

EARLY ENTERAL FEEDING DOES NOT ATTENUATE METABOLIC RESPONSE AFTER BLUNT TRAUMA

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Enteral feeding very early after trauma has been hypothesized to attenuate the stress response and to improve patient outcome. We tested this hypothesis in a prospective, randomized clinical trial in patients with blunt trauma. Following resuscitation and control of bleeding, 52 patients were randomized to receive early feedings (target, <24 hours) or late feedings (target, 72 hours). Feeding was given via nasoduodenal feeding tubes. A rapid advance technique was used to achieve full volume and strength within 24 hours (goal, 1.5 g protein/kg·day). Patients who underwent at least 5 days of therapy were considered to have completed the study: 38 in all, 19 in each feeding group. Patients were similar in age, gender, Injury Severity Score, and mean PaO₂/FiO₂ ratio. The early group, however, had more patients with a PaO₂/FiO₂ <150. After feeding began, the amount fed per day was the same in both groups. We found no significant differences in metabolic responses as measured by plasma lactate and urinary total nitrogen, catecholamines, and cortisol. Both groups achieved nitrogen retention. In addition, we found no significant differences in intensive care unit (ICU) days, ventilator days, organ system failure, specific types of infections, or mortality, although the early group had a greater number of total infections. In this study, early enteral feeding after blunt trauma neither attenuated the stress response nor altered patient outcome.

THE METABOLIC RESPONSE to severe injury is characterized in part by hypercatabolism of lean body mass and elevated resting metabolic expenditure. This process is mediated to a large degree by the macroendocrine system. The endocrine response includes increased release of cortisol, epinephrine, and norepinephrine. Attenuating the hypermetabolic state could improve outcome after trauma by shortening time to the convalescent phase and preserving lean body mass. This might reduce intensive care and overall hospital stays, and shorten time to rehabilitation.

Current practice in trauma critical care is to begin nutritional (metabolic) support following a resuscitative phase. However, this practice typically delays nutritional support for at least 24 hours, frequently longer. Intestinal

priming—by graded increases in the concentration and the rate of enteral formulas—further delays the time until full nutritional support is achieved. Thus a significant period of no or reduced enteral nutrient intake routinely follows critical injury.

Although associated with higher mechanical, infectious, and metabolic complications than enteral feeding, early feeding can be accomplished parenterally. It can begin as soon as central venous access is obtained, and in most instances does not require priming. Complications can be minimized with good care. Nonetheless, this route has considerable disadvantages, including an increased rate of infectious complications.¹

Previously, early metabolic support after injury was only considered feasible parenterally because of impaired gastrointestinal motility. However, enteral nutrition, particularly with nasoenteric feeding, has been observed to be safe and nutritionally efficacious in a number of studies; it may even be superior to parenteral nutrition in terms of metabolic function and patient outcome.¹⁻⁴ Proposed benefits of early enteral feeding include maintaining an intestinal “barrier” and better immune function, more normal splanchnic physiologic conditions, improved hepatic blood flow following shock, and better wound healing.

Dominioni hypothesized that delayed enteral feeding triggers an enhanced hypermetabolic state through higher and more persistent catecholamine release after

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burn injury.⁵ Experimental studies in burn management from the laboratory and in clinical trials also support this view.⁵⁻¹¹ However, very few data exist on early versus late enteral feeding after nonthermal injury. We hypothesized that early enteral feeding would attenuate the metabolic response after blunt trauma, and designed a prospective, randomized trial to answer this question.

MATERIALS AND METHODS

From December 1988 through May 1991, all patients admitted to our trauma intensive care unit (ICU) after blunt trauma were evaluated for inclusion in this study. Inclusion criteria were age > 17 years, Injury Severity Score (ISS) >13, feeding support anticipated for at least 7 days, and an ability to start enteral feeding via a tube placed distal to the pylorus within 24 hours after ICU admission. Exclusion criteria were contraindication to enteral feeding, e.g., new upper intestinal suture line; contraindication to placement of an enteral tube within 24 hours after ICU admission, e.g., unstable cervical fracture; admission creatinine level > 2 mg/dL; admission bilirubin > 3 mg/dL; pre-existing malnutrition according to history and physical examination; use of steroids, radiation, or chemotherapy; malignancy; or acute spinal cord injury. Dropout criteria were survival less than 48 hours; failure to receive more than 50% of prescribed nutrients; less than 5 days in the study; and withdrawal mandated by patient, family, or attending physician. Eligible patients were randomized to one of two groups: early enteral feeding (<24 hours after ICU admission) or late enteral feeding (>72 hours after ICU admission). Randomization was by card draw from sealed envelopes. The protocol was approved by the hospital's Institutional Review Board for Human Investigation. Entrance into the study required patients' informed written consent. The study was completed after the tenth study day, when oral intake could be resumed, or on the day a patient went 24 hours without receiving any nutrients.

