

Gastroduodenal Perforation and Ulcer Associated With Rotavirus and Norovirus Infections in Japanese Children: A Case Report and Comprehensive Literature Review

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Background. There is no literature review on gastroduodenal perforation or ulcer (GDPU) with rotavirus (RV) and norovirus (NoV) gastroenteritis.

Methods. Pediatric cases of GDPU or upper gastrointestinal bleeding with RV and NoV gastroenteritis were searched from September 1974 until October 2015 using PubMed, Google for English, other-language-publications, and Ichushi (<http://www.jamas.or.jp>) for Japanese-language publications. All reports confirming GDPU or upper gastrointestinal bleeding with RV and NoV gastroenteritis were eligible for inclusion in the study. In addition, clinical characteristics were reviewed.

Results. A boy with duodenal ulcer (DU) and NoV gastroenteritis was described. There were 32 GDPU cases (23 RVs and 9 NoVs cases), including our case; with the exception of 1 case, all were Japanese. Mean age, male/female ratio, and symptoms' duration before admission were 21.6 months, 2.2, and 4.0 days, respectively. Vomiting was the most common symptom, followed by diarrhea, lethargy, fever, abdominal distension, and convulsion. Dehydration, hematemesis, melena, drowsiness or unconsciousness, shock, metabolic acidosis, leukocytosis, anemia, positive C-reactive protein, high blood urea nitrogen, and hyponatremia commonly occurred. *Helicobacter pylori* was a minor cause of GDPU. Duodenal (DP) or gastric perforation (GP) developed in 14 cases (10 DP/RVs, 1 GP/RV, and 3 DP/NoVs). Duodenal ulcer or gastric ulcer (GU) developed in 18 cases (10 DU/RVs, 4 DU/NoVs, 1 GU/RV, 1 GU + DU/NoV, and 2 upper gastrointestinal bleeding/RVs). The predominant perforation or ulcer site was in the duodenum. With the exception of 2 deaths from DU, all cases recovered.

Conclusions. Race, young age, male, severe dehydration, metabolic acidosis, drowsiness and unconsciousness, and shock may be potential risk factors of GDPU associated with RV and NoV gastroenteritis. Limitation of this descriptive study warrants further investigations to determine the risk factors in these infections that could be associated with GDPU.

Keywords. gastroduodenal complications; noroviruses; perforation; rotaviruses; ulcer.

Rotaviruses (RVs) are the most common cause of epidemic gastroenteritis in children, and noroviruses (NoVs) are the second common infections [1, 2]. Rotaviruses cause 114 million diarrheal episodes per year, resulting in 24 million clinic visits, 2.4 million hospitalizations, and more than 500 000 deaths in children <5 years of age [1]. Noroviruses cause 64 000 hospitalization and 900 000 clinical visits of children in industrialized countries, and approximately 200 000 deaths of children <5 years of age in developing countries [ref in 2]. Rotaviruses, NoVs, and enteropathogenic *Escherichia coli* cause more than half of all diarrheal deaths in children <5 years of age worldwide.

RVs and NoVs do not usually induce serious gastrointestinal inflammation [1, 2]. However, gastroenteritis caused by these viruses is occasionally associated with severe gastroduodenal complications such as gastroduodenal perforation or ulcer (GDPU). We have previously reported 2 pediatric cases of duodenal perforation (DP) associated with RV and NoV gastroenteritis [3]. We have recently encountered a pediatric case of severe duodenal ulcer (DU) associated with NoV gastroenteritis. These observations suggest that the rate of GDPU associated with RV and NoV gastroenteritis may be underestimated. Although the clinical course of the majority of children with RV and NoV gastroenteritis is self-limited, the factors that could be associated with GDPU in patients infected with these common viruses that cause gastroenteritis need to be identified.

