



## Incidence and Effects of Feeding Intolerance in Trauma Patients

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### Abstract

**Background:** Although feeding intolerance is a common complication in trauma patients, the incidence, development, and effects are poorly understood. **Methods:** We performed a retrospective study in which trauma patients were classified as having feeding intolerance based on time to reach feeding goal. Subsequently, we sorted patients by gastric residual volumes (GRVs) or symptoms of slowed gastrointestinal motility. **Results:** One-third of trauma patients experienced delayed time to reach feeding goal after diet initiation. Delayed feeding was associated with prolonged intensive care unit (ICU) stays, increased readmission rates, and increased incidence of sepsis. Patients with elevated GRV (>500 mL) had significantly prolonged ICU and hospital stays and increased incidence of sepsis. Patients with >2 symptoms of slowed gastrointestinal motility had prolonged ICU and hospital stays, delayed time to reach feeding goals, significantly increased readmission rates, increased incidence of infectious and thromboembolic complications and sepsis, decreased serum prealbumin levels, and increased CRP levels. **Conclusion:** Decreased gastrointestinal motility in trauma patients is associated with worse outcomes and increased systemic inflammation. (*JPEN J Parenter Enteral Nutr.* 2019;43:742–749)

### Keywords

enteral nutrition; feeding intolerance; inflammation; prokinetics; trauma

### Clinical Relevancy Statement

A retrospective study was conducted to assess the incidence and associated complications of feeding intolerance after trauma. Approximately one-third of moderately to severely injured trauma patients developed feeding intolerance, re-

sulting in prolonged intensive care unit stays, increased infectious and thromboembolic complications, and higher readmission rates. Increased symptoms of slowed gastrointestinal motility were associated with increased markers of inflammation.

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## Background

Feeding intolerance (FI) is a common complication in trauma patients. Although several publications address FI in specific patient subpopulations, including traumatic head injury and abdominal trauma patients,<sup>1,2</sup> few publications address FI in the general trauma patient population. Furthermore, while FI has been widely studied in surgical patients,<sup>3-6</sup> the development and effects of FI in trauma patients are poorly understood. Surgical patients are often in controlled environments and can be pretreated to avoid FI; however, trauma patients cannot be pretreated and often suffer from multiple injuries which complicate treatments. Thus, the approach to treating FI in trauma patients may be different than in other surgical patients.

The significance of FI is highlighted by the benefits of early enteral nutrition (EN). In critically ill patients, adequate EN within the first 48 hours of hospital admission decreases hospital length of stay (LOS), reduces thrombotic and infectious complications, and lowers all-cause mortality.<sup>2,7,8</sup> These benefits are especially apparent in trauma patients, whose severe injuries result in hypermetabolic and hypercatabolic states, increasing their need for nutrition beyond that of a physiologically normal individual.<sup>9</sup> Early EN has become a central part of the critical care paradigm. However, the development of FI can prevent early enteral feeding.

Inflammation is a key contributor to the development of postoperative ileus (POI), according to studies in animal models and patients.<sup>10,11</sup> Tissue macrophage and mast cell activation lead to secretion of inflammatory cytokines and recruitment of leukocytes into the intestinal muscularis, resulting in smooth muscle dysfunction.<sup>10,11</sup> However, whether the same mechanism occurs in trauma patients, or non-abdominal surgical patients for that matter, remains unclear. Most trauma patients have systemic inflammation due to their injuries; however, the association between inflammation and FI is unclear.

The purpose of the present study is to gain a better understanding of the incidence, development, and effects of FI in trauma patients. To achieve this goal, we performed a retrospective study of trauma patients. For the purpose of the present study, we defined FI as a delay ( $\geq 3$  days) in reaching feeding goal after diet initiation. Subsequently, we categorized patients based on gastric residual volume (GRV) only or multiple symptoms of slowed gastrointestinal motility. We hypothesized that FI in trauma patients would be associated with adverse outcomes.

