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Enteral nutrition is associated with high rates of pneumonia in intensive care unit (ICU) patients with acute pancreatitis

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ABSTRACT

Purpose: Enteral nutrition is associated with improved outcomes in acute pancreatitis (AP), but previous studies have not focused on critically-ill patients. Our purpose was to determine the association between nutritional support and infectious complications in ICU-admitted patients with AP.
Methods: A retrospective analysis of patients with AP admitted in ICUs of 127 US hospitals from the eICU Collaborative were included. Patients were classified by type (initial and any use) of nutritional support they received: none (NN); oral (ON); enteral (EN); and parenteral nutrition (PN).
Results: 925 patients were identified. Length of stay was longer in the initial PN group (PN 21.3 ± 15.4 d, EN 19.1 ± 20.1 d, ON 8 ± 7.1 d, NN 6.6 ± 6.3 d, $p < 0.001$) and mortality was more common in the initial EN group (EN 16.7%, PN 8.9%, ON 2.7%, NN 10.9%, $p < 0.001$). Multivariate analysis found any EN use to be associated with infections (OR 2.12, 95% CI: 1.13–3.98, $p = 0.019$) and pneumonias (OR 2.04, 95% CI: 1.04–4.03, $p = 0.039$).
Conclusion: EN was associated with an increased risk for pneumonias and overall infections in critically-ill patients with AP. More studies are needed to assess optimal nutritional approaches in critically-ill AP patients and patients who do not tolerate EN.

1. Introduction

Despite considerable progress in the management of patients with acute pancreatitis, nutritional support remains challenging. Guidelines by both the American Gastroenterological Association (AGA) and the American Pancreatic Association (APA) recommend initiating enteral (EN) rather than parenteral nutrition (PN) in patients who do not tolerate oral intake [1,2]. These recommendations are based on several randomized control trials (RCTs) that have demonstrated EN to be associated with reduced mortality, multi-organ failure (MOF) and pancreatic infectious complications [3-9]. However, these RCTs have several limitations, most notably, they include patients with "predicted severe" AP, but did not enroll many truly critically-ill patients, who may not tolerate enteral nutrition due to ileus or sedation. The purpose of this study is to evaluate the relationship between different nutritional approaches and infectious complications in patients with severe AP admitted to the intensive care units (ICUs) of hospitals across the United States.

2. Methods

2.1. Setting and inclusion criteria

A retrospective analysis of the multi-institutional eICU Collaborative research database was performed [10]. The eICU database consists of over 150,000 patients admitted in ICUs of 127 hospitals across the United States between 2014 and 2015. To define AP, we first identified patients with an admission diagnosis of AP using a free-text search of the keyword "pancreatitis". Patients with chronic pancreatitis were identified using the keyword "chronic" and excluded. We then identified patients with a secondary diagnosis of AP (using the keyword "pancreatitis") recorded within 24 h from hospital admission. Duplicate records were excluded. The total number of patients diagnosed with AP was 1197, of which 664 had an admission diagnosis of AP and 533 had a secondary diagnosis of AP (within 24 h from hospital admission). Patients with no available information regarding nutritional support during their ICU stay were excluded from the analysis and the final number of patients included in the analysis was 925. The flowchart of patient selection is displayed in Supplementary Fig. 1. The admission diagnoses for patients included in the analyses are listed in Supplementary Table 1.

The following nutritional methods were considered: no nutritional support (NN, i.e. specified as nothing per os [NPO] and no other form

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of nutritional support used), oral nutrition (ON), EN (including tube feeds administered by nasogastric tube [NGT], nasojejunal tube [NJT], gastrostomy tube or jejunostomy tube) and PN. Patients were divided into groups based on the initial nutritional method employed and whether EN or PN was used at any point during their ICU stay (i.e. any EN, any PN). Determination of disease severity was made through the Acute Physiology and Chronic Health Evaluation (APACHE) IV score at admission [11]. Some patients received different types of nutritional support at the same time, e.g. EN and PN; these are denoted using the term combination.

