Nonocclusive Bowel Necrosis Occurring in Critically Ill Trauma Patients Receiving Enteral Nutrition Manifests No Reliable Clinical Signs for Early Detection

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BACKGROUND: Nonocclusive bowel necrosis (NOBN) has been associated with early enteral nutrition (EN). The purpose of this study was to determine the incidence of this complication in our trauma intensive care unit population and to define a typical patient profile vulnerable to NOBN.

METHODS: Thirteen cases of NOBN were identified among 4,311 patients (0.3%) over a 64-month period ending October 1998. Their charts were analyzed for a variety of clinical data, including prospective EN tolerance data in 4.

RESULTS: Twelve (92%) patients were enterally fed prior to diagnosis for 10 ± 8 days (range 3 to 21). Tachycardia (n = 12, 92%); fever/hypothermia, (n = 12, 92%), and an abnormal white blood cell count (n = 11, 85%) were consistently present. Abdominal distention was common but tended to be a late sign (n = 12). Seven (56%) survived. In 4 patients with tolerance data, 3 reached the goal rate of feeds prior to diagnosis. Two became distended at >12 hours from diagnosis. Gastric tonometry demonstrated a decreased NgpHi (<7.30) after starting EN in all 3 in whom it was monitored.

CONCLUSIONS: NOBN developed in 0.3% of our trauma patients. Onset occurs in the second week in high-acuity patients who have had a period of EN tolerance. Clinical findings resemble bacterial sepsis with tachycardia, fever, and leukocytosis. Gastrointestinal specific signs are not consistent or occur late. Thus, we could not identify an early, useful clinical indicator. Gastric carbon dioxide tonometry may detect a vulnerable subgroup of patients. *Am J Surg.* 2000;179: 7–12. © 2000 by Excerpta Medica, Inc.

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Clinical studies demonstrate that early enteral nutrition (EN) is feasible and beneficial following major trauma.[1–6] However, there have been disturbing case reports of nonocclusive bowel necrosis (NOBN) occurring in stressed surgical patients receiving EN.[7–14] The purpose of this study was to determine the incidence of this complication in a trauma patient population and to develop a typical profile of a high-risk patient.

METHODS

During a 64-month period ending October 1998, 4,311 trauma patients were admitted to the shock-trauma and neurosurgical intensive care units (ICUs) at Hermann Hospital. Review of the trauma registry identified 13 patients with confirmed nonocclusive bowel necrosis. Based on a review of the literature,[7–14] their charts were analyzed for a variety of pertinent data including patient demographics; injury mechanism and pattern; timing, type and route of enteral feeding; clinical status and laboratory results in the 24 hours preceding diagnosis; diagnostic radiologic studies; operative findings; pathologic analyses of resected specimens; ICU and hospital stay; and mortality. In addition, Injury Severity Scale (ISS), Revised Trauma Scale (RTS), and Acute Physiology and Chronic Health Evaluation (APACHE) II scores (as well as APACHE II scores at diagnosis) were calculated. The data were analyzed to identify the factors most frequently associated with nonocclusive bowel necrosis. From these a typical patient profile was developed.

In October 1997, as part of a standardized enteral feeding protocol, a prospective feeding tolerance data sheet was adopted for all ICU patients who were enterally fed.[15] Feeding type, strength, and rate; the presence of abdominal tenderness, distention, or diarrhea; nasogastric aspirate volume and character; abdominal girth measurements; and gastric tonometry data (if present) were recorded. Data were collected at 12-hour intervals for 120 hours, then at 24-hour intervals until discharge from the ICU. Prospective tolerance data were available and reviewed in 4 patients.