## Methods

A retrospective analysis of prospectively collected data was performed. All data came from an institutional review board-approved study of patients admitted to the Hous-

ton Hermann Memorial Level 1 trauma center, Houston, Texas, in 2012 and 2013. Data were retrospectively collected from the medical records of 202 adult trauma patients ( $> 18$  years) having  $\geq 3$  days of intensive care unit (ICU) stay. Patients with missing feeding data (55 patients), including patients who transitioned to oral feeding within the first 3 days after admission, were excluded from study; thus, data from 147 patients were analyzed. Trauma included blunt, penetrating, and burn injuries. The following data were collected: age, sex, race, body mass index (BMI), mode of injury (burn, blunt, or penetrating), injury severity scores (ISS) and body region abbreviated injury scales (AIS), laparotomy, diagnosis of ileus, hospital LOS, and ICU LOS. Diagnosis of ileus was confirmed radiographically (abdominal x-ray including kidneys, ureters, and bladder). To assess inflammatory state, we recorded serum prealbumin and C-reactive protein (CRP) levels measured within the first week after admission. Neutrophil, macrophage, lymphocyte, and eosinophil numbers on day 3 after admittance were also recorded. We recorded the following drug administration: opioids, metoclopramide, erythromycin, and neostigmine. Morphine equivalents (opioids only) were calculated using the following equation: morphine equivalents = [(morphine) + (hydromorphone  $\times 4$ ) + (oxycodone  $\times 1.5$ ) + (fentanyl  $\times 2.4$ )  $\times$  (hydrocodone)]/LOS. Outcomes, which included LOS in ICU and hospital (for initial trauma-related hospital admittance), readmission within 1 year of discharge, sepsis, infectious and thrombotic complications (during hospital stay), and in-hospital mortality, were recorded. To assess gastrointestinal motility, we recorded nausea (on 2 consecutive days), vomiting, abdominal distension (on 2 consecutive days), constipation, highest GRV over 4 hours during ICU stay, and diagnosis of ileus. We also recorded feeding goals (as set by the hospital nutritionist) and time to reach feeding goals (time after feeding initiation to reach feeding goal). Energy deficits and protein deficits in the ICU were recorded. Use of parenteral nutrition (PN) was also recorded.

Comparisons between groups were performed using a *t*-test. Analysis via  $\chi^2$  was used for comparison of categorical data. Power analysis was used to determine if the patient number was adequate. Effect size was determined using Hedges' *g* with the following effect size calculator: <https://www.polyu.edu.hk/mm/sizeeffectsizecalculator/calculator.html>.<sup>12</sup>

## Results

### All Patients

Data are reported for 147 patients. Patients were categorized based on time to reach feeding goal as follows: FI  $\geq 3$  days, or no FI (NFI)  $< 3$  days (Table 1). Based on this classification, 33% of trauma patients developed FI. No

**Table 1.** All Patients.

Category	NFI	FI	<i>P</i>
Number of patients (% of total)	98 (67.7)	49 (33.3)	
Age (years)	43.9 ± 1.7	38.8 ± 2.1	.074
Male sex (% within group)	70 (71.4)	38 (77.6)	.43
BMI	28.6 ± 0.7	28.0 ± 0.9	.62
Race: White	49 (50.0%)	25 (51.0%)	.72
Hispanic	26 (26.5%)	15 (30.6%)	
Black	14 (14.3%)	7 (14.3%)	
Other	9 (9.2%)	2 (4.1%)	
ISS (median)	23.6 ± 1.1 (22)	26.0 ± 1.9 (24)	.23
Abd AIS (% patients with AIS ≥4)	1.1 ± 0.2 (14.3)	1.6 ± 0.3 (18.4)	.12 (.52)
Laparotomy	25 (25.5%)	21 (42.9%)	<b>.032</b>
MOI: Blunt	70 (71.4%)	35 (71.4%)	1.00
Penetrating	14 (14.3%)	7 (14.3%)	
Burn	14 (14.3%)	7 (14.3%)	
Ileus (% within group)	19 (19.4)	20 (40.8)	<b>.006</b>
Abdominal distension (% within group)	46 (46.9)	30 (61.2)	.10
Nausea (% within group)	12 (12.2)	8 (16.3)	.50
Vomiting (% within group)	28 (28.6)	19 (38.8)	.21
Constipation (% within group)	37 (37.8)	26 (53.1)	.077
GRV (mL)	499.6 ± 39.7	700.8 ± 75.5	<b>.010</b>
Slowed GI motility symptoms, total	1.9 ± 0.1	2.8 ± 0.2	<b>.002</b>
Morphine equivalents (average/day)	82.0 ± 16.0	71.3 ± 16.6	.67
Treated w/prokinetics (% within group)	35 (35.7)	31 (63.3)	<b>.002</b>
LOS (days)	24.0 ± 1.8	29.6 ± 2.3	.074
ICU (days)	11.2 ± 0.9	16.7 ± 1.5	<b>.001</b>
Time to feeding goal (days)	1.2 ± 0.06	5.3 ± 0.4	<b>&lt;.001</b>
Mortality (% within group)	13 (13.3)	4 (8.2)	.36
Readmission (% within group)	24 (28.6)	21 (46.7)	<b>.040</b>
Infection complications (% within group)	54 (55.1)	30 (61.2)	.48
Thromboembolic complications (% within group)	16 (16.3)	12 (24.5)	.23
Sepsis (% within group)	21 (21.4)	21 (42.9)	<b>.007</b>

