Gut Dysfunction and Intolerance to Enteral Nutrition in Critically Ill Patients

Frederick A. Moore* and Norman W. Weisbrodt

Departments of *Surgery and bIntegrative Biology and Pharmacology, University of Texas – Houston Medical School, Houston, Tex., USA

Introduction

For patients who survive the first 48 h of intensive care, sepsis-related multiple organ failure (MOF) is the leading cause for prolonged intensive care unit (ICU) stays and deaths. Several lines of clinical evidence convincingly link gut injury and subsequent dysfunction to MOF [1]. First, patients who experience persistent gut hypoperfusion (documented by gastric tonometry) after resuscitation are at high risk for abdominal compartment syndrome (ACS), MOF, and death [2]. Second, epidemiologic studies have consistently shown that the normally sterile proximal gut becomes heavily colonized with a variety of organisms. These same organisms have been identified to be pathogens that cause late nosocomial infections. Thus, the gut has been called the ‘undrained abscess’ of MOF [3]. Third, gut-specific therapies (selective gut decontamination, early enteral nutrition (EN), and most recently immune-enhancing enteral diets) have been shown to reduce these nosocomial infections [4–7]. Of these gut-specific therapies, early EN is most widely employed. However, the most severely ill patients who should benefit most from early EN are frequently intolerant to it and are at increased risk for EN-related complications [8–11]. The purpose of this chapter will be to first provide a brief overview of why critically ill patients (using trauma patients as a model)
develop gut dysfunction and how gut dysfunction contributes to adverse outcomes. The discussion will then focus on the pathogenesis and clinical monitoring of specific gut dysfunctions that contribute to intolerance to EN. Based on this information, potential therapeutic strategies to prevent and/or treat gut dysfunction and to enhance tolerance to EN will be discussed.

How Gut Dysfunction Contributes to Adverse Patient Outcome

Multiple Organ Failure

A recent paradigm of post-injury MOF pathogenesis is depicted in figure 1 [12]. MOF occurs as a result of a dysfunctional inflammatory response and it occurs in two different patterns (i.e. early vs. late). After a traumatic insult, patients are resuscitated into a state of systemic hyperinflammation, now referred to as the systemic inflammatory response syndrome (SIRS). The intensity of SIRS is dependent upon (1) inherent host factors, (2) the degree of shock, and (3) the amount of tissue injured. Of the three, shock is the predominant factor [13]. Mild to moderate SIRS is most likely beneficial while severe SIRS can result in early MOF. As time proceeds, negative feedback systems downregulate certain aspects of acute SIRS to restore homeostasis and limit potential autodestructive inflammation. This latter response has recently been dubbed the compensatory anti-inflammatory response syndrome and results in delayed immunosuppression [14]. Mild to moderate delayed immunosuppression is clinically insignificant, but severe immunosuppression is associated with late infections. These late infections can worsen early MOF or precipitate late MOF.

Fig. 1. Postinjury MOF occurs as a result of a dysfunctional inflammatory response. SIRS = Systemic inflammatory response syndrome; ICU = intensive care unit; MOF = multiple organ failure; CARS = counter anti-inflammatory response syndrome; TPN = total parenteral nutrition.
The gut is believed to be both an instigator and victim of this dysfunctional inflammatory response (fig. 2) [1]. Shock is associated with obligatory gut ischemia [15]. With resuscitation, reperfusion results in a local inflammatory response that can injure the gut setting the stage for ACS (see below) [16]. Additionally, the reperfused gut releases mediators that amplify SIRS [17–19]. Moreover, for patients undergoing laparotomy, bowel manipulation and anesthetics cause further gut dysfunction [19]. Finally, standard ICU therapies (morphine, H2 antagonists, catecholamines, and broad-spectrum antibiotics) and intentional disuse (use of TPN rather than EN) promote additional gut dysfunction [20]. The end result is progressive dysfunction (table 1) characterized by gastroesophageal reflux, gastroparesis, duodenogastric reflux,

**Fig. 2.** The gut is the instigator and victim of a dysfunctional inflammatory response. SIRS = Systemic inflammatory response syndrome; MOF = multiple organ failure; CARS = counter anti-inflammatory response syndrome.

<table>
<thead>
<tr>
<th>Table 1. Progressive gut dysfunction in critically ill patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gastroesophageal reflux/aspiration</td>
</tr>
<tr>
<td>Gastroparesis</td>
</tr>
<tr>
<td>Duodenogastric reflux</td>
</tr>
<tr>
<td>Gastric alkalinization</td>
</tr>
<tr>
<td>Decreased mucosal perfusion</td>
</tr>
<tr>
<td>Impaired intestinal transit</td>
</tr>
<tr>
<td>Increased colonization</td>
</tr>
<tr>
<td>Increased permeability</td>
</tr>
<tr>
<td>Decreased mucosal immunity</td>
</tr>
</tbody>
</table>

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gastric alkalization, decreased mucosal perfusion, and impaired intestinal transit. As time proceeds, the normally sterile upper gut becomes heavily colonized, mucosal permeability increases and local mucosal immunity decreases [21–23]. Intraluminal contents (e.g. bacteria and their toxic products) then disseminate by aspiration or translocation to cause systemic sepsis which then promotes further gut dysfunction [24, 25].

**Abdominal Compartment Syndrome**

Intra-abdominal pressure (IAP) is monitored by urinary bladder pressure (UBP) measurements and when UBP exceeds 25 cm H₂O, extra-abdominal organ functions may become impaired. By definition, this is ACS. There are two types of ACS: primary and secondary [2]. Primary ACS occurs in patients with abdominal injuries that typically have undergone ‘damage control’ laparotomy (where obvious bleeding is rapidly controlled and the abdomen is packed) and have entered the ‘bloody viscus cycle’ of coagulopathy, acidosis, and hypothermia which promotes ongoing bleeding. Accumulation of blood, worsening bowel edema from resuscitation, and the presence of intra-abdominal packs all contribute to increasing IAP that causes ACS. Secondary ACS occurs when an extra-abdominal injury (e.g. pelvic fracture or mangled
extremity) requires massive resuscitation which causes bowel edema which increases IAP to cause ACS. Markedly elevated IAP also decreases gut perfusion which may adversely affect a variety of gut functions. ACS is a harbinger of MOF and failure to promptly recognize and treat it contributes to bad outcomes.