2.2. Outcomes

The primary outcome was infections, defined as a diagnosis of pneumonia, bacteremia, pancreatic infectious complications or other unspecified sepsis. Individual complications were identified through the "Diagnosis" table of the eICU database, which contains diagnoses documented for each patient during ICU stay in a free-text format. Only infections that occurred after initiation of nutrition were considered. The list of diagnoses that were used for each complication can be viewed at Supplementary Table 2. The threshold of significance for the primary outcome was set at 0.05. Secondary outcomes included ICU length of stay (LOS), 30-day ICU-free days, hospital LOS, 90-day hospital-free days, ICU re-admission and in-hospital mortality.

2.3. Statistical analysis

Continuous variables were summarized as mean ± standard deviation. Categorical variables were summarized as percentages. Univariate analysis was performed using ANOVA for continuous variables and chi-square for categorical variables. Stepwise logistic regression was used to identify risk factors for the development of complications, adjusting for age, sex, body mass index (BMI), admission APACHE score, mechanical ventilation, vasopressor use, initiation of nutrition within 48 h, initial nutritional approach and any use of EN/PN. Statistical analysis was performed on STATA v.15.1 (StataCorp LLC, College Station, TX).

3. Results

Overall, 925 patients met inclusion criteria (mean age 54.2 ± 17.2 y, males 544 [58.8%]). Among these, 221 (23.9%) did not receive nutritional support (NN) in the ICU. The initial nutritional method was ON in 520 (56.2%), EN in 127 (13.7%) and PN in 57 (6.2%) patients. For 83 (9%) patients, PN was used at some point during their ICU stay. For 171 (18.5%) patients, EN was used at some point during their ICU stay. Detailed baseline characteristics are displayed at Table 1. Characteristics of patients who received EN or PN at any point during their ICU stay are listed in Supplementary Table 3.

In-hospital mortality occurred in 64 patients (6.9%) and was more common in patients who received EN as the initial nutritional approach (16.7%), followed. There were no differences between the different groups in terms of ICU re-admission ($p = 0.308$). ICU LOS was longer for patients who received PN as the initial nutritional approach (PN: 11.5 ± 10.4 d, EN: 8.8 ± 7.7 d, ON: 2.9 ± 2.5 d, 1.7 ± 1.6 d, $p < 0.001$) and 30-day ICU-free days were shorter for the same group (PN: 17.5 ± 10 d, EN: 18.1 ± 10.2 d, NN: 25.2 ± 8.9 d, ON; 26.4 ± 5.1 d, $p < 0.001$). Detailed patient outcomes are displayed at Table 2.

3.1. Infections

Infections were more common in patients who received EN as the initial nutritional approach (EN: 28.4%, PN: 21.1%, NN: 14%, ON: 6.9%, $p < 0.001$, Table 2). Multivariate analysis identified a higher APACHE score (OR 1.02, 95% CI: 1.01–1.03, p < 0.001), mechanical ventilation (OR 2.33, 95% CI: 1.25–4.36, 0.008), any EN use (OR 2.12, 95% CI: 1.13–3.98, $p = 0.019$) and NN (OR 2.17, 95% CI: 1.25–3.79, $p = 0.006$) to be associated with a higher risk of infection (Table 3, Fig. 1). Among patients who required EN at some point, 47 out of 171 (27.5%) developed an infection. Among patients who were started on ON and required EN at some point, 7 out of 24 (29.2%) developed an infection. Among patients who were started on PN and required EN at some point, 4 out of 20 (20%) developed an infection.

Pneumonia was more common in patients who received EN as the initial nutritional approach (EN 22.1%, PN: 14%, NN: 5%, ON: 3.7%, $p < 0.001$, Table 2). Multivariate analysis identified a higher APACHE score (OR 1.01, 95% CI: 1.00–1.02, $p = 0.020$), mechanical ventilation (OR 3.89, 95% CI: 1.81–8.38, $p = 0.001$) and any EN use (OR 2.04, 95% CI: 1.04–4.03, $p = 0.039$) to be associated with a higher risk of pneumonia (Table 4). In a multivariate analysis of the risk factors for pneumonia in patients receiving any EN, higher APACHE score (OR 1.02, 95% CI: 1.00–1.04, $p = 0.021$) was associated with a higher risk of pneumonia, while initial PN was associated with a lower risk (OR 0.14, 95% CI:

Table 1
Baseline characteristics of the patient cohort.