In addition, trauma patients who are admitted to the ICU with known risk factors for multiple organ failure (including major torso injuries, an elevated base deficit, and expected transfusion requirement of >6 units packed red blood cells) were placed on a standardized 24-hour resuscitation protocol. A pulmonary artery catheter and gastric carbon dioxide (CO_2) tonometer were inserted to guide volume resuscitation. After resuscitation was judged to be

TABLE I

Clinical Factors at Diagnosis

	Mean ± SD	Range	Number of Patients	Percent
Heart rate	131 ± 33	40–160		
HR >100 or <50			13	100%
Mean arterial blood pressure	82 ± 30	37–121		
Systolic <90 mm Hg			9	69%
Systolic <90 mm Hg ≥30 min			5	38%
Temperature	39.2 ± 1.5	35.8–40.9		
≥39°C or <36.5°C			12	92%
Abdominal symptoms				
Distention			12	92%
Diarrhea			4	31%
Guiac + stool			1	8%
Critical care acuity				
Mechanical ventilation			13	100%
Inotropic medication			11	85%
Neuromuscular blockade			11	85%
White blood cell count	19.3 ± 13.2	3.8–55.1		
WBC >11.5 or <4.0			11	85%
Creatinine	2.2 ± 1.8	0.6–6.6		
Cr >1.2			9	69%
Blood urea nitrogen/creatinine ratio	24 ± 8	12–37		
BUN/CR >20			9	69%
pH	7.32 ± 0.15	7.01–7.52		
pH <7.3			5	38%
Base deficit	1 ± 10	20 to −17		
BD >5			5	38%
Lactate*	5.2 ± 2.1	3.4–8.3		
Lactate >2.5			4	100%
PaO2/FiO2	242 ± 82	81–337		
PaO2/FiO2 <250			5	38%

** Measured in only 4 patients.*

complete, enteral feeding access was obtained and EN started. Gastric CO_2 tonometers were left in place to monitor patients for subsequent complications (eg, septic episodes) which has been previously proposed.[16] Three of the patients had gastric CO_2 tonometry data prior to the development of NOBN. Since no data existed directly comparing intestinal with gastric CO_2, and no association had been established between either enteral feeding tolerance or NOBN and gastric $PrCO_2$ levels, gastric $PrCO_2$ was not used to guide administration of EN.

RESULTS

Thirteen cases of NOBN were identified over 64 months in 4,311 admissions to the trauma ICUs, giving an overall incidence of 0.3%. The mean ± SEM age of the patients afflicted was 33 ± 15 years (range 17 to 54). Ten (77%) of the patients were male. Injury mechanism was predominantly blunt; motor vehicle crashes occurred in 11 (85%). The mean ISS score was 25 ± 10 (9 to 41). The RTS score was a mean of 9 ± 2 (7 to 12). The mean APACHE II scores were 25 ± 9 (9 to 45) on admission, compared with 30 ± 7 (21 to 37) at diagnosis. Eight (62%) of the patients suffered a closed head injury while 4 (31%) had significant intra-abdominal injury (2 of whom suffered bowel injuries).

Of the 13 patients who developed NOBN, 12 (92%) were enterally fed prior to diagnosis. Feedings were started from 2 to 20 days after injury (mean 6 ± 5), with the duration of days that the patients received enteral nutrition from 3 to 21 (mean 10 ± 8). The diagnosis of intestinal necrosis was made at a mean of 15 ± 9 days (6 to 32). Ten (83%) of those who received EN were fed into the jejunum, while 2 (17%) were fed into the duodenum. All of the enterally fed patients were given a polymeric formulation; none received an elemental diet. Five (38%) of the patients received parenteral nutrition, 4 of whom later started enteral feedings.

Among the clinical factors analyzed in the 24 hours before diagnosis, 12 (89%) of the patients were noted to be tachycardic, with a mean rate of 131 ± 33 beats per minute (**Table I**). In addition, the mean temperature was 39.2°C ± 1.5 (35.8 to 40.9°C); temperature was ≥39°C or ≤36.5°C in 12 (92%) of patients. With regard to abdominal symptoms, 12 patients (92%) were noted to be distended on examination. When overall critical care acuity was considered, 13 patients (100%) required mechanical ventilation, 11 (85%) were receiving inotropic medications (dopamine and dobutamine), and 11 (85%) had been administered pharmacologic neuromuscular blockade. Four patients (31%) received catecholamine vasopressor agents in the 24 hours prior to diagnosis.