**Nonocclusive Small Bowel Necrosis**

Nonocclusive small bowel necrosis (NOBN) is a relatively rare, but frequently fatal entity that is associated with the use of EN in critically ill patients [11]. Patients typically present with complaints of cramping abdominal pain, progressive abdominal distention associated with SIRS. Computed tomography will reveal a thickened dilated bowel with pneumatosis intestinalis. For those who progress and require exploratory celiotomy, extensive patchy necrosis of the small bowel is found. Pathologic analysis of the resected specimens yields a spectrum of findings from acute inflammation with mucosal ulceration to transmural necrosis and multiple perforations. The consistent association with EN indicates that inappropriate administration of nutrients into a dysfunctional gut plays a pathogenic role. There are two popular hypotheses. First, metabolically compromised enterocytes become adenosine triphosphate (ATP) depleted as a result of increased energy demands induced by the absorption of intraluminal nutrients [26]. The second hypothesis is that when nutrients are delivered into the dysmotile small bowel, fluid shifts into the lumen as a result of the presence of hyperosmolar enteral formula. Additionally, CO₂ may be produced as a result of fermentation of carbohydrates by colonized bacteria. Increased intraluminal fluid and gas cause small bowel distention which, when massive, causes hypoperfusion [11].

**How Gut Dysfunctions Contribute to Intolerance to Enteral Nutrition**

The gut is a complex organ that performs a variety of functions, some of which are vital for ultimate survival of critically ill patients (e.g. barrier function, immune competence, and metabolic regulation). Unfortunately, gut dysfunction in critically ill patients is poorly characterized and routine monitoring of gut function is crude. Currently, the best parameter of gut function is tolerance to EN. For several reasons, this is an attractive parameter to monitor and potentially modulate. First, tolerance to EN requires integrative gut functioning (e.g. secretion, digestion, motility, and absorption). Second, locally administered nutrients may improve perfusion and optimize the recovery of other vital gut functions (e.g. motility, barrier function, mucosal immunity) [27, 28]. Third, tolerance correlates with patient outcome and improving tolerance will likely improve patient outcome. Fourth, refined
Gut Dysfunction and Intolerance to Enteral Nutrition

therapeutic interventions to improve EN tolerance will lessen the need to use TPN and decrease EN-associated complications.

Of the gut dysfunctions outlined in table 1, gastroesophageal reflux (GER), gastroparesis, decreased mucosal perfusion, impaired intestinal transit, and impaired gut absorptive capacity (GAC) are likely contributors to intolerance to EN. A brief overview of the pathogenesis of each of these dysfunctions and how they are monitored clinically will be reviewed to provide the rationale for proposed therapeutic strategies to improve tolerance to EN.

**Gastroesophageal Reflux**

GER is an important contributing factor to aspiration of EN which is a common cause of pneumonia in ICU patients. Reflux will occur whenever the pressure difference between the stomach and esophagus is great enough to overcome the resistance offered by the LES. Increases in gastric pressure can be due to distention with fluids and failure of the stomach to relax to accommodate fluid. Decreases in resistance at the lower esophageal sphincter (LES) can be due to relaxation of LES muscle in response to many stimuli including mediators released during injury and resuscitation [29]. Additional contributing factors include: (a) forced supine position; (b) the presence of a nasoenteric tube; (c) hyperglycemia, and (d) morphine.

Commonly used clinical monitors include laboratory testing for the presence of glucose in tracheal secretions or by observing blue food dye (BFD) which has been added to the enteral formula in tracheal aspirates [30]. Detection of glucose lacks specificity. False-positive results can occur with high serum glucose levels or the presence of blood in tracheal secretions. The use of BFD is poorly standardized and lacks sensitivity. More importantly, however, several reports document absorption of BFD in critically ill patients and is associated with death. This is presumably due to a toxic effect that BFD has on mitochondrial function. A recent consensus conference recommended that both of these techniques be abandoned [31]. Unfortunately, there are no simple monitors of GER other than observing for vomiting or regurgitation which are not very sensitive. The head of the bed should be elevated 30–45° to decrease the risk that, when GER occurs, it is less likely to result in pulmonary aspiration. Gastric residual volumes (GRVs; see below) should be monitored with the presumption that a distended stomach will lead to a higher volume GER.

**Gastroparesis**

Recent studies have confirmed that gastroparesis is common in ICU patients [32]. Gastroparesis predisposes for increased duodenogastric reflux (a potential contributing factor for gastric alkalinization) and GER (a contributing factor for aspiration). The mechanisms responsible for gastroparesis in critical illness have not been well studied. Potential factors
include: (a) medications (e.g. morphine, dopamine); (b) sepsis mediators (e.g. nitric oxide); (c) hyperglycemia, and (d) increased intracranial pressure.

The common clinical monitors for gastroparesis are intermittent measurement of GRVs when feeding into the stomach or measurement of continuous suction nasogastric tube output when feeding postpylorically. The practice of using GRVs is poorly standardized and is a major obstacle to advancing the rate of EN [33]. GRVs appear to correlate poorly with gastric. GRVs of \(<200 \text{ cm}^3\) generally are well tolerated. GRVs of \(200–500 \text{ cm}^3\) should prompt careful clinical assessment and the initiation of a prokinetic agent. With GRVs of \(>500 \text{ cm}^3\), EN should be stopped. After clinical assessment excludes small bowel ileus or obstruction, placement of a post-ligament of Treitz feeding tube should be considered.

**Impaired Mucosal Perfusion**

Shock results in disproportionate splanchnic vasoconstriction. The gut mucosa appears to be especially vulnerable to injury during hypoperfusion. The arterioles and venules in the small bowel mucosal villi form ‘hairpin loops’ [34]. This anatomic arrangement improves absorptive function, but it also permits a countercurrent exchange of oxygen from the arterioles to the venules in the proximal villus. Under hypoperfused conditions, a proximal ‘steal’ of oxygen is believed to reduce the \(pO_2\) at the tip of the villi to 0. The gut mucosa is further injured during reperfusion by reactive oxygen metabolites and recruitment of activated neutrophils. This mucosal injury, however, appears to repair itself rather quickly. Mucosal blood flow, however, does not always return to baseline with resuscitation and this is in part due to defective vasorelaxation [35]. The gut mucosa is also vulnerable to recurrent episodes of hypoperfusion from ACS, sepsis, and the use of vasoactive drugs. Whether recurrent hypoperfusion results in additional ischemia/reperfusion injury is not known, but it is reasonable to assume that hypoperfusion would decrease gut nutrient absorption and render the patient more susceptible to NOBN.

