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# Early oral vs parenteral nutrition in acute pancreatitis: a retrospective analysis of clinical outcomes and hospital costs from a tertiary care referral center

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## Abstract

Nutritional support is a crucial issue in Acute Pancreatitis (AP) management. Recommendations on nutrition in AP are still not completely translated in the clinical practice. We aimed to compare and evaluate the effects of parenteral nutrition (PN) vs oral/enteral nutrition (EN) on several clinical and economic outcomes in AP. This is a retrospective monocentric study conducted in a tertiary care center for pancreatic diseases. The primary outcomes were length of hospital stay (LOS) and associated costs. The secondary outcomes were the use and cost of antibiotics and fluid therapy, and the complication's rates. One hundred seventy-one patients were included from January 2015 to January 2018. Patients were 69 (40.4%) in PN group and 102 (59.6%) in EN group. There was a significant reduction in LOS in EN vs PN group in both mild AP ($p < 0.0001$), and moderate–severe AP ($p < 0.005$). There was a significant reduction in the total hospitalization costs in EN group vs PN group in both mild AP ($p < 0.0001$), and moderate–severe AP ($p < 0.005$). There was a significant reduction in the total costs of antibiotics and pain therapy in EN vs PN group ($p < 0.0001$ and $p = 0.05$, respectively). Finally, a significant reduction in the infected peri-pancreatic fluid collections rate ($p = 0.04$) was observed in EN vs PN group. The use of EN in AP is associated with substantial clinical and economic benefits. Thus, the application of the standard of care in nutrition and following AP guidelines is the best way to cure patients and improve healthcare system costs.

**Keywords** Oral/enteral nutrition · Parenteral nutrition · Acute pancreatitis · Hospital costs

## Introduction

Acute pancreatitis (AP) is the most common gastrointestinal disorder requiring hospitalization with high rates of morbidity and mortality [1, 2]. The incidence of AP has increased in the last 10 years due to the high prevalence and diffusion of obesity, alcohol intake, and gallstones, and it increases healthcare costs [3]. Typically, AP affects 40–60-year-old patients, and it accounts for 275.000 hospital admissions/year in the USA [4]. AP incidence is estimated to be about 10–40 cases/100.000/year worldwide [5]. The two most common etiologies of AP are alcohol consumption and gallstones, together they represent about 70% of all cases [1].

AP severity has been defined by the Atlanta criteria, initially published in 1992 and revised in 2012 [6]. According to these criteria, AP severity is classified into three classes, namely mild, moderate, and severe, considering the presence of organ failure and/or complications.

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Management of AP patients include fluid resuscitation therapy, antibiotic therapy (when indicated), pain control strategies, and nutritional support [7–9]. Among management strategies of AP patients, nutritional support is a crucial issue and scientific recommendations are still not completely translated in the clinical practice [10–14]. An old paradigm suggested that AP patients should be fasting as long as possible. However, several clinical trials have shown that parental nutrition (PN) does not improve clinical outcomes in AP patients when compared to enteral nutrition (EN). PN is even associated with a higher rate of infective complications [15]. Also, the timing of EN is a highly discussed topic in the management of AP. Recent clinical data have pointed out the advantages of enteral feeding within the first 48 h from the onset of AP [16, 17].

According to the evidence, the latest AP guidelines of the Italian Society for the Study of the Pancreas (AISP) recommend starting EN within the first 24–48 h after the onset of symptoms [18]. The latest AP guidelines of the American Gastroenterological Association (AGA) and of the International Association of Pancreas (IAP) [2, 3] recommend, in patients with mild AP, an early re-feeding, when nausea, vomiting, and abdominal pain are resolved, and after amylase and lipase reduction; while, in case of predicted severe AP (APACHE score > 7 at 48 h, C-reactive protein (CRP) > 150 mg/L, in the presence of systemic inflammatory response syndrome (SIRS) at 48–72 h), naso-enteric tube feeding should be started.