Data are listed as mean ± standard error, except where % or median are indicated. *P*-values in bold indicate significant differences.

Abd AIS, abdominal abbreviated injury scale; FI, feeding intolerance; GI, gastrointestinal; GRV, gastric residual value; NFI, no feeding intolerance; ICU, length of intensive care unit stay; ISS, injury severity score; LOS, length of hospital stay; MOI, mode of injury; w/, with.

differences in sex, BMI, or race were detected; however, age tended to be younger in the FI group compared with the NFI group (*P* = .074).

ISS (*P* = .23), abdominal AIS (*P* = .12), and incidence of severe abdominal AIS (*P* = .52) were not significantly different; however, the FI group had more laparotomies (*P* = .032) (Table 1). We detected no differences in any other regional AIS (data not shown). Of note, a majority of patients were severely injured; 79.6% and 81.6% of patients in the NFI and FI groups, respectively, had ISS scores ≥16, with no significant differences between groups (*P* = .77).<sup>13</sup> The distribution of injury mode, predominantly blunt injury, was similar between groups.

More patients were diagnosed with ileus in the FI group (40.8%) compared with the NFI group (19.4%, *P* = .006; Table 1). The incidence of other symptoms of slowed motility (abdominal distension, nausea, vomiting, and constipation) were not statistically different between the 2 groups; however, GRV was significantly increased in the

FI group. Furthermore, the total number of symptoms of slowed GI motility, which included abdominal distension, nausea, vomiting, constipation, ileus, and GRV >500, was increased significantly in the FI group compared with the NFI group (*P* = .002).

The use of morphine did not differ between the groups (*P* = .58). Significantly more patients in the FI group received prokinetics (metoclopramide and/or erythromycin), compared with the NFI group (64.0% vs 34.9%, *P* = .001). No patients received neostigmine.

ICU stays were significantly longer in the FI group compared with the NFI group (*P* = <.001), but hospital LOS was not significantly different (*P* = .074). Mortality was not significantly different between the groups; however, readmission rates were significantly higher in patients with FI (*P* = .040). No differences in infectious or thromboembolic complications between the 2 groups were observed, but more patients developed sepsis in the FI group (*P* = .007).