Monitoring gastric mucosal perfusion in the clinical setting can be done by gastric tonometry [15]. With hypoperfusion, intramucosal \(CO_2\) increases due to insufficient clearance of \(CO_2\) produced by aerobic metabolism or due to buffering of extra hydrogen ions produced in anaerobic metabolism. As intramucosal \(CO_2\) accumulates, it diffuses into the lumen of the stomach. The tonometer measures the \(CO_2\) that equilibrates in a saline-filled balloon (a newer monitor uses an air-filled balloon) that sits in the stomach. This is the regional \(CO_2\) tension (Pr\(CO_2\)) and is assumed to equal the intramucosal \(CO_2\) tension. Using this measured Pr\(CO_2\) and assuming that arterial bicarbonate equals intramucosal bicarbonate, the intramucosal pH (pHi) is calculated by using the Henderson-Hasselbalch equation. Numerous studies have documented that a persistently low pHi (or high Pr\(CO_2\) level) despite effective systemic resuscitation predicts adverse outcomes. Unfortunately, alternative
resuscitation strategies have not been able to increase pH to improve outcome and thus this monitoring tool is in search of a novel application. We have found the new Tonocap which is a combined capnograph and semi-continuous air tonometer to be useful in identifying patients early in resuscitation who are at high risk of developing ACS. After resuscitation, we have also found it to be valuable in identifying patients who will not tolerate EN. If PrCO₂ is high (>90 mm Hg) we do not start EN. If PrCO₂ is low, but rises with initiation of EN, we proceed cautiously in the advancement of rate of feeding.

**Impaired Intestinal Transit**

Laboratory models of shock, bowel manipulation and sepsis demonstrate that small bowel transit is impaired [19, 24, 36]. In all of these models, cytokines and other mediators are produced by cells in the intestine that impair enteric nerve and/or intestinal smooth muscle function [24, 37]. This impairment in turn is expressed as a decrease in the number and/or force of contractions, or as an abnormal pattern of contractions. Although the results in animal models are convincing, surprisingly, clinical studies indicate that small bowel motility and transit are more often than not well preserved after major elective and emergency laparotomies [10]. This observation coupled with the observation that small bowel absorption of simple nutrients is relatively intact provided the rationale for early jejunal feeding.

Clinical studies have documented that over 85% of critically ill patients tolerate early jejunal feeding [8, 9]. In a recent study, severely injured patients had jejunal manometers and feeding tubes placed at secondary laparotomy [10]. Surprisingly, 50% had fasting patterns of motility that included components of the normal migrating motor complexes (MMCs). These patients tolerated advancements of EN without problems. The other 50% who did not have fasting MMCs did not tolerate early advancement of EN. Of note, none of the patients converted to a normal fed pattern of motility once they reached full-dose enteral feeding. This could be due to infusion of caloric loads insufficient to bring about conversion. On the other hand, the failure to develop fed activity, a pattern of motility promoting mixing and absorption, might explain why diarrhea is a common problem in this patient group.

Although manometry can be used to monitor motility, it is not practical. Unfortunately, simpler indicators of motility such as the presence of bowel sounds or the passing of flatus are unreliable. Other, minimally invasive methods to monitor transit are needed. Contrast studies through the feeding tubes are relatively simple, but not validated.

**Impaired Gut Absorptive Capacity**

Small bowel absorption of glucose and amino acids is depressed after trauma and sepsis [38]. Multiple factors have been identified including: (a) cytosolic calcium overload; (b) ATP depletion; (c) diminished brush border enzyme activity; (d) decreased carrier activity; (e) decreased absorptive
epithelial surface area, and (f) hypoalbuminemia. In a recent animal study [26], intestinal ischemia/reperfusion caused significant mucosal injury and significant depletion of mucosal ATP. When this was combined with exposure of the bowel to alanine, the damage and ATP depletion were more severe and the absorption of glucose was impaired. In contrast, exposure of the bowel to glucose or glutamine preserved the ATP level, protected against mucosal injury and improved GAC.

The clinical significance of these observations remains unclear since most patients tolerate EN when delivered into the small bowel. However, decreased GAC may be a cause for diarrhea and may explain why patients commonly experience diarrhea with reinitiation of EN after prolonged bowel rest. Unfortunately, there are no clinical monitors for GAC.

Diarrhea may be indicative of depressed GAC, but there are other causes for diarrhea in the critically ill including: impaired transit (described above); bacterial overgrowth (e.g. reduced short-chain fatty acid (SCFA) production or the presence of Clostridium difficile); contaminated enteral formulas; abnormal colonic responses to EN (e.g. ascending colon secretion rather than absorption, or impaired distal colon motor activity), and administration of drugs which contain sorbitol (e.g. medical elixirs) or magnesium (e.g. antacids).

Strategies to Improve Tolerance of Enteral Nutrition

Gut-Specific Resuscitation

If shock-induced gut hypoperfusion is assumed to be a prime inciting event for gut dysfunction, then resuscitation protocols need to be devised to optimize early gut perfusion and prevent reperfusion injury. Traditional resuscitation is aimed at optimizing systemic perfusion and the standard of care is to first administer 50 ml/kg of isotonic crystalloids (3 liters in the normal adult), then to add packed red blood cells (PRBCs) to the regimen at a ratio of 3:1 crystalloid:blood. While this approach is effective in most patients, it is associated with problematic bowel edema in patients at high risk for MOF. Alternative resuscitation strategies to reduce reperfusion injury and reduce bowel edema may include the earlier use of PRBCs or new blood substitutes and to use hypertonic saline or colloids instead of isotonic crystalloids.