Analysis of clinical laboratory data showed that the patients with necrotic intestine had a mean white blood cell (WBC) count of 19,300 ± 13,200 (range 3,800 to 55,100);

and that 11 of the patients (85%) had either a leukocytosis ≥11,500 or leukopenia ≤4,000 (Table I). The mean serum creatinine level was 2.2 ± 1.8 and 9 patients (69%) had an elevation of their creatinine level to ≥1.2. Although serum lactate measurement was done in only 4 of the patients, it was elevated (>2.5) in all; the mean lactate value was 5.2 ± 2.1. Other parameters were not significantly abnormal.

Abdominal computed tomography was done to aid in diagnosis in 9 (69%) of the patients who were later proven to have NOBN. Interpretations were available for 8 of the 9 scans. The most consistent finding was pneumatosis intestinalis (88%), followed by free fluid (38%), thickened/dilated bowel (38%), and free peritoneal air (25%). Of the remaining 4 patients, 1 had free peritoneal air on chest radiograph, 1 had free air and grossly abnormal peritoneal fluid at the time of bedside peritoneal lavage, and 2 were taken to the operating theater based on clinical assessment alone.

All 13 patients underwent exploratory celiotomy with resection of necrotic intestine in 12. The patient who did not have resection was found to have extensive necrosis of the small bowel and colon. Seven (54%) had resection of jejunum and/or ileum; 3 (23%) had a combined resection of the ileum and right colon; while 2 (22%) had resection of the right colon only. Pathologic analysis of the resected specimens yielded a spectrum of findings from acute inflammation with mucosal ulceration to transmural necrosis and multiple perforations. Nine (69%) of the patients had repeat operations. Seven (54%) of the patients survived to discharge from the hospital. For survivors the mean hospital stay was 61 ± 35 days (28 to 136), while the mean stay in the intensive care unit was 34 ± 23 days (17 to 49).

Four patients had prospectively collected feeding tolerance data. Three reached target caloric intake between 60 and 84 hours after initiating feeds. The fourth was at 62% of goal when feeds were stopped prior to a lengthy facial reconstructive procedure; immediately upon return to the ICU, he was taken for laparotomy based on the abdominal examination and precipitous clinical deterioration. Significant abdominal tenderness was recorded in 1 patient, was not present in 1, and could not be ascertained in the remaining 2. Distention was present >24 hours in 1 patient, <24 hours in 1 patient, and <12 hours in 2 patients. Diarrhea was profuse in 2 patients immediately before diagnosis, and absent in the other 2. Nasogastric aspirate volume and character changes did not correlate with the onset of the disorder. Abdominal girth increased significantly (<2 inches) in 2 of the patients (but only 12 hours prior to diagnosis in 1 of them). In the 3 patients with gastric CO_2 tonometers, all had low NgpHi measurements (<7.30) during advancement of enteral feedings. Lowest readings were 6.95, 7.17, and 7.28 respectively during that period. The single patient who had a functional tonometer at the time of diagnosis had a NgpHi of 6.98.

A Typical Patient Profile

NOBN occurs in trauma patients of any age, with a wide range of injury severity. The most significant injuries are in areas other than the abdomen; closed head injury is a commonly associated condition. Initiation of EN is typically delayed (>48 hours from injury), but has been given for over a week before the diagnosis is made (usually during second week). All patients in our experience received a polymeric enteral formula and required high-acuity care (ie, mechanical ventilation, neuromuscular blockade, and inotropic support). The clinical course mimics sepsis with a temperature greater than 39°C, an abnormal WBC count, and tachycardia. Relative hypovolemia may be present, and the serum creatinine level is mildly elevated. Although acid-base balance may not be abnormal, an elevated lactate level, if checked, is likely to be present. Abdominal distention is present late in the course.

COMMENTS

The purpose of this report was to determine the incidence of NOBN in our trauma ICU patient population, identify unrecognized associated factors, and develop a profile of an ICU patient at high risk. Clinical studies have demonstrated that EN is feasible following both abdominal surgery and major trauma, at reduced cost compared with total enteral nutrition (TPN).[1–4] In addition, prospective randomized trials have demonstrated that EN, particularly the immune-enhancing formulas, significantly reduce septic morbidity.[5,6] As a result, early EN has become a standard ICU practice. Most patients enrolled in these studies experienced some degree of feeding intolerance but over 85% were able to receive full-dose enteral feeding by 72 hours. With its application to more critically ill ICU patients, employing less formal methodology, it is not surprising that intolerance to EN is common. It is distressing that NOBN has emerged as a devastating complication in a small subset of these patients.[7–14] The reported incidence is variable, ranging from 0.3% to 8.5% (**Table II**). The incidence of NOBN among our trauma ICU population is 0.3%.

