus, Adhesions, Intussusception, and Closed-Loop Obstructions. Nelson Textbook of Pediatrics. 20th Edition. Philadelphia: Elsevier; 2018. p. 1287–9.
7. Tripathy PK, Jena PK. Colocolic intussusception in a child with pathologic lead point along with intestinal malrotation-a rare case report and brief review. J Clin Diagnostic Res. 2016;10(12):PD09.
8. Kusmaheidi S, Diposarosa R, Nugraha HG. Pattern of Intussusception on Infants and Children in Dr. Hasan Sadikin Hospital Bandung. Althea Medical Journal. 2015;2(3):458-62.
9. Clark AD, Hasso-Agopsowicz M, Kraus MW, Stockdale LK, Sanderson CF, Parashar UD, et al. Update on the global epidemiology of intussusception: a systematic review of incidence rates, age distributions and case-fatality ratios among children aged< 5 years, before the introduction of rotavirus vaccination. Int J Epidemiol. 2019;48(4):1316-26.
10. Schollin Ask L, Svensson JF, Olén O, Örtqvist Å. Clinical presentation of intussusception in Swedish children under 3 years of age and the validity of diagnostic coding. Pediatr Surg Int. 2019;35(3):373-81.
11. Manning A, Little D. Intussusception in Infants and Children. Pediatric Gastrointestinal and Liver Disease. 5th ed. Philadelphia: Elsevier; 2015. p. 607–13.
12. Zhang M, Zhou X, Hu Q, Jin L. Accurately distinguishing pediatric ileocolic intussusception from small-bowel intussusception using ultrasonography. J Pediatr Surg. 2021;56(4):721-6.
13. Charles T, Penninga L, Reurings J, Berry M. Intussusception in children: a clinical review. Acta Chir Belg. 2015;115(5):327-33.
14. Caruso AM, Pane A, Scanu A, Muscas A, Garau R, Caddeo F, et al. Intussusception in children: not only surgical treatment. J Pediatric Neonatal Individ Med. 2017;6(1):e060135-e.
15. Ito Y, Kusakawa I, Murata Y, Ukiyama E, Kawase H, Kamagata S, et al. Japanese guidelines for the management of intussusception in children, 2011. Pediatr Int. 2012;54(6):948-58.
16. Smith CA, Maloney E. Diagnosis and Management of Pediatric Patients with Intussusception. Digestive Disease Interventions. 2019;3(04):326-32.

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Literature Review

Gastroinstestinal Bleeding in Pediatrics

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Abstract:
Gastrointestinal bleeding (GI) may occurs in infants and children. Most etiologies of GI bleeding are mild and self-limited, but may advance into life-threatening condition if not treated properly. Upper GI bleeding and lower GI bleeding can be classified based on bleeding sites that is above or below Treitz ligament. Causes of GI bleeding in infants and children varies according to their age and bleeding sites. Some conditions may be misunderstood as GI bleed such as consumption of certain red coloured food. Diagnosis of gastrointestinal bleeding in children includes complete history taking, thorough physical examination, laboratory examination, radiological examination, and other supportive modality such as endoscopy. Early diagnosis and proper therapy can improve outcomes and prevent severe conditions.

Keywords: gastrointestinal bleeding, children, infant, diagnosis

Introduction

Gastrointestinal (GI) bleeding in infants and children is a condition that may trigger parental anxiety due to its alarming nature.[1] Most etiologies of GI bleeding are mild and self-limited.[2] However, in some cases, the symptoms may develop into life-threatening emergencies. Massive bleeding is the most lethal complications as it may cause severe shock and even death.[1,3] However, episodes of severe uncontrolled bleeding are quite rare and thus, some healthcare workers might be unfamiliar in dealing with this condition.[3]

GI bleeding can be undetected, ranging from occult bleeding detectable only through laboratory examinations to gross hematemesis, hematochezia, or melena.[4] The hospitalization rate due to upper GI bleeding were estimated at around 36 to 102 cases per 100,000 population per year. Meanwhile, lower GI bleeding occurred less frequently in about 20 per 100,000 patients of all ages.[5,6] Currently, there is still lack of documentation on the actual incidence of GI bleeding among pediatric population. However, the general number is estimated to be less than the adult population. Interestingly, the most frequent chief of complaint in pediatric patients who came to the emergency room were symptoms of lower GI bleeding. The mortality rate that was caused by GI bleeding is quite high, varying from 3.5 to 14%. Thus, the author would like to provide new insight on pediatric GI bleeding to increase the awareness on the topic.