**Table 2.** GRV vs GI Symptoms.

Category	GRV ≤500 mL	GRV >500 mL	<i>P</i>	≤2 GI symptoms	>2 GI symptoms	<i>P</i>
Number of patients (% of total)	80 (54.4)	67 (45.6)		88 (59.9)	59 (40.1)	
ISS	22.2 ± 1.2	27.0 ± 1.5	<b>.014</b>	23.1 ± 1.2	26.3 ± 1.5	.11
Abd AIS	0.94 ± 0.16	1.66 ± 0.20003	<b>.009</b>	1.06 ± 0.16	1.58 ± 0.24	.07
Laparotomy	18 (22.5%)	28 (41.8%)	<b>.012</b>	19 (21.6%)	27 (55.1%)	<b>.002</b>
LOS (days)	22.6 ± 1.9	30.0 ± 2.2	<b>.012</b>	20.9 ± 1.4	33.9 ± 2.6	<b>&lt;.001</b>
ICU (days)	11.1 ± 0.9	15.5 ± 1.3	<b>.006</b>	10.6 ± 0.7	17.2 ± 3.6	<b>&lt;.001</b>
Time to feeding goal (days)	2.4 ± 0.3	2.9 ± 0.3	.30	2.2 ± 0.2	3.2 ± 0.4	<b>.023</b>
Mortality (% within group)	11 (13.7)	7 (10.4)	.54	14 (15.9)	4 (8.2)	.098
Readmission (% within group)	19 (27.5)	50 (60.2)	.06	18 (24.3)	28 (50.9)	<b>.002</b>
Infection comp. (% within group)	43 (53.8)	42 (62.7)	.27	45 (51.1)	40 (67.8)	<b>.045</b>
Thromboembolic comp. (% within group)	13 (6.2)	15 (22.4)	.35	12 (13.6)	16 (32.7)	<b>.041</b>
Sepsis (% within group)	17 (21.2)	25 (37.3)	<b>.032</b>	16 (18.2)	25 (51.0)	<b>&lt;.001</b>
Total energy deficits in ICU	-11,429.8 ± 1329.1	-14,381.3 ± 1991.0	.22	-9617.9 ± 909.6	-17,217.1 ± 2390.3	<b>.0014</b>
Total protein deficits in ICU	-704.9 ± 107.6	-1313.1 ± 482.5	.19	-568.7 ± 57.0	-1566.2 ± 539.3	<b>.034</b>
PN	6 (7.5%)	15 (22.4%)	<b>.010</b>	6 (6.8%)	15 (25.4%)	<b>.006</b>
Serum prealbumin (mg/dL)	10.8 ± 0.7	10.4 ± 0.6	.75	11.7 ± 0.6	9.1 ± 0.5	<b>.016</b>
CRP (mg/dL)	138.0 ± 5.4	156.2 ± 5.9	.056	140.7 ± 5.0	158.3 ± 4.7	.07
Monocytes (%)	7.0 ± 0.3	7.3 ± 0.4	.52	6.5 ± 0.3	8.1 ± 0.4	<b>.003</b>

Data are listed as mean ± standard error, except where % or median are indicated. *P*-values in bold indicate significant differences.

Abd AIS, abdominal abbreviated injury scale; comp., complications; CRP, C-reactive protein; GI, gastrointestinal; GRV, gastric residual value; ICU, length of intensive care unit stay; ISS, injury severity score; LOS, length of stay; PN, parenteral nutrition.

### Comparison of Outcomes Based on GRV vs Symptoms of Slowed Motility

FI is diagnosed at most hospitals based on high GRV; however, symptoms of slowed GI motility were also significantly different in the FI group compared with the NFI group (Table 1). To determine if consideration of GI symptoms is important in the outcomes of FI, we compared trauma patients based on sorting by either GRV or by symptoms of slowed GI motility (Table 2). In the first comparison, patients were sorted into 2 groups depending on GRV: patients who always had GRVs ≤500 mL or patients who developed GRVs >500 mL. Despite ISS, abdominal AIS, and laparotomy incidence being significantly higher in the GRV >500 mL group, time to feeding goal was not significantly different between the groups (*P* = .30). The group with GRV >500 mL had longer hospital and ICU stays (*P* = .012 and .006, respectively). However, outcomes, including readmission and infectious and thromboembolic complications, were not significantly different between the 2 groups (*P* = .06, .27, and .35, respectively). The incidence of sepsis was significantly higher in the GRV >500 mL group compared with the lower GRV group (*P* = .032). Energy and protein deficits were not significantly different between the 2 GRV groups (*P* = .22 and .19, respectively); however, significantly more patients in the higher GRV group received PN. Markers of inflammation, including serum prealbumin and circulating monocytes, were not

significantly different between the 2 GRV groups (*P* = .75 and .52, respectively); however, CRP tended to be higher in patients with higher GRV (*P* = .056).

To compare patients based on symptoms of slowed GI motility, patients were sorted into 2 groups: patients with ≤2 symptoms of slowed GI motility and patients with >2 symptoms of slowed GI motility (Table 2). Symptoms of slowed GI motility included abdominal distension, nausea, vomiting, constipation, GRV >500 mL, or ileus. ISS and abdominal AIS were not significantly different between the 2 groups (*P* = .11 and .07, respectively). The group with more symptoms of slowed GI motility had significantly more laparotomies compared with the group with fewer symptoms. LOS and ICU stays were significantly longer in the group with more GI symptoms (*P* < .001 for both). The group with more symptoms of slowed GI motility had significantly more complications, including infectious and thromboembolic complications (*P* = .045 and .041, respectively) and sepsis (*P* < .001), and a significantly higher incidence of hospital readmissions within 1 year of the trauma (*P* = .002). Time to reach feeding goal was significantly longer in patients with more symptoms of slowed GI motility (*P* = .023), and both energy deficits and proteins deficits (*P* = .0014 and .034, respectively) were significantly higher in the group with >2 symptoms of slowed GI motility. Significantly more patients in the group with >2 symptoms of slowed GI motility received PN. Interestingly, markers for inflammation changed