In this context, we conducted a retrospective study comparing parenteral nutrition (PN) to oral/enteral nutrition (EN) in all types of AP (mild, moderate, and severe) to evaluate the effect of early EN (< 48 h) on several clinical and economic outcomes in AP patients in the real life.

## Materials and methods

### Study design

This is a monocentric study with a retrospective design and it was conducted at the "Fondazione Policlinico A. Gemelli IRCCS" hospital, Catholic University, Rome, Italy, a tertiary care center for pancreatic diseases.

We have included in the study all the patients with AP admitted to the Internal Medicine and Gastroenterology Department of the "A. Gemelli" hospital, between January 2015 and January 2018, considering AP as a primary or secondary diagnosis of admission. In our hospital, severe necrotizing AP patients are usually managed in the Intensive Care Unit (ICU), and thus these patients are not recruited in the study. The only severe AP patients recruited in the study presented a not-necrotizing edematous AP that did not required an intensive care. Data were collected in a database and analyzed.

The inclusion criteria were: diagnosis of AP according to the 2012 modified Atlanta criteria as principal or secondary reason of hospitalization; the administration of EN or PN during the hospitalization; the availability of all patients' clinical records. Subjects with incomplete protocols for the data about the use of EN or PN were excluded.

Information regarding AP etiology, comorbidities, and blood exam results, as well as data of fluids, analgesics, and antibiotic therapy, were recorded in our database and retrieved for the study. The Charlson Comorbidity Index (CCI) was evaluated for each patient.

Patients were grouped following the Atlanta classification in mild, moderate and severe AP.

Based on the type of nutrition they underwent, patients were divided into two groups: the first group of patients received EN (EN group) when abdominal pain resolved or within 72 h from the onset of symptoms, and the second group received PN (PN group). EN group included both on-demand early oral feeding (within 48 h) and naso-enteric tube feeding (placed after 48 h from the onset of symptoms).

Olimel N4E (Baxter®, Italy) multichamber bags 1400 kcal/day (Nitrogen 8 g/day) (https://www.baxteritalia.it/sites/g/files/ebysai1416/files/2019-05/RCP%20OLIMEL%20generale%2023%20gen%202019.pdf) was administered in the PN group. In EN group, Nutrison, Nutricia® Italy, polymeric formulas ranging from 1500 to 2250 kcal/day (proteins ranging from 60 to 90 g/day) via naso-enteric tube feeding or oral nutrition of a 1800 kcal/day diet (protein 90 g/day on average) were administered.

### Health costs evaluation

Health costs were determined as follows:

A sum equal to 80,000 euros was attributed to every day of hospital stay (in accordance with data from the Italian Ministry of Economics and Finance ("*Libro Verde Ministero Economia e Finanza"*, https://www.mef.gov.it/ministero/commissioni/ctfp/documenti/Libro_verde_spesa_pubblica.pdf).
Costs related to health and drugs during hospital stay were evaluated in accordance with data published in the "Gazzetta Ufficiale dell'Agenzia Italiana del Farmaco (AIFA, https://www.aifa.gov.it/sites/default/files/Classe_A_per_Principio_Attivo_15.01.2014.pdf, https://www.aifa.gov.it/sites/default/files/Classe_H_per_Principio_Attivo_15.01.2014.pdf).

## Study outcomes

The primary outcomes of this study were length of hospital stay (LOS) and associated costs in relation to the type of nutrition. The secondary outcomes were the use and cost of antibiotics and fluid therapy, and the rates of systemic complications (sepsis/infections, anemia, and etc.), and local complications (fluid collections, infected pancreatic necrosis, splanchnic vein thrombosis, etc.).