Although few pediatric case reports of GDPU associated with RV and NoV gastroenteritis have been documented in the literature, there is no comprehensive literature review of pediatric cases of GDPU associated with RV and NoV gastroenteritis. Currently, there is no clear evidence for an association of GDPU and RV and NoV gastroenteritis. If there is an association of GDPU with these viruses that cause gastroenteritis, then the risk factors of GDPU in these common viral infections

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should be determined. In the present study, our recent case of severe DU associated with NoV gastroenteritis was described, and a literature search of pediatric cases of GDPU associated with RV and NoV gastroenteritis was conducted to clarify their clinical features and outcome as well as potential risk factors of GDPU associated with these viruses' gastroenteritis.

METHODS

Literature Search

A literature search for pediatric cases of GDPU associated with RV and NoV gastroenteritis was conducted from September 1974 until October 2015 using the PubMed and Google Scholar database for Chinese-, Croatian-, Czech-, Danish-, English-, French-, German-, Hungarian-, Italian-, Korean-, Polish-, Portuguese-, Russian-, Spanish-, and Turkish-language publications as well as using Ichushi Web database (<http://www.jamas.or.jp>) for Japanese-language publications. The search was performed using the following full keywords: "duodenal perforation (DP)", "duodenal ulcer (DU)", "epidemic gastroenteritis", "gastric perforation (GP)", "gastric ulcer (GU)", "gastroduodenal perforation/ulcer (GDPU)", "gastrointestinal bleeding", "gastrointestinal complication", "noroviruses (NoVs)", "rotaviruses (RVs)", and "viral gastroenteritis". This study was approved by the ethical committee of our institution.

Selection Criteria for Case Reports

Case reports were eligible and included in the analysis when they met the following inclusion criteria: (1) the diagnosis of either RV or NoV infections was confirmed; (2) GDPU was confirmed by endoscopy or surgical procedure, or upper gastrointestinal bleeding was likely despite the site of bleeding lesion not being confirmed by these procedures; and (3) data for demographic and clinical characteristics were reported. Exclusion criteria included children whose stool specimens tested negative for RV or NoV antigens, or these tests were not performed and thus diagnosis of RV or NoV gastroenteritis was not confirmed.

Data Extraction

The following variables were extracted: patient characteristics (eg, age, sex); acute symptoms related to gastroenteritis; duration of symptoms before hospitalization; presence or absence of dehydration; consciousness; metabolic acidosis and shock; laboratory data, including white blood cell (WBC) count, hemoglobin (Hb), serum levels of C-reactive protein (CRP), blood urea nitrogen (BUN), and sodium; results of the test for *Helicobacter pylori* (HP); medical history of RV vaccination; site of GDPU; and histopathological findings, treatment, and outcome.

RESULTS

Case Description

A previously healthy 8-year-old boy with a 7-day history of vomiting and left upper quadrant abdominal pain presented to our hospital. The patient had mild fever, lethargy, and continuous

vomiting. He did not previously receive any medications such as nonsteroidal anti-inflammatory drugs (NSAIDs). Neither diarrhea nor hematemesis was noted, but melena developed on clinical presentation. He was pale and severely dehydrated but had normal blood pressure (108/68 mmHg). On admission, physical examination revealed slightly sunken eyes, dry oral mucous membrane, and poor skin turgor. The clinical dehydration score was at least ≥ 4 based on the criteria [4]. The abdomen was soft, not distended, but tender in the left upper quadrant area with no generalized guarding. Laboratory investigations revealed leukocytosis (12 900 cells/ μ L; normal range, 3400–10 000/ μ L), severe anemia (Hb 7.9 g/dL; normal range, 11–14.5 g/dL), high levels of BUN (23.0 mg/dL; normal range, 7–20 mg/dL), and hyponatremia (129 mEq/L; normal range, 135–145 mEq/L). Serum levels of potassium, chloride, amylase, and CRP were within the normal range. Stool cultures did not reveal any pathogenic bacteria, including *Clostridium difficile*. Norovirus antigen in the stool specimen was detected using a rapid immunochromatography test (Immunocatch-Noro Test; Eiken Chemical, Co., Ltd., Tokyo, Japan). A plain x-ray and computed tomography of the abdomen revealed no abnormalities. The patient immediately received intravenous fluid therapy.