**Table 3.** Correlation of GRV and GI Symptoms With Feeding Intolerance Measures.

Category	GRV			GI Symptoms		
	R <sup>2</sup>	P	Effects Size (Hedges' g)	R <sup>2</sup>	P	Effects Size (Hedges' g)
Time to feeding goal	0.18	.027	0.21	0.24	.003	0.39
Energy deficit in ICU	0.17	.045	0.21	0.30	<.001	0.57

GI, gastrointestinal; GRV, gastric residual volume; ICU, intensive care unit.

significantly in patients with increased symptoms of slowed GI motility, including significantly lower serum prealbumin and increased circulating monocytes ( $P = .016$  and  $.003$ , respectively). CRP tended to be higher in the group with more symptoms of slowed GI motility ( $P = .07$ ). There were no significant differences in neutrophils or lymphocytes.

Associations between measures of FI (time to feeding goal and energy deficit) and predictors of FI (GRV and symptoms of slowed GI motility) were evaluated (Table 3). The correlation coefficients for GRV vs time to feeding goal or energy deficit were significant but very low ( $P = .027$  and  $.045$ ,  $R = 0.18$  and  $0.17$ , respectively). GI symptoms also correlated significantly with time to feeding goal or energy deficit ( $P = .003$  and  $P < .001$ , respectively); the correlation coefficients for these correlations were also low, but higher than GRV ( $R = 0.24$  and  $0.30$ , respectively). The effect size on feeding goal or energy deficits were higher when patients were sorted based on GI symptoms vs sorting by GRV (Hedges'  $g = 0.39$  and  $0.57$  vs  $0.21$  and  $0.21$  for time to feeding goal and energy deficit, respectively).

### Effects of Ileus in ISS-Matched Patients

As shown in Table 4, patients with ileus were compared with patients with no signs of ileus ( $\leq 1$  symptom of slowed motility). Patients with ileus had significantly higher ISS; therefore, patients were matched, according to ISS, so that the effects of ileus could be determined independent of the effects of more severe injury (ISS,  $P = .98$ ). Not surprisingly, abdominal AIS and laparotomies were significantly higher in patients with ileus vs patients with no ileus ( $P = .011$  and  $< .001$ , respectively). Hospital LOS were significantly higher in patients with ileus ( $P = .0018$ ) and ICU stays were >doubled in patients with ileus ( $7.6$  vs  $15.8$  days,  $P < .001$ ). The number of symptoms of slowed GI motility was >7 times higher in patients with ileus compared with patients with no ileus ( $0.43 \pm 0.10$  vs  $3.43 \pm 0.24$ ,  $P < .001$ ). Patients with ileus also had significantly higher GRVs ( $P < .001$ ).

As far as indicators of FI, time to reach feeding goal was significantly prolonged in patients with ileus ( $P = .017$ ). Both energy deficits and protein deficits were significantly higher in patients with ileus compared with patients with no ileus ( $P = .031$  and  $.042$ , respectively).

Infectious and thromboembolic complications were not significantly different in patients with vs without ileus. However, the incidence of sepsis and hospital readmission rates were significantly higher in patients with ileus ( $P = .004$  and  $P = .032$ , respectively). Average serum prealbumin, measured within the first week after admission, was significantly lower in patients with ileus compared with patients with no ileus ( $P = .03$ ), and CRP was significantly higher in patients with ileus ( $P = .016$ ). Monocytes did not differ significantly between the 2 groups. Interestingly, the number of circulating lymphocytes was significantly lower in the ileus group compared with patients with no ileus ( $P = .01$ ).

### Effects of Prokinetic Treatment in Ileus Patients

As shown in Table 5, only 7 patients with ileus were not treated with prokinetics. The ISS and abdominal AIS were not significantly different between the untreated and treated groups. Despite prokinetic treatment, hospital and ICU LOS were significantly longer in the treated group compared with the untreated group ( $P = .04$  and  $.007$ , respectively). Time to feeding goal and energy and protein deficits in the ICU were not improved with treatment. GRV and symptoms of slowed GI motility were significantly higher in the treatment group compared with the untreated group ( $P = .045$  and  $.002$ , respectively).