The day of trauma ICU admission was considered study day 0 (zero). Under fluoroscopic guidance, 10F nasoenteric feeding tubes were placed distal to the pylorus by experienced radiologists. The tip was usually positioned at the ligament of Treitz. In the early group, enteral feeding was begun immediately after patients returned to the ICU. In the late group, patients received no nutrients for the first 72 hours other than intravenous crystalloid solutions containing dextrose, and plasma products as necessary. Nasoenteric tubes in the late group were usually not placed until the day feeding began.

In both groups, enteral feeding was with a peptide-based formula (Reabilan HN, O'Brien Pharmaceuticals, Parsippany, NJ). Riabilan HN contains 1.33 kcal/mL, 490 mOsm/kg water, and a 125:1 nonprotein kcal/g nitrogen ratio. Per liter there are 58 g protein, 158 g carbohydrate, and 52 g fat. Full-strength formula was started at 25 mL/hour and advanced by 25 mL/hour every 4 hours, until patients' target rate was reached. Target rate was to provide 1.5 g protein/kg·day unless fluid restriction was necessary to manage closed head injury. Urinary urea nitrogen was obtained on 24-hour collections once per week. Nitrogen balance determination was then performed, and enteral administration rates were adjusted to achieve nitrogen equilibrium. Abdominal signs and symptoms were monitored daily for feeding tolerance. Diarrhea was diagnosed if there was more than one liquid stool per day of any volume.

Every day, 24-hour urine collections were obtained. Total urinary nitrogen, cortisol, epinephrine, norepinephrine, dopamine, and creatinine levels were then determined on batched samples for days 0 (nitrogen balance on day 1), 5 (days 3-6), and 10 (days 8-10).

Total urinary nitrogen was analyzed using a pyro-chemilu-

minescent system (Antek Instruments Inc., Houston, Tex). Samples were run in duplicate and were within 2% reproducibility. Urinary catecholamines were quantified by high-pressure liquid chromatography using a Hewlett-Packard 1084 system (Hewlett-Packard, San Fernando, Calif), after extraction by the method described by Riggin and Kissinger.¹² Cortisol analyses were performed using a GammaCoat (¹²⁵I) Cortisol Radioimmunoassay kit (Dade, Baxter Travenol Diagnostics, Inc., Cambridge, Mass). Lactate determinations were performed on sodium fluoride-preserved plasma on the IL Multistat III Microcentrifugal Analyzer (Instrumentation Laboratory, Fisher Scientific Company, Lexington, Mass) using the Behring lactate test kit (Behring Diagnostics, Somerville, NJ).

All patients in the study were placed on stress gastritis prophylaxis with a sucralfate or antacid regimen. Selective gut decontamination was not performed. Fluid resuscitation, antibiotics, and inotropic agents were given as clinically indicated. Any catecholamine given was not measured in urine analysis for that day.

A positive blood culture with concurrent growth of the same organism from the tip of a removed vascular line was considered evidence of catheter sepsis. All other positive blood cultures were diagnosed as bacteremias. Pneumonia was defined as significant growth on sputum culture with <10 epithelial cells, >25 leukocytes/high-power field (HPF) on a Gram's stain of tracheal secretions and a new infiltrate on chest films or increased purulent tracheal secretions associated with new fever and elevated white blood cell count (tracheobronchitis). Sinusitis was diagnosed from evidence of new air-fluid levels within sinuses on plain films or CT scan or purulent drainage from the nose. Evidence of a wound infection consisted of a positive wound culture with purulent drainage. Diagnosis of a urinary tract infection required >10⁵ organisms per HPF. A positive body cavity culture was considered evidence of an empyema or abscess.

The primary outcome variable of this study was the degree of metabolic response, as evaluated by urinary catecholamine and cortisol excretion on study days 5 and 10. This method is similar to studies in burn patients.^{8,11} Secondary outcome variables were infections, ICU days, ventilation days, and mortality.