How bowel edema effects bowel function needs to be better clarified. However, it is reasonable to assume that a grossly edematous bowel will have abnormal motility and not optimally absorb nutrients. With more severe bowel wall edema, patients develop IAP which can worsen bowel perfusion and set up a vicious cycle that leads to ACS. Routine UBP monitoring is recommended with massive resuscitations. We and others have also found that gastric tonometry is valuable in early identification of ACS.
**Enteral Feeding Protocols**

Once resuscitation is judged to be complete, enteral access should be obtained. Controversy exists over the optimal level of feeding (i.e. stomach vs. duodenum vs. jejunum). While comparative trials do not exist, clinical experience shows that feeding past the ligament of Treitz (via surgically placed jejunostomy or endoscopically placed nasojejunal tubes) is highly successful [8, 9]. While we recommend jejunal feeding in high-risk patients, access past the ligament of Treitz is not readily available in most ICUs. Recent trials that have compared gastric to duodenal feeding are underpowered, but collectively they show that duodenal feeding more rapidly achieves nutritional goals and reduces the risk for aspiration [39–41]. Regardless of the level of feeding, all patients should have the head of the bed elevated (reverse Trendelenburg preferred) to 30–45° to reduce the risk of aspiration. Feeding should be started at a low rate (e.g. 15 cm³/h) of continuous infusion and advanced at set intervals (e.g. every 8–12 h) to a modest goal (60 ml/h) while monitoring and treating signs and symptoms of intolerance (tables 3, 4). When feeding into the stomach, fear of aspiration is a major concern and increased GRV is the primary reason that limits advancement of the rate of feedings. On the other hand, diarrhea and abdominal distention are the major problems encountered in postpyloric feeding. Diarrhea can generally be successfully managed (table 4), but distention is not as amenable to intervention and may be the harbinger of NOBN.

Of note, the goals of early EN have changed. Traditionally, EN was rapidly advanced to high rates (125–150 cm³/h) to place the patient in positive caloric and nitrogen balance as soon as possible so as to prevent acute protein malnutrition. This rapid advancement is associated with high rates of intolerance and failure of EN. However, it appears that early EN exerts beneficial effects at lower rates of infusion (i.e. 60 cm³/h) presumably by promoting vital gut functions (motility, mucosal immunities and barrier function) and enhancing systemic immunity. Advancement beyond 60 cm³/h to place the patient in positive caloric and nitrogen balance should be done slowly over the first week of ICU treatment. If patients cannot achieve 60% of this targeted goal by ICU day 7, concurrent TPN should be started.

Clinical studies have demonstrated that clinical signs of NOBN are not reliable [11]. This rare but devastating complication can occur when the clinical status of the patient deteriorates. For patients who are at perceived high risk for NOBN (table 4), EN should be temporally stopped and if the condition persists low-dose (15 cm³/h) elemental formulas with high glucose and glutamine levels are initiated.

**Modified Enteral Formulas**

The earliest enteral diets used in critically ill patients were formulated (i.e. elemental amino acids, low fat) to enhance tolerances. It has subsequently been observed that critically ill patients can tolerate more complex formulas
**Table 3. Monitoring and management of intolerance to enteral nutrition**

<table>
<thead>
<tr>
<th>Indicator</th>
<th>Severity</th>
<th>Definition</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vomiting</td>
<td>(witnessed)</td>
<td>Gastric contents in oropharynx</td>
<td>Place NG suction catheter, check oropharynx function</td>
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<td></td>
<td></td>
<td></td>
<td>Check existing NG function</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>Decrease TF infusion rate by 50%</td>
</tr>
<tr>
<td>High NG tube output (for post-pyloric feeding)</td>
<td>(measured)</td>
<td>&gt;1,200 cm³/12 h</td>
<td>Check existing X-ray for post-pyloric placement of feeding tube</td>
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<td></td>
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<td></td>
<td>If &gt;48 h since last X-ray, order KUB</td>
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<td></td>
<td></td>
<td></td>
<td>If not tube post-pyloric, hold TF order new feeding tube placement</td>
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<td></td>
<td></td>
<td></td>
<td>Check NG aspirate for glucose</td>
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<td></td>
<td></td>
<td></td>
<td>If glucose present and feeding tube post-pyloric, hold TF and reassess in 12 h</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>Retest NG aspirate for glucose 12 h</td>
</tr>
<tr>
<td>High gastric residual volumes (for gastric feeding)</td>
<td>Mild</td>
<td>75–200 cm³</td>
<td>Tighten glycemic control</td>
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<td></td>
<td></td>
<td></td>
<td>Minimize narcotics</td>
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<tr>
<td></td>
<td>Moderate</td>
<td>200–500 cm³</td>
<td>As above</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>Prokinetics</td>
</tr>
<tr>
<td></td>
<td>Severe</td>
<td>&gt;500 cm³</td>
<td>Stop gastric feeding</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Clinical assessment</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Post ligament of Treitz tube</td>
</tr>
<tr>
<td>PrCO₂ by tonometry</td>
<td>Moderate</td>
<td>70 mm Hg &lt; PrCO₂ &lt; 90 mm Hg &gt;8 h</td>
<td>Change to elemental diet at present rate and advance as per protocol</td>
</tr>
<tr>
<td>If patient is in permissive hypercapnia (PrCO₂ &gt;50 mm Hg)</td>
<td></td>
<td></td>
<td>If already on elemental diet, continue to advance as per protocol</td>
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<td></td>
<td></td>
<td>or</td>
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<tr>
<td></td>
<td></td>
<td>PrCO₂–PaCO₂ gap = 30–50 mm Hg</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Severe</td>
<td>PrCO₂ &gt; 90 mm Hg for &gt;8 h</td>
<td>Stop TF infusion</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>Re-evaluate in 6 h</td>
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<tr>
<td></td>
<td></td>
<td>or</td>
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<tr>
<td></td>
<td></td>
<td>PrCO₂–PaCO₂ gap &gt; 50 mm Hg</td>
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<td></td>
<td></td>
<td></td>
<td>If PrCO₂ is still severe, start elemental formula at 15 ml/h and advance per protocol</td>
</tr>
</tbody>
</table>
**Table 4.** Monitoring and management of intolerance to enteral nutrition