On the following day, the patient continued complaining of abdominal pain. The blood pressure fell to 88/30 mmHg, but there was no sign of shock. Laboratory investigations revealed ongoing anemia (Hb of 4.6 g/dL), and thus he was transferred to the Kanazawa University Hospital for further management. Blood transfusion was immediately administered for the management of anemia, resulting in increase to Hb of 9.7 g/dL. Serum antibody against HP using an enzyme-immunoassay and a urea breath test were negative. To determine the site of the gastrointestinal bleeding, the patient underwent wireless capsule endoscopy, revealing multiple ulcers in the bulbus of the duodenum and upper part of the jejunum. Histopathological examination was not performed. He was treated with a proton pump inhibitor (PPI), and subsequent clinical course was uneventful without any recurrence of DU.

Literature Review

Literature search found 6 English-language full reports (14 cases) [3, 5–9], 7 Japanese-language full reports (10 cases) [10–16], of which 4 reports included English abstracts [10, 13, 14, 16], and 10 Japanese-language abstract-only reports (12 cases) [17–26]. Of the 36 cases reported, the site of the bleeding lesion was not confirmed by endoscopy in the 2 cases with RV gastroenteritis [9]. However, because the site of the bleeding lesion in these patients appeared to be upper gastrointestinal tract, these 2 cases were included for analysis in the study. Five cases [8, 14, 19, 25] were excluded because the diagnosis of RV and NoV infections was not confirmed. Of these, both RV and NoV antigens in their stool specimens were negative in 2 patients [8, 14], and the tests for RV and NoV antigens

in the stool specimens were not performed in the remaining 3 patients [8, 19, 25]. Thus, 31 reported cases of GDPU associated with RV or NoV gastroenteritis were eligible for inclusion in the analysis. Our most recent case was added for a total of 32 patients.

Demographic, clinical characteristics, the site of GDPU, treatment, and outcome in these patients are summarized in Table 1. There were 23 RV cases and 9 NoV cases with GDPU. Mean age of the 32 patients was 21.6 months (3–96 months), 19.7 months (3–63 months) in RV cases and 26.4 months (12–96 months) in NoV cases. Male/female ratio was 22:10 (2.2). Medical history was unremarkable in all patients except 2: 1 had hypothyroidism [5] and 1 had Perthes disease [15]. There was no evidence for medical history of RV vaccination in any patients reported.

As shown in Table 1, vomiting (29 of 32, 90.6%) is the most common symptom, followed by diarrhea (24 of 32, 75.0%), lethargy (25 of 32, 78.1%), fever (12 of 32, 37.5%), abdominal distension (9 of 32, 28.1%), and convulsion (1 of 32, 3.1%). Duration of the symptoms related to gastroenteritis before the hospitalization was 1–7 days (mean, 4.0 days). Dehydration occurred in all patients except 1 (31 of 32, 96.9%). Hematemesis (13 of 32, 40.6%), melena (25 of 32, 78.1%), drowsiness or unconsciousness (10 of 32, 31.2%), shock (13 of 30, 43.3%), and metabolic acidosis (7 of 11, 63.6%) were also common symptoms. Leukocytosis ($>10\,000/\mu\text{L}$; 12 of 16, 75.0%), anemia ($\text{Hb} < 11\text{ g/dL}$; 21 of 25, 84.0%), and positive CRP ($>0.3\text{ mg/dL}$; 9 of 16, 56.3%) were frequently found. High levels of BUN ($\geq 21\text{ mg/dL}$; 9 of 15, 60.0%) and hyponatremia ($<135\text{ mEq/L}$; 11 of 14, 78.6%) were commonly observed. *Helicobacter pylori* was only detected in 15.0% patients (3 of 20).