Initial Approach	NN ($n = 221$)	ON ($n = 520$)	EN ($n = 127$)	PN ($n = 57$)	*P*-value
Age (y)	54.8 ± 18	54.2 ± 17	54.5 ± 16.5	50.7 ± 16.9	0.724
Sex					0.001
Male	126 (57%)	291 (56%)	96 (75.6%)	31 (54.4%)	
Female	95 (43%)	229 (44%)	31 (24.4%)	26 (45.6%)	
Admission BMI (kg/m^2)	29.1 ± 6.6	29.1 ± 7.8	30.3 ± 8.4	30 ± 7.7	0.372
Admission APACHE IV score	52.6 ± 25.4	49.9 ± 20	68.6 ± 32.2	70.7 ± 27.8	<0.001
Mechanical ventilation	37 (18.3%)	40 (7.7%)	88 (69.3%)	37 (64.9%)	<0.001
Vasopressor use	29 (13.1%)	55 (10.6%)	45 (35.4%)	20 (35.1%)	<0.001
Duration of initial approach (d)	–	1.8 ± 3.1	3.7 ± 4.7	3.7 ± 4.5	<0.001
Initiation within 48 h from hospital admission	–	390 (75%)	65 (51.2%)	7 (12.3%)	<0.001
Delay between hospital and ICU admission	0.9 ± 2.8	0.8 ± 2.9	0.9 ± 2.2	2.3 ± 3.5	<0.001
Additional forms of nutritional support used^					<0.001
PN	–	12 (2.3%)	14 (11%)	57 (100%)	
Enteral nutrition	–	24 (4.6%)	127 (100%)	20 (35.1%)	
ON-EN combination	–	5 (1%)	9 (7.1%)	1 (1.8%)	
EN-PN combination	–	3 (0.6%)	8 (6.3%)	7 (12.3%)	
ON-PN combination	–	2 (0.4%)	–	2 (3.5%)	
Nutrition approach at ICU discharge					<0.001
Oral	–	501 (96.4%)	45 (35.4%)	8 (14%)	
Enteral	–	11 (2.1%)	68 (53.5%)	9 (15.8%)	
PN	–	4 (0.8%)	5 (3.9%)	35 (61.4%)	
ON-EN combination	–	3 (0.6%)	6 (4.7%)	–	
EN-PN combination	–	1 (0.2%)	3 (2.4%)	5 (8.8%)	

NN: No nutrition, ON: Oral nutrition, EN: Enteral Nutrition, PN: Parenteral nutrition, APACHE: Acute Physiology and Chronic Health Evaluation, ICU: Intensive care unit.

Table 2
Patient outcomes.

Initial Approach	NN (n = 221)	ON (n = 520)	EN (n = 127)	PN (n = 57)	P-value
ICU LOS (d)	1.7 ± 1.6	2.9 ± 2.5	8.8 ± 7.7	11.5 ± 10.4	<0.001
30-day ICU-free days	25.2 ± 8.9	26.4 ± 5.1	18.1 ± 10.2	17.5 ± 10	<0.001
Hospital LOS	6.6 ± 6.3	8 ± 7.1	19.1 ± 20.1	21.3 ± 15.4	<0.001
90-day hospital-free days	74 ± 26.6	79.9 ± 15	59.5 ± 30.2	62.9 ± 24.1	<0.001
Infection	31 (14%)	36 (6.9%)	36 (28.4%)	12 (21.1%)	<0.001
Pancreatic infectious complication	1 (0.5%)	2 (0.4%)	4 (3.2%)	3 (5.3%)	0.001
Pneumonia	11 (5%)	19 (3.7%)	28 (22.1%)	8 (14%)	<0.001
Aspiration pneumonia	3 (1.4%)	1 (0.2%)	9 (7.1%)	2 (3.5%)	<0.001
Bacteremia	5 (2.3%)	7 (1.4%)	2 (1.6%)	1 (1.8%)	0.844
Unspecified sepsis	19 (8.6%)	14 (2.7%)	16 (12.6%)	7 (12.3%)	<0.001
ICU readmission	27 (12.2%)	89 (17.1%)	24 (18.9%)	9 (15.8%)	0.308
In-hospital mortality	24 (10.9%)	14 (2.7%)	21 (16.7%)	5 (8.9%)	<0.001

NN: No nutrition, ON: Oral nutrition, EN: Enteral Nutrition, PN: Parenteral nutrition, ICU: Intensive care unit, LOS: Length of stay.