## Statistical analysis

Data with normal distribution were evaluated through Kolmogorov–Smirnov test. Continuous data were expressed as mean ± standard deviation (SD). Categorical data were codified through numbers (*n*) and percentages (%). Statistical significance was assessed with Student's *t* test for normally distributed continuous data; either the chi-square test (with Yates' correction when appropriate) or Fisher's exact test was used for categorical data. A $p$ value $< 0.05$ was considered statistically significant. Data analysis was carried out on STATA® (Version 13, Stata Corporation; College Station, TX, USA).

**Table 1** Baseline Characteristics of enrolled patients

| | Total ($n=171$) | PN ($n=69$) | EN ($n=102$) | $p$ value |
|---|---|---|---|---|
| Age (years ± SD) | 53.6 ± 18.8 | 52.6 ± 19.1 | 54.3 ± 18.7 | 0.55 |
| Male sex (%) | 105 (61.0%) | 46 (66.7%) | 59 (57.8%) | 0.25 |
| Smoke (%) | 56 (32.8%) | 27 (39.1%) | 29 (28.4%) | 0.14 |
| Exitus (%) | 2 (1.2%) | 1 (1.5%) | 1 (1.0%) | 1.00 |
| Etiology (%) | | | | |
| Alcohol | 33 (19.3%) | 14 (20.3%) | 19 (18.6%) | 0.79 |
| Biliary | 71 (41.5%) | 28 (40.5%) | 43 (42.3%) | 0.84 |
| Drugs | 8 (4.7%) | 1 (1.5%) | 7 (6.8%) | 0.10 |
| Post-ERCP | 8 (4.7%) | 6 (8.6%) | 2 (1.9%) | **0.04** |
| Other | 51 (29.8%) | 20 (29.0%) | 31 (30.4%) | 0.71 |

Statistically significant value is expressed in bold ($p \leq 0.05$)

*SD* standard deviation, *PN* parenteral nutrition, *EN* oral/enteral nutrition, *ERCP* endoscopic retrograde cholangiopancreatography

## Results

A total of 171 patients were included in the study from January 2015 to January 2018. PN group included 69 (40.4%) patients, and EN group included 102 (59.6%) patients. Characteristics at baseline and AP etiology are reported in Table 1. Biliary origin was the most common cause overall. With regard to severity, 103 (60.2%) patients had mild AP, 60 (35.1%) had moderate AP and 8 (4.7%) had a severe disease based on the Atlanta classification [6]. Among mild AP patients, 34 (33%) received PN, and 69 (67%) received EN (oral nutrition). Among moderate–severe AP patients, 35 (51.5%) received PN, and 33 (48.5%) received EN (oral nutrition) ($p = 0.016$). Only two patients among the severe AP EN group received nasoenteric tube feeding, because did not tolerate oral feeding.

We performed a statistical analysis of primary and secondary outcomes considering both mild and moderate–severe AP patients. In this way, we conducted a subgroup analysis evaluating the different outcomes of EN vs PN in both mild and moderate–severe AP, separately.

Patients with mild AP in the EN group fasted (considering oral nutrition) for fewer days (EN fasting 2.1 ± 1.2 days vs PN fasting 6.2 ± 2.8 days, $p < 0.0001$). We showed a shorter LOS in EN vs PN in mild AP patients (EN average LOS 6.5 ± 2.5 days vs PN average LOS 10.5 ± 5.1 days, $p < 0.0001$). In the same way, patients with moderate–severe AP in the EN group fasted for fewer days (EN fasting 2.7 ± 1.7 days vs PN fasting 7.3 ± 5.3 days, $p < 0.0001$). We showed a shorter LOS in EN vs PN in moderate–severe AP patients (EN average LOS 9.4 ± 4.6 days vs PN average LOS 14.3 ± 7.4 days, $p < 0.005$). These data are summarized in Tables 2 and 3.

Considering the secondary outcomes, there were no differences in the use of fluid-therapy in both groups ($p = 0.12$). There was a significant reduction in the use and total costs of antibiotic therapy in EN group in comparison to the PN group (127.3 ± 223.5 euros vs 235.7 ± 463.7 euros, respectively, $p < 0.0001$), and in the use and total costs of pain-therapy in EN group in comparison to PN group (10.6 ± 24.9 euros vs 18.1 ± 26.5 euros, $p = 0.05$). These results are summarized in Table 4.