Fourteen patients developed gastroduodenal perforation; 10 DP patients, 1 GP patient with RV gastroenteritis, and 3 DP patients with NoV gastroenteritis (Table 1). Perforation site was the bulbous of the duodenum in all patients except 1 who developed the perforated fundus of the body of the stomach. Eighteen patients developed gastroduodenal ulcer; 12 RV cases and 6 NoV cases. Duodenal ulcer occurred in 10 RV cases and 5 NoV cases, and 1 NoV case had GU simultaneously. Gastric ulcer also occurred in 1 NoV case. In the remaining 2 RV cases, the site of the bleeding lesion was not confirmed by endoscopy, but it appeared to be in the upper gastrointestinal tract [9]. The site of ulcer was the bulbous of the duodenum in all but 1 with the posterior wall of the stomach. Each among the 2 DU patients also had multiple ulcers in the upper part of the jejunum or the stomach, respectively. The data for histopathology of the perforated site were available in 9 patients; there was no mural change in 2 patients, mural thickening in 4 patients, and ulcerative change in 3 patients. One patient developed pancreatitis due to the fluid leakage from DP.

For the management of anemia and hypovolemic shock caused by blood loss, the 10 DU patients received blood transfusions (Table 1). The surgical repair for the perforated site was

successful in all 14 patients with DU or GP, 5 of whom received a PPI postoperatively. Endoscopic homeostatic therapy ([EHT] 3 cases), transcatheter arterial embolization ([TAE] 2 cases), and clipping (2 cases) were performed among the 16 patients with gastroduodenal ulcer. The remaining patients received only conservative therapy, including a PPI. The 2 (6.3%) DU patients associated with RV gastroenteritis died of hypovolemic shock due to ulcer bleeding. The remaining patients completely recovered without recurrence of GDPU.

DISCUSSION

The present study suggests that race, young age, male gender, severe dehydration, metabolic acidosis, drowsiness or unconsciousness, and shock are associated with GDPU in RV and NoV gastroenteritis. This study also highlights the importance of awareness for the risk of GDPU that may prevent severe or lethal outcome in these common infections among young children.

It may be argued that RVs and NoVs as the most common causes of gastroenteritis in this age group were detected only by chance due to a persistent shedding of these viruses in the gastrointestinal tract in young children with GDPU, and that GDPU have formed for unknown reasons. A prolonged shedding of RV and NoV into the stool can occur for up to 2 months after the recovery of the diseases in natural infections of non-immunocompromised children [27, 28]. All patients presented here had been previously healthy until they were infected with RVs or NoVs, and they developed GDPU in their acute but not recovery phase of the diseases. In addition, none of the patients received NSAIDs, and HP does not appear to be a cause of GDPU in these patients. Thus, it is unlikely that GDPU is merely coincidental and unrelated to RV and NoV gastroenteritis. Due to the nature of the present descriptive study, the cause-effect relationship between GDPU and viral gastroenteritis cannot be definitively established. However, the study strongly suggests a possible link between GDPU and RV and NoV gastroenteritis in young children.

It is surprising that all but 1 case of GDPU [7] associated with RV or NoV gastroenteritis have been reported from Japan. To the best of the author's knowledge, all but 1 [7] described here represent a total number of pediatric reported cases of GDPU associated with RV and NoV gastroenteritis in Japan during an era without RV vaccination. This observation leads to hypothesis that unidentified factor(s) may play a role in the pathogenesis of GDPU associated with RV and NoV gastroenteritis. As in diarrheal deaths [1, 2], male preponderance was shown in childhood GDPU associated with RV and NoV gastroenteritis, suggesting that gender may be a risk factor of GDPU associated with these viruses' gastroenteritis. As shown in diarrhea-associated deaths [29, 30], the age at onset of the disease of <5 years in the majority of the GDPU patients suggests that this age group is a risk factor of GDPU-associated mortality. A prevalence of

Table 1. Gastroduodenal Perforation and Ulcer Associated With Rotavirus and Norovirus Gastroenteritis in Japanese Children Except 1 Patient^a