<table>
<thead>
<tr>
<th>Indicator</th>
<th>Severity</th>
<th>Definition</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abdominal distention and/or cramping or tenderness (if detectable)</td>
<td>Mild</td>
<td>Hx and/or PE</td>
<td>Maintain TF infusion rate Re-examine in 6 h</td>
</tr>
<tr>
<td></td>
<td>Moderate</td>
<td>Hx and/or PE</td>
<td>Stop TF infusion Order AP supine KUB X-ray – assess for small bowel obstruction if SBO, notify primary team Place gastric tonometer NG catheter – replace existing NG catheter if not gastric tonometer Re-examine in 6 h If moderate distension for ≥24 h, switch to elemental for 72 h</td>
</tr>
<tr>
<td></td>
<td>Severe</td>
<td>Hx and/or PE</td>
<td>Stop TF infusion Set i.v. fluid infusion rate = 250 ml/h Consider CBC, lactate, ABG, Chem7, CT scan abdomen</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>Mild</td>
<td>1–2 × per shift or 100–200 cm³/12 h</td>
<td>Maintain or increase TF infusion rate per protocol</td>
</tr>
<tr>
<td></td>
<td>Moderate</td>
<td>3–4 × per shift or 200–300 cm³/12 h</td>
<td>Maintain TF infusion rate Re-examine in 6 h</td>
</tr>
<tr>
<td></td>
<td>Severe</td>
<td>&gt;4 × per shift or &gt;300 cm³/12 h</td>
<td>Decrease TF infusion rate by 50% Give diphenoxylate/atropine (Lomotil) 10 cm³ every 6 h via feeding tube Review MAR; note antibiotic, other GI drugs Order stool studies; fecal leukocytes, toxin assays If persistent (with diphenoxylate/atropine) &gt;48 h, switch to elemental feeding</td>
</tr>
<tr>
<td>Perceived high risk for nonocclusive bowel necrosis</td>
<td>Inotropes</td>
<td>Low dose</td>
<td>Re-assess 6 h Stop EN if clinical course worsening</td>
</tr>
<tr>
<td></td>
<td></td>
<td>High dose</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Vasopressors</td>
<td>Norepinephrine, phenylephrine</td>
<td>Start elemental diet at 15 cm³/h and do not advance</td>
</tr>
</tbody>
</table>
Table 4. (continued)

<table>
<thead>
<tr>
<th>Indicator</th>
<th>Severity</th>
<th>Definition</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Epinephrine, high-dose dopamine</td>
<td></td>
<td></td>
<td>Reassess in 24 h</td>
</tr>
<tr>
<td>Worsening respirator failure</td>
<td></td>
<td>Start elemental diet at 15 cm³/h and do not advance</td>
<td></td>
</tr>
<tr>
<td>Prone position</td>
<td></td>
<td></td>
<td>Reassess in 24 h</td>
</tr>
<tr>
<td>Paralytics</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intermittent dialysis</td>
<td></td>
<td>Start elemental diet at 15 cm³/h and do not advance</td>
<td></td>
</tr>
<tr>
<td>With hypotension Or need for vasopressors</td>
<td></td>
<td></td>
<td>Reassess in 24 h</td>
</tr>
</tbody>
</table>

and that the use of new immune-enhancing formulas is associated with better outcomes. Research needs to be done on determining how to modify these formulas to enhance tolerance in the most stressed patient. For example, the addition of soluble fiber to standard enteral formulas may decrease the incidence of diarrhea. Pectin and partially hydrolyzed guar are soluble fibers that are fermented in the colon to produce SCFAs [42]. SCFAs have positive trophic effects on colonocytes and promote water absorption. Other proposed mechanisms by which fibers may decrease diarrhea is by prolonging intestinal transit time, decreasing Clostridium difficile toxin production and by binding bile salts.

**Prokinetic Agents**

Because gastroparesis and ileus are commonly seen postoperatively and following resuscitation, and because they can complicate initiation of enteral feeding, agents to ‘normalize’ gastrointestinal (GI) motility have been sought [43, 44]. Evaluation of such prokinetic agents is difficult because it is not enough to just stimulate contractions. Contractions at adjacent sites must be coordinated in order for normal digestion, absorption, and transit to take place. Coordinated contractions are under the control of hormonal and neural, both central and peripheral, pathways and it is these pathways that are affected by the cytokines and other mediators that are upregulated following a traumatic insult [45]. Prokinetic strategies are aimed at either blocking these mediators or of overriding them by stimulating normal pathways.

**Opiate Antagonist.** One major cause of ileus is stimulation of opioid receptors. Stress provokes release of endogenous opioids and opioids are the most common treatment for pain in ICU patients. In animal models and humans, both endogenously released and exogenously administered opioids
act on receptors in both the central nervous system (CNS) and in the enteric nervous system (ENS) to alter intestinal function, especially motility [46]. Although actions at both the CNS and ENS are involved, recent studies indicate that if opioid actions at the ENS are blocked, ileus may be prevented or resolved without interfering with the desired opioid actions on the CNS and other systems. An investigational opioid receptor antagonist that has limited systemic absorption after oral administration and minimal access to the CNS has been shown to speed recovery of bowel function and shorten the duration of hospitalization after surgery [47]. This study needs to be expanded to include additional patients, especially those who have undergone resuscitation.

Erythromycin. Agents like erythromycin that act on receptors for motilin, the naturally occurring hormone responsible in part for regulating normal GI motility, have been shown to enhance gastric emptying and intestinal transit in animal models and in some clinical trials. However, their effectiveness postoperatively has been disappointing [42, 43, 48]. In addition, in animal studies, the dose of erythromycin that can initiate an MMC is close to that which can induce nausea and vomiting [49]. If the same occurs in humans, this will limit its usefulness. Other ‘motilides’ are under investigation, but their usefulness has not been established.

Serotonin (5-HT) Antagonists and Agonists. One of the major transmitters within the ENS is serotonin. By acting at various serotonin receptors, it can either enhance or inhibit intestinal contractions and transit. In animal and some human studies, motility has been enhanced by 5-HT₃ receptor antagonist and by 5-HT₄ agonists [50]. Although the results were never that impressive or consistent, a few agents have been used in clinical situations. Side effects, however, have resulted in their being removed from the market. Still, this is a fertile area for future research.