**Table 2** Fasting days, average hospitalization days and related costs in mild AP comparing PN and EN groups

| | PN group ($n=34$ ± SD) | EN group ($n=69$ ± SD) | $p$ value |
|---|---|---|---|
| Fasting (days) | 6.2 ± 2.8 | 2.1 ± 1.2 | **< 0.0001** |
| Average hospitalization (days) | 10.5 ± 5.1 | 6.5 ± 2.5 | **< 0.0001** |
| Hospitalization cost (€) | 8400 ± 4.080 | 5200 ± 2000 | **< 0.0001** |

Statistically significant values are expressed in bold ($p \leq 0.05$)

*SD* standard deviation, *PN* parenteral nutrition, *EN* oral/enteral nutrition

Finally, there was a trend towards reduction in the complication rates in the EN group in comparison to the PN group (33.3% vs 46.4%, $p=0.08$), and a significant reduction in the infected peri-pancreatic fluid collections rate in EN group vs PN group (23.5% vs 38.2%, $p=0.04$) (Table 5).

## Discussion

The most recent AGA, IAP/APA, and AISP guidelines on nutrition in AP recommend an early oral nutrition (within 24 h from the onset of symptoms) in patients affected by mild AP [3, 18, 19]. Similarly, for patients with severe AP, guidelines recommend to begin EN as soon as abdominal pain resolves and nausea improves, but not later than 48 h from the onset of symptoms [11, 12, 18]. In this way, patients should be encouraged to begin oral diet once symptoms improved, but, if they persist symptomatic after 72 h, a naso-enteric tube placement is indicated to start enteral tube feeding. Nevertheless, to date, clinicians rarely embrace these recommendations and fasting is maintained for several days in patients with AP, feeding patients with PN [15].

The present retrospective study has showed a good—even if not complete—adherence of our center to the international guidelines on nutrition in AP patients. In fact, in this study, only 69 patients out of 171 (40.4%) maintained fasting for more than 48 h, whereas the majority of patients (59.6%) received EN within 48 h from admission, as recommended by the current guidelines.

In our study, mild AP patients were mostly fed with EN vs PN (67% vs 33%, respectively), whereas moderate–severe AP patients were equally fed with EN vs PN

**Table 3** Fasting days, average hospitalization days and related costs in moderate/severe AP comparing PN and EN group

| | PN ($n=35\pm$SD) | EN ($n=33\pm$SD) | $p$ value |
|---|---|---|---|
| Fasting (days) | 7.3 ± 5.3 | 2.7 ± 1.7 | **< 0.0001** |
| Average hospitalization (days) | 14.3 ± 7.4 | 9.4 ± 4.6 | **< 0.005** |
| Hospitalization costs (€) | 11440 ± 5920 | 7520 ± 3680 | **< 0.005** |

Statistically significant values are expressed in bold ($p \leq 0.05$)

*SD* standard deviation, *PN* parenteral nutrition, *EN* oral/enteral nutrition

**Table 4** Costs related to fluid, antibiotic and analgesic therapy in patients with AP comparing EN and PN (both mild and moderate–severe acute pancreatitis)

| Costs (€) | Total [$n=171$] (€ ± SD) | PN [$n=69$] (€ ± SD) | EN [$n=102$] (€ ± SD) | $p$ value |
|---|---|---|---|---|
| Fluid-therapy/die | 2.6 ± 3.1 | 2.2 ± 2.8 | 2.9 ± 3.2 | 0.12 |
| Fluid-therapy /hospitalization | 22.7 ± 27.9 | 25.6 ± 33.9 | 20.7 ± 22.9 | 0.26 |
| Antibiotic therapy/die | 17.2 ± 23.5 | 21.7 ± 24.9 | 14.2 ± 22.0 | **< 0.05** |
| Antibiotic therapy/hospitalization | 195.3 ± 312.2 | 235.7 ± 390.2 | 127.3 ± 223.5 | **< 0.001** |
| Analgesic/die | 1.3 ± 2.3 | 1.5 ± 2.3 | 1.2 ± 2.4 | 0.30 |
| Analgesic /hospitalization | 13.6 ± 25.8 | 18.1 ± 26.5 | 10.6 ± 24.9 | **0.05** |