Classifications of GI bleeding

Establishing the etiology through anamnesis and complete physical examination should only be conducted once the patient is stabilized. Distinguishing between local or systemic cause of hemorrhage should be the main concern during the investigation efforts.[1] Systemic causes are frequently associated with systemic disorder (such as coagulation disorder, hemophilia, Von Willebrand disease, etc) and/or bleeding from other organs in the body. On the other hand, local causes are bleeding which can be tracked from inside the GI system. Other methods of classification are through the anatomical location: upper or lower GI system, separated by the ligament of Treitz.[7] **Table 1** shows the clinical features could be used to differentiate the source of the bleeding.

Table 1. Clinical differences between upper and lower GI bleeding.

Source of Bleeding	General Manifestation
Upper GI Bleeding	• Hematemesis • Melena • Hematochezia (in profuse bleeding)
Small Intestine Bleeding	• Melena or hematochezia
Lower GI Bleeding	• Commonly hematochezia, except in slow motility

Diagnosis Approach

Figure 1 shows the steps to approach GI bleeding. The clinical approaches that should be conducted in children with GI bleeding include determination of the presence of hemodynamic emergencies, finding the source of bleeding, and composing differential diagnosis based on clinical symptoms and patient's age.[4]

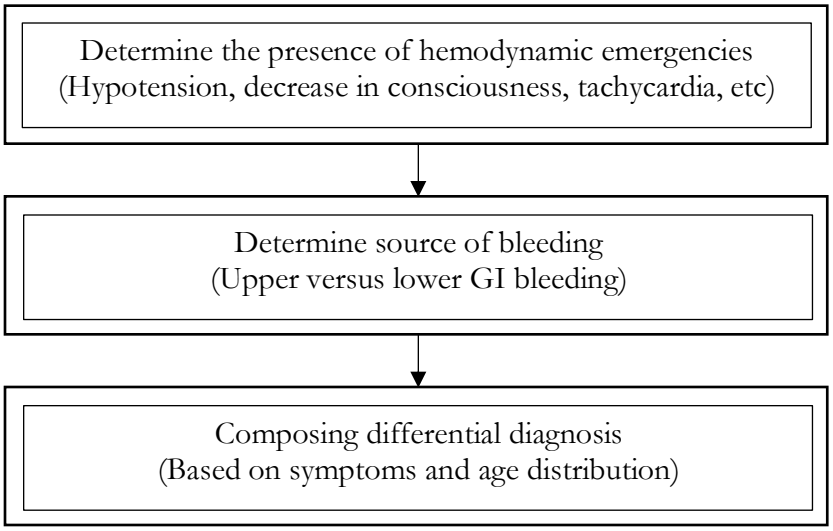

Figure 1. Clinical approach on GI bleeding in children

1. Anamnesis

The most common etiologies of GI bleeding may vary between age groups. In neonates, GI bleeding often occurs as a consequence of infective colitis. Meanwhile, in critically ill neonates, necrotizing enterocolitis or stress ulcers are the most possible suspects. In infants, GI bleeding is often caused by infectious colitis, cow's milk protein allergy, and intussusception. In children and adolescents, bleeding may occur due to gastritis or peptic ulcer, in addition to infective colitis. Other causes of GI bleeding are the rupture of esophageal or gaster varices and stress ulcers in severely ill child.[7] The details of the most commonly found diagnosis according to the age group and location of the GI bleeding are shown in **Table 2**.[7-10]

Table 2. Causes of GI bleeding based on the age group.