### Discussion

We examined the incidence of FI in adult, moderately to severely injured trauma patients, with  $\geq 3$  days of ICU stay, including all types of trauma: penetrating, blunt, and burns. FI was defined as  $\geq 3$  days to reach feeding goal after diet initiation, based on the recommendation for early enteral feeding within 24–48 hours.<sup>6,14</sup> According to our results, almost 33% of trauma patients took 3 days or longer to reach feeding goal. Overall, 26% of trauma patients were diagnosed with ileus (Table 1). In addition, 40% of trauma patients in this study had >2 symptoms of slowed GI motility, including nausea, vomiting, abdominal distension, constipation, diagnosed ileus, and elevated GRV. Taken together, these results demonstrate the high percentage of trauma patients that suffer from perturbed



**Table 4.** Effects of Ileus, ISS Matched.

Category	No Ileus	Ileus	<i>P</i>
Number of patients	28	28	
ISS	20.5 ± 1.1	20.5 ± 1.3	.98
Abd AIS	0.50 ± 0.17	1.46 ± 0.33	<b>.011</b>
Laparotomy	2 (7.1%)	14 (50.0%)	<b>&lt;.001</b>
LOS (days)	17.1 ± 2.1	31.2 ± 3.8	<b>.0018</b>
ICU (days)	7.6 ± 0.8	15.8 ± 2.0	<b>&lt;.001</b>
Time to feeding goal (days)	1.5 ± 0.2	3.1 ± 0.6	<b>.017</b>
GI symptoms	0.43 ± 0.10	3.43 ± 0.24	<b>&lt;.001</b>
GRV (mL)	161.7 ± 22.4	868.9 ± 109.1	<b>&lt;.001</b>
Mortality (% within group)	5 (17.9)	2 (7.1)	.22
Readmission (% within group)	4 (18.2)	12 (46.2)	<b>.032</b>
Infection comp. (% within group)	10 (35.7)	15 (53.6)	.18
Thromboembolic comp. (% within group)	4 (14.3)	10 (35.7)	.064
Sepsis (% within group)	4 (14.3)	14 (50.0)	<b>.004</b>
Total energy deficits in ICU	-8392.3 ± 1411.3	-17,806.1 ± 3776.9	<b>.031</b>
Total protein deficits in ICU	-558.3 ± 100.1	-1266.6 ± 305.8	<b>.042</b>
Serum prealbumin (mg/dL)	12.4 ± 1.4	7.6 ± 0.5	<b>.030</b>
CRP (mg/dL)	115.4 ± 11.3	168.4 ± 5.7	<b>.016</b>
Monocytes (%)	7.5 ± 0.5	7.1 ± 0.5	.54
Lymphocytes (× 100/u)	1.1 ± 0.08	0.8 ± 0.08	<b>.01</b>

Data are listed as mean ± standard error, except where % is listed. *P*-values in bold indicate significant differences.

Abd AIS, abdominal abbreviated injury scale; comp., complications; CRP, C-reactive protein; GI, gastrointestinal; GRV, gastric residual value; ICU, intensive care unit; ISS, injury severity score; LOS, length of stay.

gastrointestinal motility. The prevalence of FI in critically ill patients reported in the literature depends on the patient population and the definition of FI, and ranges from 2%–75%.<sup>3</sup> In patients with abdominal trauma, approximately 50% developed FI, defined as having abdominal distension, vomiting, diarrhea, or GRV >200mL.<sup>2</sup> In critically ill septic burn patients, 35% developed FI, defined as GRV between 150–500 mL for 2 consecutive measurements, GRV >500mL for 1 measurement, or when vomiting occurred.<sup>15</sup> Considering that we included patients with and without abdominal trauma, the incidence of FI in our study is similar to previous reports.