Systemic hypoperfusion is commonly believed to be a prelude to intestinal necrosis. However, NOBN is extremely unusual in unfed patients who survive resuscitation from hemorrhagic shock. In our group only 1 patient might fit this pattern as he was in profound hemorrhagic shock on presentation, and developed necrosis in the watershed area of the distal ileum and right colon. During hypovolemic shock the intestine is subjected to increased sympathetic nerve stimulation augmenting vasomotor autoregulatory escape, with improvement of the blood flow to perfusion pressure ratio.[17] In addition, there is a redistribution of flow within the intestinal wall favoring the mucosa.[17] Another major factor protecting the gut from ischemic injury is its ability to increase oxygen extraction sixfold by increasing perfused capillary density.[17] By these mechanisms the gut can survive short periods of profound hypoperfusion. Despite these compensatory mechanisms, clinically relevant shock insults have been demonstrated to cause sloughing of the mucosa at the tips of the villi. This occurs for two reasons. First, the arterioles and venules supplying the villi are in close proximity and, therefore, form a countercurrent mechanism. With relative hypoperfusion the large pO_2 gradient between the arteriole and venule in the proximal villus causes an exchange of O_2, reducing the pO2 at the tip of the villi to near zero. Second, reperfusion generates reactive oxygen metabolites that can directly cause injury as well as recruit activated neutrophils amplifying that injury. Fortunately, this superficial mucosal injury is repaired by 24 hours and there is no evidence of a persistent

TABLE II

Review of Case Series of Necrotic Bowel and Enteral Feeding

Author and Year	Number of Patients	Incidence	Age	Formula	Route	Site of Necrosis	Mortality	Warning Symptoms and Signs	Associated (Hypothesized) Factors
Thompson 1983	1 (trauma)	nr	20	nr	Needle catheter jejunostomy	Entire SB 1	100%	Distension, abdominal tenderness	Pneumatosis intestinalis
Gaddy 1986	5 (mixed)	8.5	55	Elemental (3) Polymeric (2)	Jejunostomy	Jejunum 2 Ileum 1 Diffuse 3	100%	Distension, high NGT output	Hypotension, substrate by increased metabolic demands
Brenner 1987	1 (cancer)	4.0	73	Elemental	Needle catheter jejunostomy	Entire SB 1	100%	Distension, nausea and vomiting, elevated creatinine, hyperglycemia, pneumatosis intestinalis	Malnutrition w/ immune system depression, contaminated formula, hypovolemia
Smith-Choban 1988	5 (mixed)	3.5	73	Elemental > polymeric	Needle catheter jejunostomy	Small bowel 2 Colon 2 Diffuse 2	100%	Distension, abdominal pain, abdominal tenderness, portal vein gas	Multifactorial, risk factors, substrate
Schunn 1985	4 (cancer)	0.3	64	Polymeric	Jejunostomy	Jejunum 4 ileum 2 Colon 1	50%	Distension, abdominal pain, high NGT output	Hyperosmolar substrate, contamination, substate breakdown products, local vasospasm, disordered peristasis
Kowal-Vern 1997	10 (burn)	0.5	38	nr	Nasoenteric	Duodenum 1 Jejunum 4 Ileum 3 Colon 4 Diffuse 3	60%	Acidosis, increasing fluid requirement, respiratory insufficiency	TBSA burn >40%, preceding sepsis
Marvin 1999	13 (trauma)	0.3	33	Polymeric (12)	Jejunostomy Nasoduodenal Nasojejunal	Jejunum 7 Ileum 6 Colon 4 Diffuse 3	46%	Distension, tachycardia, fever, low NgpHi	See discussion
Total or Average	39	0.5	46				67%		

Low cardiac output, hypotension, atherosclerosis of coronary, cerebral or peripheral vessels, diabetes melitus, congestive heart failure, or chronic obstructive pulmonary disease.

abnormality of the intestinal wall histology. However, gut ischemia-reperfusion may alter enterocyte or smooth muscle function (ie, absorption or motility), or set the stage for microvascular disregulation, that could render the gut more susceptible to further insult.