Age group	Site of Bleeding	Common	Rare
Infant	Upper GI tract	Esophagitis	Peptic Ulcer
	Lower GI tract	• Anal fissure • Cow milk protein allergy • Necrotizing enterocolitis	• Vascular lesion • Hirschsprung enterocolitis • Meckel diverticulum • Intestine duplication • Intussusception Infective enterocolitis
Children	Upper GI tract		
	Esophagus	• Esophagitis • Mallory-Weiss tear	• Esophagitis • Esophageal varices • Corpus alienum • Cyst duplication
	Gastric	• Gastritis: prolapse gastropathy; nonsteroidal anti-inflammatory drug (NSAID) overuse • Stress ulcer	• Gastritis • Peptic ulcer • Leiomyoma • Varices • Vascular malformation
	Duodenum	• Duodenitis • Crohn's disease	• Ulcer • Vascular malformation • Foreign object • Lymphoid hyperplasia • Varices • Cyst duplication
	Lower GI tract	• Anal fissure • Intussusception • Infective enterocolitis • Inflammatory bowel disease (> 4 years) • Meckel diverticulum • Perianal vasculitis due to streptococcus infection • Polyps	• Inflammatory bowel disease (< 4 years) • Vascular malformation • Intestine duplication • Henoch-Schonlein purpura (HSP) • Dysentery • Hemorrhoid • Rectal/colon varices • Ulcer • Nodular lymphoid hyperplasia Rectal trauma

Upon assessing pediatric patients with GI bleeding, these particular questions should be addressed quickly: (1) Is the patient really experiencing GI bleeding? (2) Is the volume of blood loss significant enough to cause hemodynamic problems? (3) Is there any active bleeding occurring at the moment? (4) What actions should be taken immediately? One of the approaches often overlooked during the approach of whether the patient really experiencing GI bleeding is the tracing the history of food or drug consumption is important to investigate the possibility of GI bleeding in children.[11-16] Conditions that are often mistaken as GI bleeding are listed in **Table 3**.[17]

Table 3. Conditions that were commonly misinterpreted as GI bleeding.

Hematemesis	• Swallowing mother's blood while lactation (if the cracked nipple is present), or during birth • Nasal or pharyngeal bleeding • Food coloring, beet
Melena	• Iron preparation • Nasal or pharyngeal bleeding • Red dragon fruits, blueberries, spinach, beet, bismuth, charcoal
Hematochezia	• Menstruation • Hematuria

2. Physical examination

Careful physical examination is also necessary to confirm the diagnosis and severity of GI bleeding. The laboratory and radiological examinations may take time to be completed. In this case, the common cause may be identified from physical examination. Again, the initial approach to GI bleeding in children is emphasized on the assessment of hemodynamic emergencies. Tachycardia is the most profound early sign of shock in children.[16] Other signs of hypovolemic state include fatigue, pallor, and hypotension.[16,18] Furthermore, postural hypotension with ≥ 10 mmHg decrease in blood pressure is likely to indicate at least 20% of blood loss. Prompt fluid therapy must be conducted in order to prevent morbidity and mortality.[16,19] Some of the common findings found among patients with GI bleeding are shown in **Table 4**.

Table 4. Signs and symptoms associated with GI bleeding.

Skin	Pallor, jaundice, ecchymosis, abnormal blood vessels, skin rash, skin turgor, hematoma, petechiae, purpura, warm/cold acral, spider angioma
Head, eye, ear, nose, and throat	Nasopharyngeal injection, oozing, enlarged tonsils, bleeding
Cardiovascular	Blood pressure Heart rate: examined in supine, sitting, and standing position Pulse rate: examined in supine, sitting, and standing position Gallop Capillary refill time
Abdomen	Mass, hepatomegaly, splenomegaly, tenderness, caput medusae
Perineum	Fissure, fistula, rash, induration, hemorrhoid, or vascular lesion
Rectum	Fresh blood, melena, tenderness

The following manifestations could serve as guidance in determining the severity of bleeding:[16,18,20]

1. The patient's general condition and hemodynamic status: pallor, restlessness, sweating, lethargy, abdominal pain, orthostatic changes of the pulse > 20 bpm, or ≥ 10 mmHg decrease in blood pressure when changing the position from supine to sitting; these conditions is related with the presence of profuse bleeding.
2. The volume of blood loss: the volume loss is proportionate with the increase is morbidity and mortality
3. Origin of the bleeding: bleeding from ruptured varicose veins or ulcer may cause serious blood loss

3. Laboratory Examination

Below are some of laboratory test that could help to identify the cause and severity of GI bleeding:[18,21]

1. Hemoglobin or hematocrit examination to determine the amount of blood loss.
2. Platelet count and function as well as the partial thromboplastin time (APTT) and prothrombin time (PT) to rule out systemic disorders. Thrombocytopenia is often associated with sepsis, certain viral infections,

idiopathic thrombocytopenic purpura (ITP), hypersplenism, necrotizing enterocolitis, and others.