0.02–0.90, $p = 0.039$, Supplementary Table 4). Among patients who required EN at some point, 36 out of 171 (21.1%) developed pneumonia. Among patients who were started on ON and required EN at some point, 6 out of 24 (25%) developed pneumonia. Among patients who were started on PN and required EN at some point, 2 out of 20 (10%) developed pneumonia.

Pancreatic infections were more common in patients who received PN as the initial nutritional approach (PN: 5.3%, EN: 3.2%, NN: 0.5%, ON: 0.4%, $p = 0.001$). Multivariate analysis found that any PN use (OR 7.39, 95% CI: 2.01–27.13, $p = 0.003$) was associated with a higher risk for pancreatic infections (Supplementary Table 5). Finally, there were no differences between groups for the occurrence of bacteremia (NN: 2.3%, ON: 1.4%, EN: 1.6%, PN: 1.8%, $p = 0.844$). Multivariate analysis identified only a higher APACHE score (OR 1.02, 95% CI: 1.00–1.04, $p = 0.025$) to be associated with a higher risk for bacteremia (Supplementary Table 6).

3.2. In-hospital mortality

In-hospital mortality was more common in patients who received EN as the initial nutritional approach (EN: 16.7%, NN: 10.9%, PN: 8.9%, ON: 2.7%, $p < 0.001$). Multivariate analysis identified a higher APACHE score (OR 1.03, 95% CI: 1.02–1.05, p < 0.001), mechanical ventilation (OR 4.08, 95% CI: 1.55–10.76, $p = 0.004$), vasopressor use (OR 2.97, 95% CI: 1.34–6.61, $p = 0.007$), NN (OR 4.53, 95% CI: 1.72–11.95, $p = 0.002$) and any EN use during ICU admission (OR 4.04, 95% CI: 1.02–16.05, $p = 0.047$) to be associated with a higher risk for in-hospital mortality (Supplementary Table 7).

Table 3
Results of multivariate analysis for infections.

	OR (95% CI)	P-value
Age	1.00 (0.99–1.02)	0.511
Female sex	0.96 (0.60–1.53)	0.851
BMI	1.01 (0.98–1.04)	0.602
APACHE score	1.02 (1.01–1.03)	<0.001
Mechanical ventilation	2.33 (1.25–4.36)	0.008
Vasopressor use	0.71 (0.38–1.34)	0.291
Initial nutritional approach		
ON	Ref	
NN	2.17 (1.25–3.79)	0.006
EN	1.32 (0.48–3.65)	0.594
PN	1.00 (0.27–3.71)	0.996
Any PN use	1.46 (0.54–3.92)	0.453
Any EN use	2.12 (1.13–3.98)	0.019
Nutrition initiation < 48 h	0.97 (0.57–1.66)	0.918

OR: Odds ratio, CI: Confidence interval, BMI: Body mass index, APACHE: Acute Physiology and Chronic Health Evaluation, ON: Oral nutrition, NN: No nutrition, EN: Enteral Nutrition, PN: Parenteral nutrition.

4. Discussion

Our study found that EN was independently associated with a higher risk for overall infectious complications in critically-ill patients with acute pancreatitis, primarily driven by a higher incidence of pneumonias. PN was associated with a slightly higher incidence of pancreatic infectious complications, but this small difference was offset by the much higher incidence of pneumonias in the EN group. Eckerwall and colleagues [12] identified a higher incidence of pulmonary and overall complications in pancreatitis patients receiving EN via NGT compared to patients receiving TPN, which is consistent with our findings. In that study, most complications were identified within the first 3 days suggesting that it is at the initiation of enteral feeding when patients may be at the highest risk related to EN. The association between EN and pneumonias has not been identified in other RCTs of nutritional support strategies in acute pancreatitis, which focused on the risk of pancreatic infectious complications and organ failure. However, as previously mentioned, the number of critically-ill patients in many of these studies was low, as they focused on patients with predicted severe pancreatitis, many of whom went on to have more benign clinical courses. Because severe acute pancreatitis is relatively rare, individual RCTs do not capture large numbers of the sickest patients. By identifying patients from a national ICU database, this study provides insight into the care of the most critically-ill pancreatitis patients that smaller RCTs are unable to provide.