The primary outcome data, particularly the urinary catecholamine and cortisol determinations after injury, were not normally distributed. There was a positive skew in both groups. A two-sample *t* test was not appropriate given these distributions, so three nonparametric statistical tests that do not require uniform distributions were used: (1) the Mann-Whitney *U* test, (2) the Kolmogorov-Smirnov test, and (3) the median test. Significance of secondary outcome variables was determined by Chi-squared or Fisher's exact test methods. Because the distributions on the primary outcome variables were not normal and nonparametric tests of data significance were used, type 1 or type 2 errors or issues of sensitivity and specificity could not be addressed. Data are presented as means ± standard deviations.

RESULTS

Initially, 52 patients with blunt trauma were entered into this study. Fourteen patients (seven from each group), were subsequently dropped from analysis: three advanced to a regular diet much earlier than anticipated, three received steroids after entering the study, two pulled out tubes that were not replaced, one had an enterorrhaphy that was previously overlooked, one had a duodenal perforation detected on study day 4, one had severe hyponatremia secondary to mannitol administra-

tion, in one a tube could not be placed, in one case the physician withdrew the patient from the study because of instability, and in one case the patient withdrew (refused feeding tube placement). The remaining 38 patients were randomized, 19 to each group.

Patient characteristics are given in Table 1. The patients in both groups were severely injured. As was expected from the study design, the time from trauma ICU admission to feeding was significantly different between groups (early, 31 ± 13 hours; late, 82 ± 11 hours, $p < 0.001$); so were the times from injury to feeding (early, 39 ± 12 hours; late, 90 ± 12 hours, $p < 0.001$) and from hospital admission to feeding (early, 38 ± 11 hours; late, 88 ± 11 hours, $p < 0.001$). Although the mean $\text{PaO}_2/\text{FiO}_2$ ratios were similar between groups (early, 201 ± 114 ; late, 248 ± 100), the early feeding group had more severe acute lung injuries ($\text{PaO}_2/\text{FiO}_2 < 150$) $p < 0.05$.

The target rate of enteral feeding was achieved in most patients in both groups within 12 hours and in all patients in less than 24 hours from the time of tube placement. The formula was tolerated well. Most patients had some abdominal distention, but abdominal discomfort was infrequent. Diarrhea (> one liquid stool/day) was absent on 86% of days (233 of 270 patient feeding days). More than three liquid stools/day occurred on 3% of feeding days. Patients were unable to receive the desired daily nutrient intake for a variety of reasons, including tube malfunction, tube dislodgement, and NPO status for surgical and other procedures and tests. Nonetheless, the target amount was given on 60% of feeding days; >80% of the target amount was given on 73% of days. Overall, patients in both groups received 83% of the target amount for the entire study.

The early feeding group received more protein and kilocalories than the late group for the overall study period (Table 1, $p < 0.001$). This resulted from the difference in non-nutrient days before feeding began, a func-

tion of the study design. Once feeding began, each group received the same amount of protein and kilocalories (Table 1).

We found no significant differences in primary outcome variables (Table 2). Nitrogen balance was significantly different on study day 1 when the early group received nutritional support and the late group did not. During concomitant feeding days, nitrogen balance was the same. We also found no differences in plasma lactate values or in secondary outcome variables in this study. Days in the ICU (early, 11.8 ± 7.9 ; late, 9.9 ± 6.7), ventilator days (early, 10.2 ± 8.1 ; late, 8.1 ± 6.8), organ system failure (two each), deaths (two each), and individual types of infections (Table 3) did not significantly differ. The total number of acquired infections, however, was greater in the early feeding group ($p < 0.05$, Table 3). In performing the latter analysis, the data were analyzed by patient to ensure there was no bias arising from a few patients having all the infections.

DISCUSSION

In this study, the metabolic response was not attenuated by early enteral feeding in severely injured blunt trauma patients. Urinary catecholamine, cortisol, total nitrogen, and plasma lactate measurements were similar irrespective of the timing of enteral nutrition. In addition, early enteral feeding did not alter ICU stay, ventilator days, or mortality. Total infectious complications were increased in the early feeding group.