While NOBN tended to develop weeks into their hospital course, the majority of our patients were not persistently hypotensive prior to diagnosis (38%). When systemic hypotension did occur late, it tended to appear after gastrointestinal symptoms were already evident, and was likely a symptom of NOBN, not a cause. Similar scenarios are described among the case series reported.[7–14] Therefore, it is unlikely that either early hypovolemic shock with incomplete resuscitation or episodic hypotension later in the patient's course would be solely responsible for this problem.

It has been noted that NOBN frequently occurs in a patchy distribution with intervening areas of nonnecrotic bowel. This presentation is strikingly similar to neonatal necrotizing enterocolitis (NEC). Like NEC, NOBN is associated with EN in 90% to 95% of cases, and thus EN is believed to be a major contributing factor in both syndromes. A role in the pathogenesis of NOBN by EN is suggested by the observation that in the single case re-

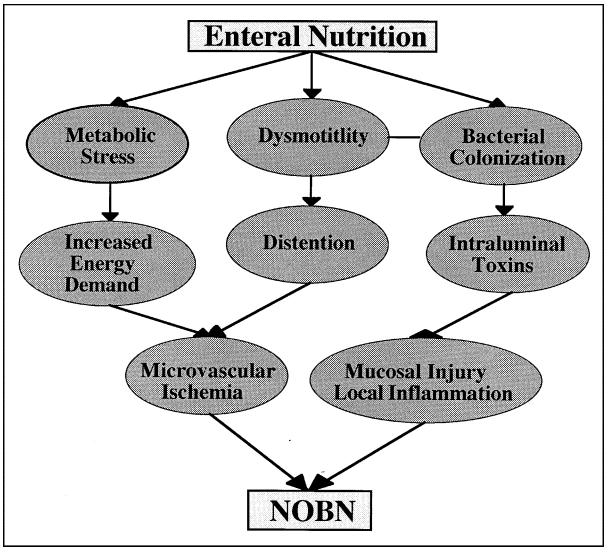

Figure. Proposed pathophysiology of nonocclusive bowel necrosis (NOBN).

ported by Brenner and Schellhammer,[9] the ileal conduit, constructed out of intestinal continuity, was normal while the remainder of the small bowel was necrotic. As with NEC, the etiology of NOBN is likely multifactorial, with the presence of enteral substrate a key component.

There are several theories of how EN contributes to the pathogenesis of NOBN that are not mutually exclusive (**Figure**). First, the obligatory absorption of intraluminal nutrients may deleteriously increase energy demands in metabolically stressed enterocytes. The absorption of nutrients (eg, glucose and amino acids) is coupled to an adenosine triphosphate (ATP)-dependent sodium pump. Other nutrients such as dipeptides and tripeptides are coupled to the entry of hydrogen ions (H^+). To avoid an intracellular acidosis, these protons are extruded from the cell by an ATP-dependent countertransport mechanism. The notion that enterocytes are metabolically stressed following trauma is supported by gastric tonometry studies.[17,18] It has been observed that high-risk patients have a persistently low NgpHi despite successful resuscitation. This may occur for a variety of reasons, including an imbalance between energy demand and perfusion, disproportionate splanchnic vasoconstriction with shunting of blood away from the mucosa, and a primary defect in enterocyte mitochondrial function.