Age (mo)	Sex	Symptoms	Symptoms' Duration Until Admission (d)	Dehydration	Hematemesis/Melena	Consciousness	Shock	Metabolic Acidosis	WBC Counts (/ μ L)	Hb (g/dL)	CRP (mg/dL)	BUN (mg/dL)	Serum Na (mEq/L)	H. pylori	Site of GDPU Lesions	Blood Transfusion	Therapy	Outcome	Ref
Rotavirus Gastroenteritis																			
12	M	Diarrhea/lethargy/vomiting	3	+	+/+	Normal	-	-	9800	9.6	NA	46.0	136	NA	DP, anterior bulbus, no mural change	-	Surgery	CR	[3]
3	F	Abd. distention/lethargy/vomiting	1	+	-/-	Normal	+	+	22 400	NA	NA	26.3	NA	NA	GP, gastric fundus	-	Surgery	CR	[5]
9	F	Diarrhea/fever/lethargy/vomiting	3	+	+/+	Decreased	+	+	15 600	7.1	<0.2	22.8	NA	-	DU, duodenal bulbus	+	PPI	CR	[6]
9	M	Abd. distention/diarrhea/fever/lethargy/vomiting	5	+	+/-	Normal	+	NA	15 600	NA	<0.2	NA	NA	-	DP, postpyloric	-	Surgery	CR	[7] ^a
18	M	Diarrhea/lethargy/vomiting	6	+	+/+	Normal	+	NA	NA	6.8	NA	NA	NA	-	DU, bulbus/2nd portion	+	Conservative	CR	[8]
11	M	Diarrhea/lethargy/vomiting	3	+	-/+	Decreased	+	NA	NA	3.9	NA	NA	NA	+	DU, 2nd portion	+	TAE	CR	[8]
12	M	Lethargy	4	+	-/+	Normal	-	NA	14 500	8.6	7.6	24.3	133	-	unknown	-	Conservative	CR	[9]
12	F	Lethargy	4	+	-/+	Normal	-	NA	14 800	7.3	<0.3	18.1	130	-	unknown	-	Conservative	CR	[9]
12	M	Lethargy	4	-	-/+	Normal	+	NA	5500	4.3	1.1	11.1	137	-	DU, bulbus	+	EHT + PPI	Died	[9]
19	M	Convulsion/diarrhea/fever/vomiting	3	+	+/+	Unconscious	-	+	8300	12.7	3.7	56.0	127	-	DP, posterior bulbus	-	Surgery + PPI	CR	[10]
34	M	Abd. distention/diarrhea/fever/vomiting	6	+	-/-	Decreased	-	+	18 300	12.4	1.5	11.0	132	-	DP, anterior bulbus	-	Surgery + PPI	CR	[10]
18	M	Diarrhea/lethargy/vomiting	5	+	-/+	Normal	-	NA	9500	11.9	<0.3	15.1	NA	-	DP, bulbus	-	PPI	CR	[11]
28	M	Diarrhea/fever/vomiting	2	+	-/+	Normal	-	NA	38 050	8.8	0.17	23.0	132	-	DU, posterior bulbus	-	EHT + H2b	CR	[12]
14	F	Abd. distention/diarrhea/lethargy/vomiting	3	+	+/+	Unconscious	+	NA	19 600	10.0	1.0	33.0	134	+	DP, anterior bulbus, mural ulcer	-	H2b, Spontaneous closure	CR	[13]
30	M	Abd. distention/diarrhea/fever/lethargy/vomiting	2	+	-/+	Normal	-	NA	NA	8.7	7.3	NA	133	-	DP, posterior bulbus, mural thickening	-	Surgery	CR	[14]
33	F	Abd. distention/diarrhea/fever/lethargy/vomiting	7	+	-/-	Normal	-	NA	NA	9.5	9.8	NA	NA	-	DP, posterior bulbus, mural thickening	-	Surgery	CR	[14]
63	M	Diarrhea/lethargy/vomiting	5	+	+/+	Unconscious	+	+	12 400	7.8	0.46	12.7	121	-	DU, bulbus, mural thinning, ulcer	+	Surgery + PPI	Died	[15]
18	M	Diarrhea/lethargy/vomiting	5	+	-/+	Normal	-	NA	NA	NA	NA	NA	NA	NA	DU, anterior bulbus	-	PPI	CR	[17]

Table 1 continued.