The higher risk for pneumonias in the EN group is likely attributable to aspiration of GI contents. The incidence of pneumonias in AP patients receiving EN has been reported to be 12% by Bakker and colleagues [13], which is lower than rate identified in our study (21%), although this could be attributed to lower disease severity. Critically-ill patients receiving early, high-caloric EN are known to be at risk for developing pneumonias [14]. Patients with more severe AP may be predisposed to EN intolerance and aspiration for several reasons, and indeed a higher APACHE score was a risk factor for pneumonias among EN patients. Ileus occurs in more than 20% of patients with necrotizing AP [15] and may cause EN intolerance. Although data on EN tolerance was not available for this study, 22 out of 127 EN patients (17.3%) required PN at some point, suggesting that they did not tolerate EN. Patients with severe AP may also receive high-dose vasopressor therapy and the maximum cumulative vasopressor dose is a risk factor for EN intolerance [16], although this was not associated with pneumonias in our study. Patients with severe AP are also often mechanically ventilated and this was a risk factor for both infections and pneumonias in our study, but EN has previously shown to be well-tolerated in these patients [17,18] and our multivariable analysis showed EN to be associated with pneumonia independent of mechanical ventilation. While guidelines issued by the Society of Critical Care Medicine (SCCM) [19] and the European Society of Intensive Care Medicine (ESICM) [20] recommend delaying EN in patients with hemodynamic or ventilatory instability due to the associated visceral hypoperfusion that may reduce EN tolerance, the widely