3. Crossmatch tests if transfusion is most likely required for the patient.
4. Liver function test. Decreased albumin accompanied by impaired coagulation may indicate cirrhosis, which leads to portal hypertension and esophageal varices.
5. The increase in urea and creatinine levels indicates a possible decrease in renal function due to hypovolemic shock. Blood urea nitrogen (BUN) to creatinine ratio could be used to determine between upper or lower GI bleeding. Increased BUN refers to upper GI bleeding due to ingested blood. The elevation of BUN to creatinine ratio ≥ 30 indicates upper GI bleeding with 98% sensitivity and 69% specificity.
6. The Apt-Downey test may be performed to distinguish whether hematemesis in infants is caused by bleeding from their GI tract, ingestion of the maternal blood during birth, or suckling from cracked nipples. This test is based on the infants' blood containing >60% of fetal hemoglobin, which is alkaline resistant. Maternal blood contains mature hemoglobin, which would turn into yellow-brown hematin when mixed with alkali.

4. Radiological Examination

The role of radiological examination in diagnosing GI bleeding is now being replaced by endoscopy. However, not all health centers can perform endoscopy. Furthermore, the radiological examinations could help examine the areas that were not observable using endoscopy. The following are radiological examinations to identify GI bleeding:[22-25]

1. Plain abdominal x-ray may show the signs of necrotizing enterocolitis (NEC), such as bowel dilatation, bowel wall thickening, and pneumatosis intestinalis (air in the subserosa/submucosa).
2. Ultrasonography (USG) of the abdomen is indicated for patients with GI bleeding accompanied by hepatosplenomegaly. USG is also helpful in detecting portal hypertension and chronic liver disease.
3. Abdominal CT-scan and MRI are useful to determine intra-abdominal vasculature.
4. Meckel's scan could be performed to explore Meckel's diverticulum.
5. Angiography is indicated in active bleeding lesions or recurrent chronic bleeding that is not evident in the previous examination. Bleeding rate >0.5 mL/min is required to recognize the source of bleeding.

5. Endoscopy

Endoscopy is an excellent diagnostic tool for finding the etiology of GI bleeding. It provides a great visualization of GI mucosa and may help to identify the bleeding source. Some therapeutic measures such as polyp extractions may also be performed during endoscopic examination.[26,27]

Summary

Gastrointestinal bleeding may occur in infants and children, triggering parental anxiety. Classification can be made based on bleeding sites; that is upper and lower GI bleed that are separated by Treitz ligament. Some conditions may be misunderstood as GI bleeding. Causes of GI bleeding may vary between different age group in children. Most etiologies of GI bleeding are mild and self-limited. Diagnostic approaches in GI bleeding are based on history taking, physical examination, laboratory tests, radiological imaging as well as endoscopy.

Conflict of Interest

None declared.

References:

1. Ament ME. Diagnosis and management of upper gastrointestinal tract bleeding in the pediatric patient. Pediatr Rev. 1990;12(4):107-16.
2. Arvola T, Ruuska T, Keränen J, Hyöty H, Salminen S, Isolauri E. Rectal bleeding in infancy: clinical, allergological, and microbiological examination. Pediatrics. 2006;117(4):e760-e8.
3. Boyle JT. Gastrointestinal bleeding in infants and children. Pediatr Rev. 2008;29(2):39-52.
4. Elta GH, Takami M. Approach to the patient with gross gastrointestinal bleeding. Atlas of Gastroenterology. 2009:1-9.
5. Genuino LG VC, Sio-Aguilar JO. Self-instructional material gastrointestinal bleeding in children2009 [cited 2009 15th August]. Available from: http://d.scribd.com/docs/j5cjs2b436mtr5k3mj0.pdf.
6. Sackett D, Straus S, Scott Richardson W, Rosenberg W, Haynes R. Evidence-Based Medicine: How to Practice and Teach EBM, 2nd edn Edinburgh and London: Churchill Livingstone. 2000.
7. Lawrence WW, Wright JL. Causes of rectal bleeding in children. Pediatr Rev. 2001;22(11):394-5.
8. Wilcox CM, Alexander LN, Cotsonis GA, Clark WS. Nonsteroidal antiinflammatory drugs are associated with both upper and lower gastrointestinal bleeding. Dig Dis Sci. 1997;42(5):990-7.
9. Lazzaroni M, Petrillo M, Tornaghi R, Massironi E, Sainaghi M, Principi N, et al. Upper GI bleeding in healthy full-term infants: a case-control study. Am J Gastroenterol. 2002;97(1):89-94.
10. Silber G. Lower gastrointestinal bleeding. Pediatrics in Review. 1990;12(3):85-92.
11. Ghosh S. Watts D. Kinnear M. Management of gastrointestinal haemorrhage. Postgrad Med J. 2002;78(915):4-14.
12. Palmer K. Acute upper gastrointestinal haemorrhage. British Medical Bulletin. 2007;83(1):307-24.
13. Russell R. Non-steroidal anti-inflammatory drugs and gastrointestinal damage—problems and solutions. Postgraduate Medical Journal. 2001;77(904):82-8.
14. Hudson N, Hawkey CJ. Non-steroidal anti-inflammatory drug-associated upper gastrointestinal ulceration and complications. Eur J Gastroenterol Hepatol. 1993;5(6):412-9.
15. Gabriel SE, Jaakkimainen L, Bombardier C. Risk for serious gastrointestinal complications related to use of nonsteroidal anti-inflammatory drugs: a meta-analysis. Ann Intern Med. 1991;115(10):787-96.
16. Fennerty MB. Pathophysiology of the upper gastrointestinal tract in the critically ill patient: rationale for the therapeutic benefits of acid suppression. Crit Care Med. 2002;30(6):S351-S5.

17. RY H. Pediatrics, Gastointestinal bleeding: Differential diagnoses and workup 2018 [cited 2022 17th July]. Available from: http://emedicine.medscape.com/article/802064-diagnosis.
18. Wyllie R, Hyams JS, Kay M. Pediatric gastrointestinal and liver disease E-Book: Elsevier Health Sciences; 2020.
19. Squires Jr RH. Gastrointestinal bleeding. Pediatrics in Review. 1999;20(3):95-101.
20. Chaibou M, Tucci M, Dugas M-A, Farrell CA, Proulx F, Lacroix J. Clinically significant upper gastrointestinal bleeding acquired in a pediatric intensive care unit: A prospective study. Pediatrics. 1998;102(4):933-8.
21. Urashima M, Toyoda S, Nakano T, Matsuda S, Kobayashi N, Kitajima H, et al. BUN/Cr ratio as an index of gastrointestinal bleeding mass in children. J Pediatr Gastroenterol Nutr. 1992;15(1):89-92.
22. Tröger J, Seidensticker PR. Paediatric imaging manual: Springer Science & Business Media; 2008.
23. Padia SA, Bybel B, Newman JS. Radiologic diagnosis and management of acute lower gastrointestinal bleeding. Cleve clin J Med. 2007;74(6):417-20.
24. Racadio JM, Agha AK, Johnson ND, Warner BW, editors. Imaging and radiological interventional techniques for gastrointestinal bleeding in children. Seminars in pediatric surgery; 1999: Elsevier.
25. Howarth DM, editor The role of nuclear medicine in the detection of acute gastrointestinal bleeding. Seminars in nuclear medicine; 2006: Elsevier.
26. Zuccaro Jr G. Management of the adult patient with acute lower gastrointestinal bleeding. Am J Gastroenterol. 1998;93(8):1202-8.
27. Lee KK, Anderson MA, Baron TH, Banerjee S, Cash BD, Dominitz JA, et al. Modifications in endoscopic practice for pediatric patients. Gastrointest Endosc. 2008;67(1):1-9.

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