The mean time from ICU admission to early feeding in this study was 31 ± 13 hours, and from injury to early feeding, 39 ± 12 hours. These times may be too long to prevent an enhanced macroendocrine response to injury. Perhaps beginning feeding just a few hours after injury would be effective. Additionally, the study period (10 days) may have been too short to detect a difference between groups. In this regard, experimentally burned guinea pigs fed within 2 hours after injury had lower 24-hour urinary vanillylmandelic acid excretion levels at 12–13 days, compared with animals fed after 72 hours.⁶

We encountered many practical difficulties in placing nasogastric tubes early in acute blunt trauma patients. Stabilizing cardiorespiratory conditions and determining the status of the cervical spine delayed some tube placements. Likewise, time to tube placement was delayed in patients undergoing early surgical procedures, such as long bone stabilization or maxillofacial trauma. In the case of patients with maxillofacial injuries additional assistance from the maxillofacial service was required to properly place the tubes. The radiology staff was cooperative with enteral tube placement, but not after normal daytime hours. These difficulties could be overcome by surgical jejunostomy at the time of laparotomy in some patients, and by manual placement without fluoroscopic guidance in others. Manual placement is gaining popularity; with experience, it can be done with success equal to that of fluoroscopic placement.¹³ Placing jejunostomy

Table 1
Patient characteristics

	Early (n = 19)	Late (n = 19)	Significance
Age (years)	44 ± 22	41 ± 18	NS
Male to female ratio	14:5	8:11	NS
Injury Severity Score	34 ± 11	32 ± 9	NS
ICU admit to feeding (hours)	31 ± 13	82 ± 11	$p < 0.001$
Admission $\text{PaO}_2/\text{FiO}_2$	201 ± 114	247 ± 100	NS
Admission $\text{PaO}_2/\text{FiO}_2 < 150$	11	4	$p < 0.05$
Protein (g/kg·day)	1.3 ± 0.3	$0.9 \pm 0.2^*$	$p < 0.001$
		$1.2 \pm 0.3^\dagger$	NS
Kcal/kg·day	30 ± 6	$19 \pm 5^*$	$p < 0.001$
		$28 \pm 6^\dagger$	NS
Plasma lactate day 0 (mg/dL)	2.8 ± 1.5	2.4 ± 1.2	NS
Plasma lactate day 1 (mg/dL)	1.6 ± 0.6	1.5 ± 0.7	NS

* Entire study period including nonnutrient days.

† After feeding began.

Table 2
Primary outcome variables (24-hour urine collections)

	Study Day	Early	Late	Significance
Total urinary nitrogen (g)	0	6.9 ± 3.0	7.5 ± 2.9	NS
	3-6	14.7 ± 5.7	11.5 ± 4.3	NS
	8-10	15.0 ± 7.8	15.7 ± 8.1	NS
Nitrogen balance (g)	1	-1.6 ± 7.7	-12.0 ± 3.6	$p < 0.001$
	3-6	-4.7 ± 4.9	-2.6 ± 6.3	NS
	8-10	-5.9 ± 5.7	-2.8 ± 4.9	NS
Epinephrine (μg/g Cr)	0	44 ± 108	8 ± 16	NS
	3-6	12 ± 17	7 ± 13	NS
	8-10	14 ± 12	21 ± 38	NS
Norepinephrine (μg/g Cr)	0	43 ± 45	89 ± 109	NS
	3-6	79 ± 68	91 ± 71	NS
	8-10	102 ± 68	79 ± 57	NS
Dopamine (μg/g Cr)	0	65 ± 85	119 ± 167	NS
	3-6	218 ± 294	183 ± 181	NS
	8-10	281 ± 138	300 ± 148	NS
Cortisol (μg/g Cr)	0	716 ± 390	818 ± 1018	NS
	3-6	403 ± 176	415 ± 295	NS
	8-10	323 ± 153	354 ± 215	NS

Table 3
Infections

	Early	Late	Significance
Pneumonia	8	4	NS
Urinary tract	4	2	NS
Abdominal abscess	1	0	NS
Wound infection	3	1	NS
Catheter sepsis	1	1	NS
Bacteremia	2	0	NS
Sinusitis	9	6	NS
Other	1 (eye)	0	NS
Total	29	14	$p < 0.05$

tubes at the time of surgical intervention remains controversial, and also introduces potential complications.¹⁴⁻¹⁷