POI is associated with increased incidence of infectious and thromboembolic complications, as well as patient discomfort.<sup>5,16</sup> POI also delays enteral feeding, leading to

**Table 5.** Effects of Treatment in Patients With Ileus.

Category	Untreated	Treated	<i>P</i>
Number of patients (% of total)	7 (25)	21 (75)	
ISS	20.4 ± 2.3	20.5 ± 1.6	.49
Abd AIS	1.3 ± 0.7	1.5 ± 0.4	.38
Time to feeding goal (days)	2.3 ± 0.6	3.3 ± 0.8	.23
LOS (days)	19.9 ± 3.5	35 ± 4.6	<b>.04</b>
ICU (days)	7.4 ± 1.2	18.7 ± 2.4	<b>.007</b>
GRV	549.3 ± 180.8	975.5 ± 126.0	<b>.045</b>
GI symptoms	2.3 ± 0.4	3.8 ± 0.2	<b>.002</b>
Total energy deficits in ICU	-13,139.3 ± 3251.3	-19,361.7 ± 4912.9	.24
Total protein deficits in ICU	-830.7 ± 217.4	-1419.2 ± 401.4	.21

Data are listed as mean ± standard error, except where % is listed. *P*-values in bold indicate significant differences.

Abd AIS, abdominal abbreviated injury scale; GI, gastrointestinal; GRV, gastric residual value; ICU, intensive care unit; ISS, injury severity score; LOS, length of stay.

prolonged hospital stays and increased healthcare costs. Patients undergoing abdominal surgery, who were diagnosed with and coded for POI, had an average hospital cost double that of patients who were not coded for POI.<sup>17</sup> Total costs attributed to managing POI in the United States was calculated as \$1.46 billion annually.<sup>17</sup> FI, in our study, was associated with significantly prolonged ICU stays (Table 1) and a higher incidence of sepsis. Although we did not record patient care costs, we can safely assume that increased complications and extended ICU and hospital stays resulted in increased patient care costs, and increased patient readmission rates indicate that patient quality of life and patient care costs continued to be impacted, even after release from the hospital.

FI is often diagnosed in trauma patients based on elevated GRV,<sup>3,18,19</sup> which is used to guide treatment. However, our results indicate that multiple symptoms of slowed GI motility may be more closely associated with FI and worsened outcomes. This is in line with the latest feeding recommendations in critically ill patients which state that feeding should not be withheld on the basis of high GRVs without other signs of FI.<sup>14</sup> The correlation coefficients for the association between GI symptoms and time to feeding goal or energy deficit are higher than the correlation coefficient for the relationship between GRV and these indicators of FI (Table 3). The effect size is also higher when patients are sorted based on all symptoms of slowed GI motility rather than elevated GRV alone (Table 3). The data in Table 2, showing worsened outcomes for patients with >2 symptoms of slowed GI motility, support the data in Table 3. Patients with >2 symptoms of slowed

GI motility took significantly longer to reach feeding goal and had significantly higher energy and protein deficits compared with patients with fewer symptoms of slowed GI motility. In contrast, the patients with higher GRV did not have significantly worse outcomes. Furthermore, time to reach feeding goal and energy and protein deficits were not significantly different in the group with higher GRV. Use of PN was significantly higher in the elevated GRV group but not different than the group with  $\geq 2$  symptoms of slowed GI motility. Thus, the occurrence of multiple symptoms of slowed GI motility may be a better predictor of FI and the associated complications than elevated GRV alone. However, neither sorting method had a very strong correlation with FI. To successfully test the effects of new prokinetics, a better method for diagnosing and/or predicting the development of FI is needed.

According to the results in Table 2, patients with  $>2$  symptoms of slowed GI motility had significantly worse outcomes, including significantly more infectious and thromboembolic complications, significantly higher incidence of sepsis, and significantly higher readmission rates 1 year after hospitalization for trauma. Overall, these data suggest that slowed GI motility is associated with worsened outcomes, and these patients would benefit if effective prokinetic treatment was available.

The overall incidence of ileus in this study was 25.5% (Table 1, both NFI and FI groups). The effects of ileus on patient outcomes in the absence of the effects of injury severity were investigated by matching patients according to ISS. Not surprisingly, patients with ileus had a significantly higher number of laparotomies and abdominal AIS scores (Table 4). These results are in agreement with reported incidences of ileus, which are particularly high after abdominal surgeries; the incidences are 25%, 10%–15%, and 60% for colectomies, gynecologic surgeries, and rectal surgeries, respectively.<sup>4,16,20</sup> Ileus is likely a major risk factor for the development of FI; in our study, patients with ileus were more likely to develop FI, as evidenced by doubled time to reach feeding goals and significantly increased energy and protein deficits in the ICU. The occurrence of ileus was associated with worsened outcomes including longer hospital and ICU LOS, and significantly higher incidence of sepsis and hospital readmission rates.