Microvascular splanchnic vasoconstriction is partially mediated through the renin-angiotensin system.[17] This is due to an increased density of angiotensin II receptors in the splanchnic vascular smooth muscle. Hypersensitivity of the splanchnic bed to angiotensin can induce nonocclusive mesenteric ischemia in experimental animals.[17] Other factors that could promote selective mucosal ischemia (SMI) include the presence of endotoxin and use of alpha-adrenergic agents or dopamine. Failure of normal compensatory mechanisms discussed above with abnormal redistribution of flow away from the mucosa could lead to SMI and possibly necrosis. The concept of SMI is supported by the observation of decreased NgpHi in patients with increased total splanchnic blood flow.[19]

A second theory is that EN is administered in the setting of ileus allowing bacterial overgrowth, and possibly causing progressive distention that could impair mucosal perfusion resulting in ischemic injury (Figure). While small intestinal dysmotility is not well studied in trauma patients, it does occur in animal models following systemic stress insults. Additionally, small bowel dysmotility has been associated with feeding intolerance and the development of NEC.[20] Premature infants who are intolerant of enteral feeding demonstrate a prominence of clustered phasic activity, absence of migrating motor complexes, and an absence of the normal sporadic repetitive complexes of the fed state.

Lack of the normal interdigestive motor activity has been shown to be associated with bacterial overgrowth of the small intestine.[21] Although specific infectious agents have not been shown to be associated with NOBN, significant bacterial overgrowth is likely. Sepsis preceding NOBN has been identified as an associated factor in two of the case series (Table II).[12,13] The patients in our series were being treated with an average of two antibiotics at the time of diagnosis. It is possible that treatment of other septic foci prior to diagnosis may have selected bacteria more injurious to the intestinal mucosa. Substrate fermentation by the colonizing bacteria may lead to intraluminal gas production resulting in the common finding of pneumatosis intestinalis seen on computed tomography scan. In addition, high concentrations of endotoxin have been demonstrated on the mucosal surface of ischemic intestine.[22] Increasing concentrations of luminal toxins derived from the overgrowth of bacteria could cause a mucosal-submucosal inflammatory response. This coupled with intraluminal gas production from substrate fermentation could set up a vicious cycle of inflammation, distention, and dysmotility resulting in transmural necrosis.

A third theory is that EN contributes to this process by generating intraluminal toxins that cause direct mucosal injury or initiate destructive submucosal inflammation (Figure). In neonates, it is hypothesized that milk-based formulas are broken down into carbohydrates and proteins. Any undigested carbohydrate is fermented by gut bacteria into organic acids. If the mucosa is dysfunctional or motility is impaired, the luminal pH drops. Proteins, such as casein, in the melieu of a pH less than 5 can injure the mucosa directly, lead to bowel wall edema, or even cause transmural necrosis.[23] It is possible that a combination of the polymeric substrate, bacterial overgrowth, and dysmotility creates similar conditions in the intestinal lumen of these patients.

NOBN is an unusual complication in trauma ICU patients. Short of abandoning EN (with its proven benefits), it is unlikely that NOBN can be completely prevented. Our understanding of its epidemiology and pathophysiology is too limited to recommend that EN should be withheld from patients perceived to be at high risk. In fact, our data refute the commonly held perception that NOBN occurs primarily as a result of early aggressive EN in incompletely resuscitated patients. Most of our cases occurred in patients where EN was started in a delayed fashion, and full-dose EN was tolerated for days prior to the development of NOBN. The type of enteral formula may

play a role. All of our patients received a polymeric diet. It is conceivable that a more refined elemental diet may have been better tolerated. However, patients have been reported to develop NOBN while receiving elemental formulas.[8–10]

Despite our best efforts to formalize EN and heighten surveillance, we could not identify clinical parameters that reliably diagnose this entity before bowel necrosis had occurred. Since NOBN typically occurs after the patients have been enterally fed an average of 8 days, initially advancing feeds more slowly is unlikely to prevent its occurrence. TPN has been proposed by some as a safer alternative in these patients. However, since a large proportion of the surgical ICU population resembles the NOBN typical patient profile, TPN would have to be the nutritional route of choice in the majority of ICU patients. It has been demonstrated that TPN is associated with a higher rate of septic complications than EN.[5] Thus, no convincing evidence exists that using TPN would be a "safer" route. Improvement in our ability to monitor enteral feeding tolerance is essential if we are to eliminate this disastrous complication. Our experience with simultaneous gastric and intestinal CO_2 tonometry indicates that this monitor may detect patients who will not tolerate EN and thus be at risk for NOBN.[18] Another potential monitoring device that has been useful in neonates at high risk for NEC is small bowel monometry. Obviously, more work must be done in these areas.

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