It may also be that the metabolic response to injury is different between burn patients and trauma patients so that the effect of enteral feeding cannot be demonstrated. Insufficient data are available to evaluate this possibility. We are aware of no other study comparing early versus late enteral feeding after blunt or penetrating trauma. Poret et al. studied immediate enteral and *parenteral* feeding in patients receiving a surgical jejunostomy after laparotomy for blunt and penetrating injuries.³ They found no difference in urinary catecholamine responses in the first 4 days. As previously mentioned, laboratory and clinical studies from some centers support a reduction in metabolic and hormonal response to burn injury.⁵⁻¹¹ This attenuation of the hypermetabolic response after early versus late *gastric* feeding is contested in some animal studies of thermal injury. Wolfe et al. found that early gastric feeding of burned guinea pigs actually increased metabolism (oxygen consumption) on the third postburn day.¹⁸ Early gastric feeding in burned rats did not alter heat production, which is a good indicator of

metabolism in experimental thermal injury, in another 14-day study.¹⁹

No clinical benefit could be shown for early enteral feeding. Although not the primary focus of this study, ICU and ventilator days were not affected, nor was the incidence of individual types of infection, organ failure, or mortality. Note that studies showing a reduced incidence of infection after trauma with early enteral feeding differ from the present study. Patients in those studies^{1,20} had a mix of blunt and penetrating injuries requiring laparotomy, surgical jejunostomy, and *immediate* feeding. Control groups were parenterally fed; late enteral feeding was not studied. In our study, the significance of the increased incidence of total infections in the early feeding group remains unexplained. Perhaps it is related to the occurrence of more acute lung injury in the early group. The ISS for the subgroup of patients with acute lung injury was not significantly different from that of the remaining patients.

The peptide-based formula that we used was tolerated well. Although abdomens commonly became distended, nausea, cramping, and diarrhea (liberally defined) were not common. No reduction in formula strength was required in any patient. All patients advanced rapidly on full-strength regimens and achieved their target rate within 24 hours. Maintaining target goals of daily nutrient intake with enteral feeding was not possible, but 83% of the cumulative target amount was achieved for both study populations.

The data are beginning to verify the longstanding clinical preference for enteral feeding, as long as it begins soon after the injury. However, when the diet is controlled for, early (24 hours) versus late (72 hours) timing of enteral feeding does not appear to alter the metabolic response to injury or clinical outcome in blunt trauma. Recent studies are evaluating the effect of the type of enteral diet. Modified amino acids improve nitrogen

retention²¹; a diet fortified with omega-3 polyunsaturated fatty acids, ribonucleic acid, and arginine has recently been associated with a significantly shorter hospital stay.²² Although more research is necessary, early enteral feeding, particularly with products that enhance nitrogen retention and immune function, is the preferred route for nutrition and metabolic support in trauma patients.

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DISCUSSION

Dr. Ernest E. Moore (Denver, Colorado): This is a timely report as we are seeing a new generation of enteral diets being promoted as immunoregulatory. Indeed, postinjury gut inflammation may establish the environment conducive for multiple organ failure.

The authors have rejected their study hypothesis that early enteral feeding reduces stress response and improves patient outcome. My job as a reviewer is to critically analyze the study design and data analysis to see if we can accept these conclusions. I will begin with the study design and data analysis to see if we can accept these conclusions. First, the study design. The issue is whether the enteral feeding was introduced early enough. Alexander's classic work in guinea pigs demonstrated that the stress response was reduced with enteral feeding introduced within hours of burn injury, and his subsequent clinical work has suggested the same. If we believe that reperfused gut is a source of proinflammatory mediators, it is conceivable that a 30-hour hiatus may have been too long. The second question is, aside from potential type 2 errors because of the relatively small number of patients, are the study groups comparable? Your entry criterion was an ISS of 13: the mean ISS in these groups was 33. I think we have to assure ourselves there are no other major confounding variables. For example, how many of your patients had elevated intracranial pressure that increased catecholamine production? How many of these patients returned to the operating room and had general anesthesia? How many were on a mechanical ventilator and had drugs that would affect the metabolic response? What was the relative pattern of fractures? In fact, the enteral group had an increased pulmonary shunt before treatment. Did these patients have aspiration or pulmonary contusions that would already establish them at higher risk for complications? As a corollary, in view of the ISS of 33, were the patients too massively injured for feeding to have a measurable impact on their metabolic response?

In the area of data analysis, the first question is that of optimal markers of a stress response. The data variance for the catecholamine and cortisol is quite wide. Did you look at other markers? For example, Lowry's work showed that glucagon was most profoundly affected by early enteral feeding in humans following endotoxin shock challenge. Did you look at other mediators like IL-6 or PGE₂ that are released from the gut, or acute phase proteins, or your favorite, oxygen consumption? Second, if the proposed mechanism of aggressive enteral feeding involves reduced gut bacterial translocation, did you look for attenuation of this in terms of circulating endotoxin levels or evidence of TNF activity? And finally, I question whether you chose the optimal sampling time. Specifically, your first sample was taken between days 3 and 6. It seems conceivable that the study group was at 75% enteral feeding and the control group at 25%, but we do not know whether low enteral dose feeding will confer the same benefit.