Statistically significant values are expressed in bold ($p \leq 0.05$)

*SD* standard deviation, *PN* parenteral nutrition, *EN* oral/enteral nutrition

**Table 5** Complications in patients with AP comparing EN and PN (both mild and moderate–severe acute pancreatitis)

| Complications | Total ($n=171$, %) | PN ($n=69$, %) | EN ($n=102$, %) | $p$ value |
|---|---|---|---|---|
| Pseudocyst/walled off pancreatic necrosis (WOPN) | 50 (29.4) | 26 (38.2) | 24 (23.5) | **0.04** |
| Local infections | 6 (3.5) | 3 (4.4) | 3 (2.9) | 0.61 |
| Sepsis | 9 (5.3) | 5 (7.4) | 4 (3.9) | 0.32 |
| Anemia | 10 (5.8) | 4 (5.8) | 6 (5.8) | 1.00 |
| Abdominal thrombosis | 9 (5.3) | 4 (5.8) | 5 (4.9) | 0.78 |
| Other | 12 (7.2) | 8 (11.7) | 4 (4.1) | 0.06 |
| Total | 66 (38.6) | 32 (46.4) | 34 (33.3) | 0.08 |

Statistically significant value is expressed in bold ($p \leq 0.05$)

*PN* parenteral nutrition, *EN* oral/enteral nutrition

(48.5% vs 51.5%, respectively). These data confirm the recurrent practice of clinicians to use PN in patients with more critical conditions, such as patients with moderate–severe AP, despite guidelines have demonstrated the superiority of EN vs PN also in this kind of patients. Indeed, a recent meta-analysis including 5 RCTs and 348 patients confirmed that in critically ill severe AP patients, EN should be preferred to PN, because it is associated with a significant reduction in overall mortality and multi-organ failure (MOF) rates [20]. Then, another recent meta-analysis including 9 RCTs and 500 severe AP patients showed that EN is associated with a reduction of LOS and a lower infectious and organ failure rates, indicating that in more critical patients EN is safer and more effective than PN [21].

In this retrospective analysis, we observed a significantly shorter average LOS in patients receiving EN in comparison to patients receiving PN, both in mild and moderate/severe AP ($p < 0.0001$ and $p < 0.005$, respectively). Hence, these data confirm that EN may have a positive impact on AP-related symptoms, thus allowing earlier discharge. Several evidences have shown the harmful consequences of prolonged starvation and the use of PN, such as enteral nutrient deprivation, atrophy of gut-associated lymphoid tissue (GALT), the production of inflammatory mediators in gut mucosa, alteration in gut mucosal barrier due to a loss of epithelial tight junctions and adherence proteins, and gut dysbiosis due to a overgrowth of pathogenic bacteria over physiologic flora [22]. These mechanisms are able to determine systemic bacterial, pancreatic enzymes, and inflammatory mediators translocation leading to sepsis and organ failure that may be associated with AP [15]. In this way, prolonged starvation and PN are linked to a prolonged LOS and a higher risk to develop infectious complications. On the contrary, the shorter LOS in patient fed with EN has been able to decrease the risk of infections. In this way, in 2008, the results of a RCT on 131 mild AP patients were published demonstrating that feeding patients with a soft solid oral diet was associated with a significant reduction of LOS of a median of 2 days [23]. It is also important to underline that AP patients often present other risk factors for the development of infections, such as chronic alcohol abuse, immunodepression, old age, etc. To confirm, in 2010, a systematic Cochrane review including 8 RCTs and 348 patients demonstrated that EN vs PN was associated with a significant reduction in mortality, MOF, systemic infections and operative interventions rates. These benefits appeared to be higher in patients with a more severe AP. Furthermore, these authors showed that there was also a trend towards a reduction in LOS in patients fed with EN [24]. Moreover, a meta-analysis published in 2018 including 11 trials and 562 AP patients (281 EN vs 281 PN) further confirmed a significant reduction in mortality, infections and complications rates, and also a reduction in the mean LOS in the EN group [25].