Antioxidants
The cycle of organ hypoperfusion during shock followed by reperfusion following resuscitation results in the formation of reactive oxygen species that are detrimental. Thus, it is logical to propose that administration of antioxidants could prove beneficial. In many animal models, administration of agents such as superoxide dismutase, ethyl pyruvate, and melatonin limit damage induced by ischemia/reperfusion [51, 52]. In a recent study, administration of α-melanocyte-stimulating hormone to rats preserved both the function and the structural integrity of the intestine following mesenteric ischemia/reperfusion [36].

Probiotics and Prebiotics
A probiotic is defined as a live microbial feed supplement which beneficially affects the host by improving its intestinal microbial balance [53]. Probiotics are most commonly lactobacilli, bifidobacteria or saccharomyces and are available in the form of powders, capsules, and enriched yoghurts.
A prebiotic is defined as a nondigestible food ingredient that beneficially affects the host by selectively stimulating the growth and/or activity of specific bacteria in the colon. Probiotics are usually nondigestible oligosaccharides. The most extensively studied are the fructoligosaccharides (FOS) such as oligofructose and inulin. FOS are fermented in the colon which promotes the proliferation of bifidobacteria with a reduction in clostridia and fusobacteria. Manipulation of the colonic microflora may reduce the incidence of EN-associated diarrhea by suppressing enteropathogens and by producing SCFA.

References

33. McClave SA, Snider HL. Clinical utility of gastric residual volumes as a monitor for patients on enteral tube feeding. JPEN J Parenter Enteral Nutr, in press.


**Discussion**

*Dr. Martindale:* Do you think we should all be using a tonometer routinely in our intensive care units (ICUs)?

*Dr. Moore:* It isn’t that practical. The tonometer is an attractive concept but we would hope that in some future studies we could provide some good data. This is our experience: we do it routinely in all our shock resuscitation patients. They have a tonometer in, it stays until we get the patients up to their full dose of enteral nutrition and then the tonometer is removed.

*Dr. Peeters:* I might add that some of the data that we showed on tonometry came from our hospital, and I must say that it is an enormous burden of work when you have to use those things. I don’t think it is very practical.

*Dr. Chioléro:* I have a further question on gastric tonometry. If I correctly understood, in patients with an increased CO₂ gap, you would not start early feeding or you would be more cautious?

*Dr. Moore:* There are levels that make us nervous: A PrCO₂ of 70 would make me be cautious, but above 90 we would not feed. Most of our patients after shock resuscitation are in the 50–60 range, so we would start feeding and watch and see where the PrCO₂ goes to. Now I must make a comment for people who are unfamiliar with this technology. The saline tonometry was extremely labor intensive. Gas tonometry is a nasogastric tube through which you intermittently put gas down into the balloon and you aspirate it back and analyze it like end tidal CO₂. So it is not as labor intensive as the saline technology.

*Dr. Ribeiro:* Regarding those patients with nonocclusive bowel ischemia which developed late related to enteral nutrition, did you consider the possibility of a certain degree of intolerance from the beginning that you could have assessed?

*Dr. Moore:* Since we have refined this enteral feeding protocol we haven’t seen any cases of this. What we have learned, and I think Dr. Kudsk mentioned it earlier, is that when somebody suddenly gets septic, the first thing you have to do is turn off the enteral feeding. The second thing is if you start advancing in care and you can’t assess tolerance, then you should stop enteral feeding. So when we start getting critical hypoxemia and start flipping people over in the bed and paralyzing them, I am a little skeptical that enteral nutrition is going to change the outcome of that patient, and I certainly don’t want to contribute to their demise. So we have set criteria where we cut back to 15 cm³/h. Actually we give the patients Gatorade based upon the work that
Dr. Kozar did in the laboratory, and then we would wait a day or so and see if the patients get better. If they don't get better then we would start supplement with total parenteral nutrition (TPN).

**Dr. Cynober:** I understand that initial resuscitation is something crucial to protect against gut injury and I would like to know the importance of very early resuscitation. For example in a number of countries the dogma is to transport the patient as soon as possible to emergency units or ICUs, and in other countries the dogma is to make the initial resuscitation on site. Is there some objective data about the timing of initial resuscitation on gut function and metabolic alterations?

**Dr. Moore:** A major limitation in our resuscitation strategies is that we focus on systemic resuscitation and there has not been any emphasis to think about how you could decrease edema and inflammation in the gut. Therefore I think that earlier resuscitation would be advantageous, in fact that is what our data show. Abdominal compartment syndrome is the most extreme form of shock-induced gut dysfunction, and when these patients come to our ICU they have it. This means that we need to get a hold of these patients earlier on and begin to do more judicious resuscitation that is really directed at limiting this gut edema. We can argue about crystalloids versus colloids, and we certainly could argue for a long time about it, but it is the American standard to give crystalloids. In our basic laboratory models it is very surprising how efficacious hypertonic saline is. We can totally abrogate the impaired transit with gut ischemia reperfusion, the influx of neutrophils, protection of mucosa, and so we are quite interested in using hypertonic saline to try to figure out the mechanisms that are causing the inflammation in the gut. I assume that other resuscitation fluids could be equally good. We are interested in hemoglobin solutions. I think at some point they will become available to us. They are probably going to allow you to perfuse the gut better. So you have this defect in vaso-relaxation, the gut is vaso-constricted, the artificial hemoglobin solution should actually perfuse the gut a lot better than the resuscitation we have currently.

**Dr. Berger:** About gut edema, do you have any data from your patients regarding absorption capacity of that gut?

**Dr. Moore:** Gut absorption is a very difficult thing to quantitate and we actually had a methodology to look at gut absorption but it did not work out. In the laboratory when we looked at gut edema and its affect on absorption using the Ussing chamber. The gut edema adversely affects transit but that level of gut edema does not seem to affect the Ussing chamber numbers. The problem with the Ussing chamber is that it is really a tissue that is sort of dying as you are studying it, so sometimes it is difficult to know whether it is accurate or not, but that is the best we understand at the animal level.

**Dr. Planas:** Sorry, but I was unable to see in your protocol at what frequency you monitor the gastric residual volume in your patients? Second question, is it not too high to wait until 400 ml to stop enteral nutrition? And third, what do you do with the gastric residual?