Dr. Charles E. Wiles, III (Baltimore, Maryland): Our recent observations confirm the authors' conclusions on this paper, and I would like to ask them to concentrate on a couple of questions Gene Moore asked.

The first question is, are there some patients who are at particular risk of multiple organ failure and bad outcome more than others? For example, does pulmonary injury have a major effect, or are there patients we can identify in whom the systemic inflammatory response is activated and intervene early?

And the second question that begs to be asked is, is the key

element the route of administration of feedings? Is the key element what you feed by that route or another route? Or is the key a combination of both? Thank you.

Dr. John R. Hall (Chicago, Illinois): Two questions, please. Recent studies have shown that maybe 70% of patients with esophageal tubes have gastroesophageal reflux. I was wondering if in your earlier group was the increased incidence of infection a result of pneumonia? My second question is that early caloric protein supplementation has been shown in some data to be beneficial to patients with head injuries. Did you look at patients with head injuries in particular to see if there was a difference in them?

Dr. Steven D. Eyer (Closing): All those are excellent questions. I would first like to thank Doctor Moore. I recognize him as a leader in early feeding of trauma patients, and his comments were insightful and to the point.

Was the feeding early enough? Maybe not. Certainly in the burn patients and guinea pig studies, these animals and humans were fed within 2 to 4 hours, at the extreme 12 hours after the injury. In fact, if we timed our feeding including injury, we have to add an additional 8 hours to the time from injury to the time that they sustained their early feeding.

Getting these patients fed early is extremely difficult from a practical standpoint. If you do a laparotomy, which is a small percentage of these patients, you can place surgical jejunostomies or perhaps you could assist the anesthesiologist in nasoduodenally placing tubes distal to the pylorus. Otherwise, you might take the tack of Doctor Zaloga, who feels that we should manually place these tubes, and with his experience, he has become as able to do this as his radiologist at his own institution, and in fact I look forward to trying to take up these techniques myself.

The point of fact is that you are going to have a lot of patients with delays, e.g., cervical spine clearance or fractures, returns to the operating room, and it is not going to be a priority to get enteral tubes distal to the pylorus. I think something that begs to be asked is the business of gastric atony. My own impression is gastric atony may indeed be a matter of gastric blood flow, and early resuscitation and perhaps enhancement of gastric blood flow through enteral stimulant by gastric feeding may obviate gastric atony after severe blunt injury, and

I would like to see that particular aspect studied, because we can all get feeding tubes into the stomach.

Doctor Moore also asked about the reliability of results when we measure them at study days 5 and 10, where it may be that during the initial 3 days when they are not being fed, we would find differences in our results. In fact, it may be that just putting 10 mL per hour into the stomach or the gut would be enough to achieve the proper response if it could be timed appropriately.

We had small numbers. I think Doctor Moore understands from doing these studies himself that small numbers are typical of these types of studies. They are difficult to do and quite expensive. Fifteen percent of our patients had major head injuries; 40% of our patients had major extremity injuries. I cannot quantitate those by types.

Many metabolic drugs were used during the course of this study. On days where, for example, catecholamines were infused, we did not measure those drugs or those catecholamine levels as our primary outcome variable on those particular days.

We initially intended to study plasma glucagon. In fact, the samples are still frozen in our laboratory. But the expense of the study got so high that we eliminated them from analysis.

We do like to do oxygen consumptions in Minnesota. Not every patient had pulmonary artery catheters. We could not measure it that way. And our metabolic cart results, which we did do on every patient were unreliable. They were not able to achieve a good steady state at any time point consistently during the study and we eliminated them from any analysis. We did not measure TNF or IL-6 levels because of cost.

Doctor Wiles, I would also like to thank you for your very complimentary remarks. As far as identifying patients with a systemic inflammatory response syndrome early, that is the project of ongoing studies right now, and I too look forward to being able to find identifiable factors. You asked a second question, but I didn't quite catch it.

Doctor Hall asked if there were differences in pneumonias. I must say in quantifying infections, pneumonia is a very difficult thing. You have to be very objective about it, but there is still some subjectivity. We analyzed the data with and without pneumonias included and there was still a significant difference in total infections when pneumonias were excluded in the early group.