Age (mo)	Sex	Symptoms	Symptoms' Duration Until Admission (d)	Dehydration	Hematemesis/Melena	Consciousness	Shock	Metabolic Acidosis	WBC Counts (/ μ L)	Hb (g/dL)	CRP (mg/dL)	BUN (mg/dL)	Serum Na (mEq/L)	H. pylori	Site of GDPU Lesions	Blood Transfusion	Therapy	Outcome	Ref
8	F	Diarrhea/vomiting	5	+	-/+	Normal	-	NA	NA	NA	NA	NA	NA	-	DP, anterior bulbus	-	Surgery + PPI	CR	[18]
8	M	Diarrhea/vomiting	4	+	-/+	Normal	-	NA	NA	NA	NA	NA	NA	NA	DU, bulbus/2nd portion	+	PPI	CR	[19]
36	M	Diarrhea/fever/vomiting/lethargy	7	+	-/+	Unconscious	+	NA	NA	5.7	NA	NA	NA	NA	DU, bulbus/2nd portion	+	EHT	CR	[20]
17	F	Diarrhea/lethargy/vomiting	6	+	-/+	Normal	+	NA	NA	8.2	NA	NA	NA	NA	DU, bulbus	-	Conservative	CR	[21]
29	M	Abd. distension/diarrhea/vomiting	2	+	+/+	Normal	-	NA	NA	NA	NA	NA	NA	NA	DP, bulbus/2nd portion, ulcer, peritonitis	-	Surgery	CR	[22]
Norovirus Gastroenteritis																			
24	M	Diarrhea/vomiting/lethargy	3	+	-/+	Normal	-	-	17 480	4.6	2.9	15.0	135	NA	DP, anterior bulbus, no mural change	-	Surgery	CR	[3]
19	F	Diarrhea/fever/lethargy/vomiting	7	+	+/+	Normal	+	NA	NA	4.6	NA	NA	NA	+	GU, posterior wall	-	Clipping	CR	[8]
15	M	Diarrhea/fever/lethargy/vomiting	3	+	-/+	Normal	+	NA	NA	6.6	NA	NA	132	-	DU, bulbus	-	Conservative	CR	[8]
12	F	Abd. distension/lethargy/vomiting	2	+	+/-	Decreased	-	+	11 030	11.7	0.3	24.0	134	NA	DP, anterior bulbus, mural thickening	-	Surgery + PPI	CR	[16]
18	M	Lethargy/vomiting	3	+	+/+	Normal	-	+	NA	6.5	NA	NA	NA	NA	GU, DU	+	PPI	CR	[23]
18	M	Diarrhea/vomiting	3	+	+/-	Normal	NA	NA	NA	4.7	NA	NA	NA	NA	DU, anterior bulbus	-	Clipping + H2b	CR	[24]
12	F	Abd. distension/lethargy/vomiting	3	+	+/-	Decreased	NA	-	NA	NA	NA	NA	NA	NA	DP, anterior bulbus, mural thickening	-	Surgery	CR	[25]
24	M	Diarrhea/fever/lethargy/vomiting	3	+	-/+	Decreased	+	NA	NA	5.8	NA	NA	NA	-	DU, anterior bulbus	+	TAE + PPI	CR	[26]
96	M	Fever/lethargy/vomiting	7	+	-/+	Normal	-	-	13 320	4.6	0.1	23.0	129	-	DU, upper jejunum	*	PPI	CR	Presnt case

Normal values of serum sodium concentration; 135–145 mEq/L. Note that all but 1 Norwegian child [7]^a were Japanese children.

Abbreviations: Abd., abdominal; BUN, blood urea nitrogen (normal values, 7–20 mg/dL); CR, complete recovery; CRP, C-reactive protein (normal values, <0.3 mg/dL); DP, duodenal perforation; DU, duodenal ulcer; EHT, endoscopic hemostatic therapy; GDPU, gastroduodenal perforation or ulcer; GP, gastric perforation; Hb, hemoglobin (normal values, 11–14.5 g/dL); H2b, H2 blocker; NA, not available; PPI, proton pump inhibitor; Ref, reference; TAE, transcatheter arterial embolization; WBC, white blood cell count (normal values, 3400–10 000/ μ L).