**Dr. Moore:** I think I will refer this to Dr. McClave since he is the person who has the most experience with this.

**Dr. McClave:** We have just finished a study in which we put yellow colometric microspheres into the formula and infused them into the stomach, and then every 4 h we checked the residual volumes. The patients were on ventilation so we checked the tracheal and oropharyngeal secretions, and then we could put the secretions under a fluorometer and we knew exactly when the yellow bits were coming from the stomach after the oropharynx and the trachea. In the range of residual volumes of at least 400 cm³, there was absolutely no correlation between gastric residual volumes and whether they were aspiring or regurgitating. They were regurgitating 30% of the time, aspiring about 22% of the time and there was no connection. So I think it is one of
these monitors that is not a good marker of tolerance, and I think it results in more inappropriate sensation.

Dr. Zazzo: In your last study did you correlate the presented enteral tolerance with the volume of resuscitation and/or duration of shock and/or systemic acidosis or lactate level?

Dr. Moore: We did not do that because in the end the study was not large enough to make any of those correlations. Most of the patients that go into that resuscitation protocol receive in excess of 15 units of blood and for every unit of blood they are receiving at least 1 liter of crystalloid, so that is the degree of shock. Most of those people start off with a lactate level that is somewhere in the range of about 5. At the end of resuscitation we don’t always normalize lactate, and that is usually a predictor of pretty bad outcome.

Dr. Allison: We think of the capillary permeability being increased with injury in shock, and this creates the appearance of edema in the skin when you resuscitate. But the starling balance across the capillary membrane is different in the skin and the gut. For example, in the liver it is very much in favor of leaking and a fast flux. I don’t quite recall whether there are any data on the gut itself. In other words the gut may be even more vulnerable to edema than the systemic tissues.

Dr. Moore: It is somewhere between the skin and the liver. It is actually kind of interesting when you operate on these patients because some of them don’t have gut edema and other ones really get bad edema. One of our pediatric surgeons is interested in this. His animal models have shown that it is intra-abdominal hypertension in ranges that you and I wouldn’t be nervous with which should be about 15. A bladder pressure of 15 would cause venous obstruction. When you have this venous obstruction and you start resuscitating the patient more, you just get into this crystalloid loading because the reason we are doing it is because they have high intra-abdominal pressures. So we continue to volume load them, the pressure is going higher and then somewhere in the range of 25 or 30 the lymphatics turn off because of pressure, and then you get really bad edema. So I think that what we learned from our resuscitation protocol is that when those patients get those high intra-abdominal pressures we have to really rethink what we are doing, and I don’t know if decompressing the abdomen of everybody is going to be appropriate. But there are things like paralyzing somebody to reduce the intra-abdominal pressure; you can go to inotropes, or colloids. While there is a US bias that we shouldn’t use a lot of colloids, we would like to study this more in animals before we start doing it in people.

Dr. Carlson: The practice of open abdomen surgery or damage control surgery in the US is very different to the UK. In the UK we have used the open abdomen exclusively in the management of severe abdominal sepsis. But our experience in the UK has been rather different in that we tend leave the abdomen really open, whereas I noticed in one of your slides you had a kind of piece of plastic which looked pretty tight. I guess the question is to what extent do you think you might be able to abrogate some of these problems by literally completely leaving the abdomen open and decompressing it.

Dr. Moore: In that particular patient, when that bag was placed it was extremely loose, and I guess we and other US surgeons have evolved this from when we do damage control. The idea was that you stop the bleeding by putting the packs in and then you would tamponade the abdominal bleeding, intentionally causing a lot of pressure. That would really set you up to get an abdominal compartment syndrome because then you go back to the ICU, increased bladder pressure, start some more bleeding, and then you have intra-abdominal hypertension. So what the dogma is now is that we should place bags on everybody. Despite that, we are seeing this problem occurring in that particular patient, he really did have bladder pressures that had gone to high levels, and he had to be taken back and have a bigger
Dr. Déchelotte: It makes sense not to overfeed a gut when the early phase of vasorelaxation has not yet occurred, but on the other hand I was told this morning that it contributes to systemic inflammatory response syndrome. So what would you expect from a combination of nutrients to be given very early to this kind of patient to enhance some vasorelaxation. There are a few papers with glutamine in ischemic reperfusion with the enteral blood flow in nonstressed animals. In your trauma models did you check whether you could enhance that?

Dr. Moore: It is very hard in the patients to prove that the gut is priming the systemic neutrophils because we would have to have a catheter in the portal vein or in the lymphatics. But what we know is that, when we look at circulating neutrophils, the priming starts within 3 h of resuscitation. It peaks at about 12 h and at about 24 h it starts coming down. After 24 h the circulating neutrophils don't work anymore, and that is because all the ones that are dangerous have already sequestered in the lung. So unless you are going to do something very early, like in the helicopter. This will be feasible in the future, right now I don't know how we would deliver that. I assume we could give some sort of intraluminal something to stop it or intravenous injection to stop the ischemia reperfusion insult to the gut.

Dr. Rosenfeld: What is your comment about active oxygen saturation when you evaluate the gut perfusion, SHO₂?

Dr. Moore: I have no experience on that. Enlighten me how that might work.

Dr. Rosenfeld: There is some work from Takala about the SHO₂ and vasoactive drugs to improve gut perfusion.

Dr. Moore: That requires the placement of some fairly sophisticated catheters. If I recall his studies he was measuring hepatic venous outflow, and to do that you have to have a special catheter that can be flooded into the liver. He did show interesting results that inotropes and vasodilators, which we would normally think would improve gut perfusion, really were harmful. So a lot of what we do in clinical medicine, we don't really understand the effects on the gut.

Dr. Rosenfeld: We don't have very good data because tonometry is controversial too. You showed excellent data right now and we are measuring intra-abdominal pressure to better resuscitate our patients and we see this as a way to monitor, but we need to monitor gut perfusion to better check if the gut is really in a good situation to enterally feed these patients.

Dr. Moore: I actually have recruited a bioengineer and his project is going to take all the available monitoring techniques that we can think of, and start trying them, because at this point they really are extremely crude. We put an nasogastric tube into somebody, we feel and we listen to their abdomen, which is a pretty crude approach to figure out what is happening to the gut. We hope that in the future we will come across with some easy way to monitor. I actually think if we could find a good way of identifying gut motility that would be a good sign of who could be fed, so that is what the manometry data shows us.