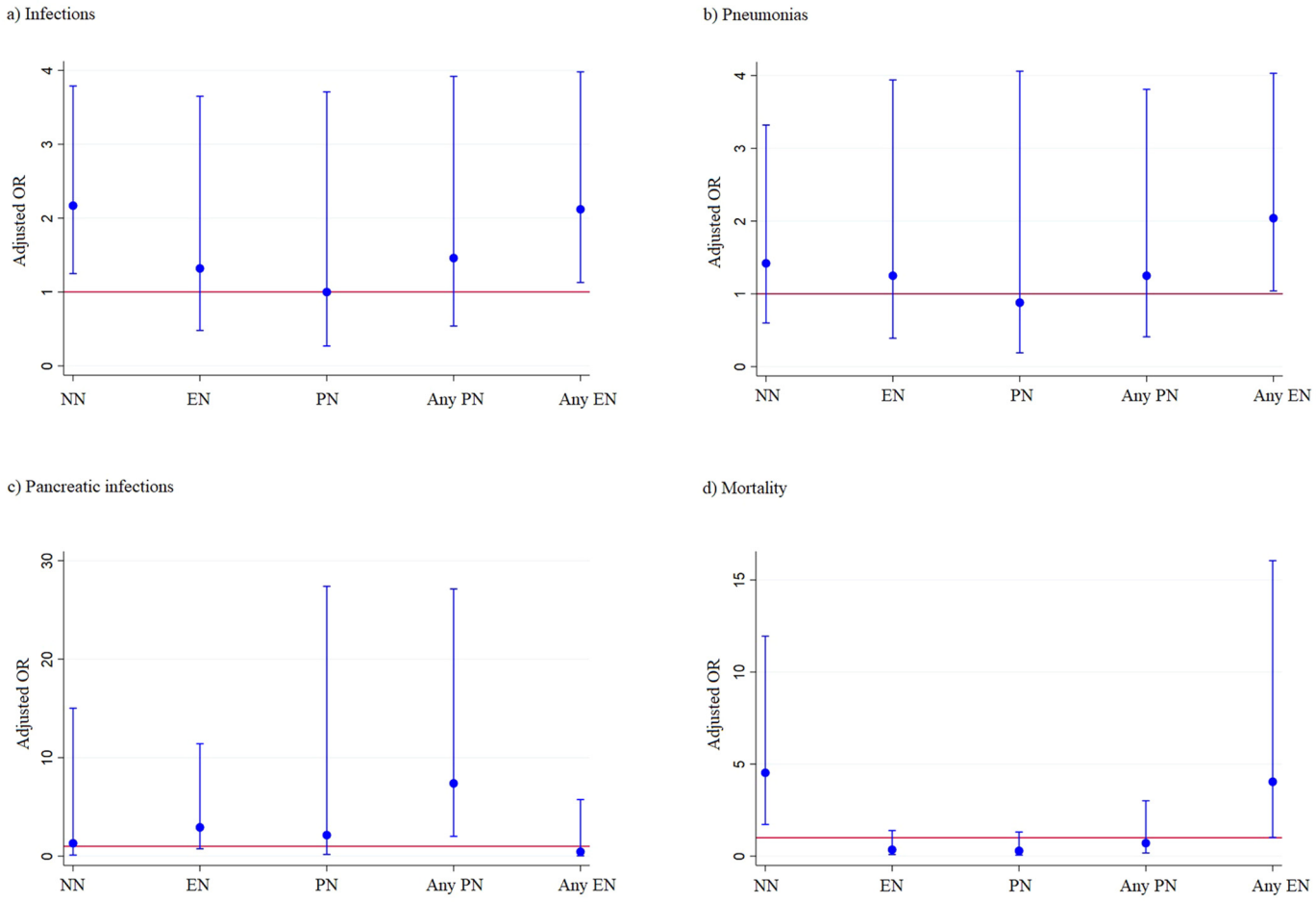

Fig. 1. Adjusted odds ratio (OR) for each nutritional method and: a) infections, b) pneumonias, c) pancreatic infections, and d) mortality.

promulgated benefits of EN in reducing pancreatic infectious complications may encourage clinicians to persist longer with EN in AP patients compared to other critically-ill patients, despite EN intolerance. In fact, the SCCM guidelines recommend taking steps to improve EN tolerance in AP patients with intolerance, rather than discontinuing EN [19]. This persistent use of EN despite intolerance may place patients with severe AP at risk for aspiration and pneumonia.

The discrepancy between our findings and several of the RCTs on the issue (excepting the Eckerwall study cited above) may be explained by the higher disease severity in our cohort. The mean APACHE IV scores of the EN and PN groups (both initial and any use) were approximately 70, which corresponds to a 22% mortality risk [11]. In contrast, RCTs comparing EN to PN in severe AP included patients of lower disease severity, with mean APACHE II scores between 8 and 13 [4,5,8,9,12], corresponding to 7–14% mortality risk [21]. The lower disease severity in these studies is important because higher disease severity was a risk factor for pneumonias. There are several ways that clinicians taking care of critically-ill AP patients may prevent pneumonias. Guidelines should be followed for holding EN in selected critically-ill patients [19,20]. A lower threshold for initiating PN may be instituted, either as an adjunct to EN or as total PN. Patients with severe AP on EN may also benefit from prokinetic agents, chlorhexidine mouth washes, head of bed elevation, nutritional consults and specialized institutional protocols to improve tolerance and reduce aspiration. It is important to note that it is "any EN" and not "initial EN" that was associated with a higher infection risk, as the latter could be a proxy for disease severity on presentation, as patients transitioned from ON to EN were of lower disease severity.

An important question remaining to be answered concerns the superiority of either NG or NJ routes for enteral feeding in severe AP. Small RCTs have failed to detect differences in outcomes between the NG and NJ routes [22-24], but Eckerwall and colleagues [12] using only NGTs found a higher risk of pulmonary complications compared to PN. It is possible that the higher incidence of pneumonias in our study could be attributed to NG feeding, but unfortunately NG vs. NJ feeding is not specified in the eICU database. Additionally, the NN group was also independently associated with in-hospital mortality. This group represents a combination of patients who were discharged

Table 4
Results of multivariate analysis for pneumonias.