Moreover, we found that EN is also significantly associated with reduced daily and overall hospitalization costs in both mild and moderate–severe AP. A reduction in costs was also due to the reduced administration of drugs, such as antibiotics or analgesics in the EN group, in comparison to the PN group.

Due to the heavy fluid re-distribution to the third space in the pancreatic and retro-peritoneal tissues, guidelines recommend intense hydration in AP-patients during the first days of hospitalization. In this way, we did not find any statistically significant differences in the quantity and duration of fluid-therapy between EN vs PN patients, as far as all AP patients require the same quantity of fluids during the onset of AP.

Therefore, a borderline statistically significant difference in the use of analgesic therapy between EN vs PN patients was also found ($p = 0.05$), with a consequent positive impact on health costs and LOS. The differences in the use of antibiotic therapy were statistically significant in the two groups ($p < 0.05$), further reducing the costs and also evidencing the importance of EN in maintaining gut homeostasis and reducing inflammation. It also underlines the importance of the use of antibiotic therapy only when it is clearly indicated, that is in patients who have a documented infection.

Finally, we showed a reduction in the development of overall complications in the EN vs PN group, although the result was not statistically significant ($p = 0.08$). Still, among AP complications, we showed that the number of peripancreatic collections was instead significantly reduced in EN vs PN group ($p = 0.04$). These data further confirm the positive role of EN in limiting gut dysbiosis and the consequent bacterial translocation thus reducing both infectious and local peripancreatic complications.

Even if our study confirmed the literature data about the superiority of EN vs PN in both mild and moderate–severe AP, the choice of nutritional route should be carefully evaluated in each single case according to the clinical conditions of the patient. In this way, the use of PN is clearly needed in context of intestinal failure or bowel obstruction. However, PN is not recommended as nutritional support in AP if bowel function is preserved. In case of AP patients with the persistence of nausea, vomiting, and abdominal pain precipitating in a malnutrition state, an association of PN with EN may be considered. International guidelines warn physicians against the use of PN as unique nutritional support since it is unsafe as reported by several trials and meta-analyses [15].

## Conclusion

This real-life study analyzing a 3-year clinical experience of tertiary care referral center for pancreatic diseases showed that the use of EN vs PN in all types of AP is associated with

some benefits, such as the reduction of LOS and health costs, and a reduction in systemic and local complications. These results are consistent with previous studies, indicating that the old paradigm of prolonged fasting in AP is not useful and even harmful, for both patients and the healthcare system.

Moreover, we have highlighted that EN has a positive role in the course of AP patients, because it is able to improve symptoms and reduce AP-related complications, such as systemic infections and infected peripancreatic collections, protecting the gut mucosal barrier and reducing bacterial translocation. Thus, the application of the standard of care in nutrition and following AP guidelines may have a beneficial role in the modern precision medicine to cure patients and reduce healthcare system costs.

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## Compliance with ethical standards

**Conflict of interest** The authors declare that they have no potential conflict of interest.

**Statement of human and animal rights** The procedures employed to draft this manuscript respect the ethical standards in the Helsinki Declaration of 1975, as revised in 2000, as well as the national law.

**Informed consent** A formal consent was obtained from all the recruited patients. This study was approved by the Ethical Committee of the Catholic University of the Sacred Heart.

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