Dr. Martindale: What do you think about the optimal substrate? You mentioned you gave Gatorade at 15 cm³/h. Why aren't you using something like glutamine? I think your own data show that glutamine is beneficial.

Dr. Moore: We will have more definitive data. Gatorade is just sugar and salt, it can't hurt anybody. When we place patients on low-dose elemental diets, the Gatorade was cheaper.

Dr. McClave: An issue of the goal of enteral feeding is what volume or amount we need to get the job done. Dr. Kudsk alluded to a study by Alexander in which they
actually showed that if the animals were unstressed they took 25% of kilocalories to stop translocation, but if they were injured the animals first took 50% of the kilocalories. Dr. Demayo did permeability studies in Chicago. He studied bone marrow transplant patients and ranked them by the percent of kilocalories they got and the number he came up with was 50% of kilocalories: below that permeability went way up, and above 50% permeability was contained and maintained. So my question is how do you come up with that 60 cm$^3$/h, that magic number, and do you think that is enough to get the job done?

**Dr. Moore:** I don't have any other data than what you repeated. But historically we started our enteral feeding protocol 20 years ago. We were trying to meet the patients metabolic demands within 72 h, and that meant we pushed patients to about 2,500 cm$^3$/day. We published studies on that and what we found was that when you start really getting to the higher volume you start having intolerance. Now when we come to 60 cm$^3$/h, if you believe in the immune-enhancing diet studies and you think that they are efficacious, go and see how much they are getting in, they are only getting about 1,200 cm$^3$, and so that is how we came up with 50–60 cm$^3$/h. It is probably not an unreasonable goal in the short run, and then by ICU day 7 we tried to get people up into a positive caloric and positive nitrogen goal and, if we are not at that level by day 7, then they get started on supplemental TPN, and I would say probably about 10% of our ICU patients get put on to some supplemental TPN, and we tend to go hypocaloric in large patients.

**Dr. Herndon:** I would like to congratulate you on your nice presentation and your emphasis on monitoring gastrointestinal function and making improvements in that area. I was surprised at how conservative you are, unusually so. We have done several clinical experiments recently in which we have given animals 60% total body surface burns and effectively completely resuscitated the animals orally. They can even be improved by using hypertonic saline resuscitation, but you can resuscitate a pig with a 60% burn with World Health Organization tablets in water, something that may be pertinent if we are faced with mass disasters. Your delay of 2–3 days before you start feeding is to me very conservative. We begin feeding within 3–4 h of the time of resuscitation and we find motility is quite adequate, and in fact it is a period in which you can avoid ileus by early feeding. Regarding Dr. Kudsk's data about bombesin, we used bombesin a long time ago and it worked well. IGF-1 can also be used as a stimulatory agent given early. There are some other drugs that can be given early that would stimulate motility. My second comment would be that this abdominal compartment syndrome seems to be an institution-specific phenomenon.

**Dr. Moore:** Let me answer the first question. When I am talking about minor injury patients, I don't mean burn patients. I think burn patients are different. There are certainly manometric studies that show that burn patients do not have this gastric apnea, that is without feeding, so I think they are different animals. As far as aggressive early feeding, in our original studies we started feeding in the operating room. So for the less severely injured patients it is clearly feasible to start feeding early. I don't think that. I guess my theories on ICU care are that you have to have a goal you are trying to achieve, and during resuscitation of the patients is not the time to be starting enteral feeding into the under-perfused gut. As I showed with the data from gastric tonometry, a certain portion of these patients really are hypoperfused and I think if you start feeding you will run into significant problems. As far as the institution specificity, I will be happy to show you a review article of the literature.

**Dr. Herndon:** Let me finish my question before you answer. I do think that, if you look at the patients who develop this kind of massive edema, delay in resuscitation is a very important issue as well as the amount of fluid that is given in the emergency room, as you showed in your own slides. We did a study on 169 patients looking at this
phenomenon and those individuals who developed it. Abdominal compartment syndrome had a 2-hour delay to get intravenous infusions started. They were patients who already had very high lactic acid and lactate levels when they arrived and began resuscitation. They had high osmolarity. Also predictive, and you might look at it in the future, is the thromboxane level, it is elevated 200-fold in people who are predisposed to this particular kind of problem. Your comments that hypertonic saline and colloid-based resuscitation may decrease this phenomenon I think are well founded.

Dr. Moore: It is very interesting to see the people that develop this massive edema in the operating room because there really are these patients for whom an ultrasound was done in the emergency department, the blood pressure is 60, and you are saying we have got to get out of here, and there is no attempt to resuscitate them because we don't want to increase their pressure and just have them bleed more. You get the patient to the operating room, open up and find something that is really bleeding. You pack it and ask the anesthesiologist to start resuscitating. My colleagues just claim that this is a starling phenomenon and has nothing to do with ischemia/reperfusion. I think it really does. Anyway I agree with you that this entity, the problem when you look at the incidence of this syndrome, really is the denominator. So when people study it they either say I am looking at all the patients in the ICU then the incidence is about 0.5%, or they look at all the patients who are under damage control and the incidence is 40%. So if you take the most severely ill patients you are going to find it. If you look at our denominator we have had 196 patients over a 3-year period, that represents about 5% of our trauma admissions to the ICU, and those are extremely sick patients.

Dr. Nitenberg: For gastric residual volume I do not have the same experience because in our country Blechner and Mintake observed that there was an apparent correlation between a gastric residual volume over 100 ml and the risk of aspiration pneumonia. We are presently conducting a study to control that. We administer enteral nutrition until the gastric residual volume is 500 ml and then we administer prokinetics and, on the other hand, we administer prokinetics very early when the gastric residual volume is 100 ml, and we will see if there is any difference. My other comment and question are about the real value of an elevated bed to protect from aspiration pneumonia. I think there is no proof about that. There was a nice study presented last year at the European Congress of Intensive Care Medicine by people from the Netherlands, and they compared the risk of aspiration pneumonia with a bed at 45° and with the supine position. They found no difference in the rate of aspiration pneumonia. But it is very difficult to respect guidelines because they observed that the true inclination of the beds was in fact 28° because of the many interventions of nurses and physicians around the patient. I think there is a long way to go in respecting guidelines and to prevent that.