	OR (95% CI)	P-value
Age	0.99 (0.98–1.01)	0.474
Female sex	0.85 (0.46–1.58)	0.611
BMI	0.99 (0.95–1.03)	0.687
APACHE score	1.01 (1.00–1.02)	0.020
Mechanical ventilation	3.89 (1.81–8.38)	0.001
Vasopressor use	0.97 (0.47–2.04)	0.946
Initial nutritional approach		
ON	Ref	
NN	1.42 (0.60–3.32)	0.424
EN	1.25 (0.39–3.94)	0.708
PN	0.88 (0.19–4.06)	0.872
Any PN use	1.25 (0.41–3.81)	0.697
Any EN use	2.04 (1.04–4.03)	0.039
Nutrition initiation < 48 h	0.86 (0.45–1.67)	0.663

OR: Odds ratio, CI: Confidence interval, BMI: Body mass index, APACHE: Acute Physiology and Chronic Health Evaluation, ON: Oral nutrition, NN: No nutrition, EN: Enteral Nutrition, PN: Parenteral nutrition.

from the ICU before initiation of nutritional support (as shown by the low admission APACHE score) and patients who died before nutritional support was initiated. The higher risk of mortality is probably related to the latter group of patients. It is possible that lack of nutritional support may have contributed to the higher mortality, which is in accordance with previous studies [25]. Furthermore, the number of patients in the study did not allow a direct head-to-head comparison of different nutritional methods, such as EN vs. PN, so our study is not meant to address this question.

This study has several limitations. First of all, it is a retrospective study and has an inherent selection bias – many factors that we cannot completely account for likely went into the decisions about what types of nutritional support to use in these patients. Multi-institutional cohorts are also biased by heterogeneities in treatment practices among institutions. However, we accounted for these factors as best we could using multivariate analysis, and patients with severe AP are rare, necessitating multi-institutional cohorts to appropriately capture differences in outcomes. Nutritional decision-making in severe AP is highly complex with patients switching among multiple regimens during their ICU and hospital stays. This makes attribution of causality difficult in our study population, but it also reflects clinical reality in a way that may not be captured in a strict RCT protocol. Complications that occurred after ICU discharge are not captured in this cohort and thus our study likely underestimates the incidence of pancreatic infectious complications, operative interventions and long-term mortality. However, early in-hospital mortality is more frequent than late mortality and many of the most severe complications would lead to ICU readmission or death, both of which are outcomes that we captured [26]. Information on necrotizing pancreatitis, pseudocyst formation, EN tolerance, duration of each nutritional approach and end-of-life decision-making are not available in the database. Finally, different modes of EN administration (e.g. NG vs. NJ) were not captured by the eICU database, which may have provide additional insights regarding optimal feeding techniques for these patients. However, previous RCTs have not demonstrated differences in outcomes between different EN administration routes [22-24].

In conclusion, this study found that EN is associated with infectious complications, especially pneumonias, in a large multi-institutional cohort of critically-ill patients with AP, while PN was associated with a higher risk for pancreatic infections. The tendency to push EN in critically-ill AP patients with poor EN tolerance in the name of reducing pancreatic infectious complications should be reconsidered. It is possible that the morbidity of this approach has been masked by the small numbers of truly critically-ill patients in many studies of nutritional support in AP, and the morbidity of associated pneumonias may outweigh the benefits of reduced pancreatic infections. Future studies focusing on critically-ill AP patients and patients who do not tolerate EN could aim to improve outcomes by seeking to identify criteria for starting and for holding EN, describing the optimal routes of EN administration, and exploring the role of adjuncts such as pro-motility agents.

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CRediT authorship contribution statement

Apostolos Gaitanidis: Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Visualization, Writing – original draft, Writing – review & editing. **Kerry Breen:** Data curation, Formal analysis, Resources, Validation, Visualization, Writing – review & editing. **April Mendoza:** Formal analysis, Investigation, Validation, Writing – review & editing. **Jason Fawley:** Data curation, Formal analysis, Investigation, Methodology, Resources, Validation, Writing – review & editing. **Jarone Lee:** Investigation, Methodology, Resources, Software, Validation, Writing – review & editing. **Jonathan Parks:** Formal analysis, Methodology, Project administration, Resources, Software, Writing – review & editing. **Haytham M.A. Kaafarani:** Funding acquisition, Methodology, Project administration, Supervision, Writing – review & editing. **George Velmahos:** Conceptualization, Funding acquisition, Project administration, Software, Supervision, Writing – review & editing. **Peter J. Fagenholz:** Conceptualization, Data curation, Funding acquisition, Project administration, Resources, Supervision, Visualization, Writing – review & editing.

Declaration of Competing Interest

Nothing to declare.

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