The cause of FI in trauma patients is unclear. Inflammation is thought to be a key contributor to the development of POI after abdominal surgery,<sup>10,11</sup> and our data support this paradigm for FI in trauma patients also. Serum prealbumin levels were significantly lower and CRP tended to be higher in patients with  $>2$  symptoms of slowed GI motility compared with patients with fewer symptoms (Table 2). Furthermore, circulating monocytes were increased in patients with  $>2$  symptoms of slowed GI motility. Ileus was also associated with increased systemic inflammation as evidenced by significantly lower serum

prealbumin and significantly higher CRP levels. Of note, about half of patients who developed FI in our study did not have laparotomies; thus, gut manipulation alone could not have triggered the activation of tissue macrophages. Overall, these data suggest that patients with slowed GI motility or ileus had increased systemic inflammation. However, we could only assess the routinely measured parameters concerning systemic inflammation. Thus, we can make no definitive conclusions at this time. Despite these limitations, this study provides a framework for designing and assessing the appropriateness of both animal models of FI after traumatic injury and prospective human patient studies. In addition, understanding the involvement of inflammation in the development of FI can direct efforts to earlier detection of gastrointestinal dysfunction. Our previous laboratory studies suggest that pathologic distension of the gut wall can increase intestinal dysfunction<sup>21,22</sup>; early detection and treatment of slowed intestinal motility may prevent intestinal distension and, thus, be important in attenuating or even preventing FI.

We examined the effectiveness of pharmacologic treatment in patients with ileus only. Treatment with prokinetics (metoclopramide and/or erythromycin) did not improve hospital or ICU LOS. In fact, patients with ileus who were treated with prokinetics had significantly longer hospital and ICU LOS compared with untreated patients. Indicators of FI increased in the treated group, including time to feeding goal and energy and protein deficits. Although some studies in critically ill patients showed that erythromycin and metoclopramide are effective in resolving FI,<sup>23,24</sup> our data are consistent with a Cochrane review showing a consistent lack of effect for erythromycin, and inconsistent effects of metoclopramide for the treatment of ileus.<sup>25</sup> Patients in our study were given 250 mg of erythromycin and/or 10 mg of metoclopramide every 6 hours. Several recent studies showed that the effectiveness of erythromycin disappeared after several days at this dosing regimen, which may account for the overall lack of effect on outcomes.<sup>24,26</sup> Furthermore, prokinetics may be effective in a patient subset that we were unable to delineate in our study.

There were several limitations to our study. This was a retrospective study and, thus, the conclusions are limited. In addition, we did not differentiate between lack of feeding due to poor gastrointestinal dysfunction and lack of feeding due to other causes, such as operating room visits. When studying the effectiveness of prokinetics, patient numbers were small, and worse symptoms may have prompted treatment in these patients. Despite these limitations, our data and other studies suggest that the prokinetics currently available to treat FI are either ineffective or, at most, only marginally effective in improving gastrointestinal motility in trauma patients.

There is a dire need for new and more effective prokinetics. To develop new prokinetics, a more thorough under-

standing of how impaired gastrointestinal motility develops in trauma patients is necessary. Furthermore, the ability to predict which patients will develop FI is necessary for new drugs to be successfully tested. GRV or symptoms of slowed gastrointestinal motility are poor predictors of FI. A reliable early biomarker, such as an inflammatory mediator, would be optimal for predicting and treating patients with compromised gastrointestinal motility before further damage, such as mucosal dysfunction, occurs. Effective and early treatment of compromised gastrointestinal motility may improve outcomes in trauma patients.

In summary, we demonstrate that approximately one-third of trauma patients develop FI. Decreased gastrointestinal motility, associated with an elevated inflammatory response, is associated with worsened outcomes. A better understanding of the mechanism(s) by which FI in trauma patients develops is needed to identify new drug targets for treating FI.

### Statement of Authorship

C. E. Wade, J. B. Holcomb, and K. Uray contributed to the conception/design of the research; F. R. Virani, T. Peery, O. Rivas, J. Tomasek, R. Huerta, J. Lee, and K. Uray were responsible for the acquisition, analysis, and/or interpretation of the data; and F. Virani, T. Peery, and K. Uray drafted the manuscript. All authors critically revised the manuscript, agree to be fully accountable for ensuring the integrity and accuracy of the work, and read and approved the final manuscript.

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