RV [29] and NoV infections [30] among children <5 years of age may not simply account for this finding because the immunocompromised elderly population also developed DP associated with NoV gastroenteritis [31]. Impaired immunity in the young [1, 2] may play a crucial role in the pathogenesis of GDPU associated with these viruses' infections.

Similar to previously described studies on diarrhea-associated deaths of children <5 years of age [32, 33], the present study showed that severe dehydration with electrolyte imbalance, drowsiness or unconsciousness, and shock were associated with GDPU in childhood RV and NoV gastroenteritis. In addition, lethargy, metabolic acidosis, high levels of BUN, and hyponatremia, suggestive of severe dehydration [34], occurred in the majority of the patients with GDPU in RV and NoV infections. Leukocytosis and positive CRP, as seen in many cases with GDPU, have been shown to be positively correlated with severity of gastroenteritis caused by RVs and NoVs [35], suggesting that severity of RV and NoV gastroenteritis may be a risk factor of GDPU.

The predominant site of perforation or ulcer is the bulbous of the duodenum in the majority of patients, suggesting duodenum as a main target tissue of perforation or ulcer in RV and NoV gastroenteritis. Rotaviruses and NoVs infect the duodenal enterocytes [1, 2]. The balance between promoting factors (reduced levels of acid and pepsin) and natural defenses (bicarbonate and blood flow) may play a pathogenic role for GDPU [36]. Gastric acid and pepsin can cleave RVs, reducing its infectivity [37]. Secretion of gastric acid and pepsin is reduced in younger children [37]. Sodium bicarbonate can kill NoVs [38]. Vomiting may reduce these factors. In addition, bicarbonate is required to maintain intestinal epithelial integrity [39]. Reduced bicarbonate and metabolic acidosis are associated with severe dehydration [39]. Taken together, these factors may result in severe gastroduodenal mucosal barrier dysfunction and injury, leading to GDPU.

Severe dehydration and shock, commonly associated with GDPU patients, may induce ischemia and hypovolemia. In the presence of adequate tissue perfusion, ulcer does not develop even under conditions of acid back-diffusion [36]. Ischemia with functional defect in the gastroduodenal mucous membrane barrier could reduce mucosal resistance in young children with gastroduodenal ulcer or erosions [40]. The mucosal blood flow is low in the duodenal bulbous [41], suggesting that duodenum, in particular the bulbous, may be more susceptible to ischemia. In fact, gastroduodenal ischemia could cause gastroduodenal ulcers [42]. Although no ischemic or necrotic lesion was found in the GDPU patients, this result does not exclude a role of acute and transient ischemia of small intestine caused by severe dehydration and shock as precipitating factors for GDPU [36].

The mortality of gastroduodenal perforation is 27.2% for infants [43] and 3.8% to 25% for older children [44, 45], whereas the mortality of upper gastrointestinal bleeding is 1.7%–5% for

children [45, 46]. Although all reported patients with gastroduodenal perforation recovered, surgical delay (>12 hours) for DP likely causes serious complications and poor outcome [44]. The 2 DU patients (6.3%) died of ulcer bleeding despite EHT, suggesting that severe ulcer bleeding is a predictor of poor outcome. Thus, timely diagnosis and treatment including surgical interventions are crucial for preventing lethal outcome in these patients.

Limitations of the present study include its retrospective and observational nature and lack of appropriate controls without GDPU for a statistical comparison of risk factors of GDPU associated with RV and NoV gastroenteritis. Although the present study cannot definitively determine the association of GDPU with RV and NoV gastroenteritis, this study strongly suggests a potential link between these events.

CONCLUSIONS

The present study suggests that race, young age, male gender, severe dehydration, metabolic acidosis, drowsiness or unconsciousness, and shock should be associated with GDPU in childhood RV and NoV infections. Although GDPU is rare, it may be an underestimated complication in young children with RV and NoV gastroenteritis. When clinical condition of these children suddenly deteriorates, awareness of the risk of GDPU may lead to timely diagnosis and intervention, preventing severe or lethal outcome. Due to limitations of the present descriptive study, further investigation are needed to obtain clear evidence for the association between GDPU and RV and NoV gastroenteritis and its risk factors in these common viruses' infections.

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