OPEN ACCESS

Original research

High versus gradually increasing energy nutrition in the early phase of acute pancreatitis (GOULASH): a multicentre double-blind randomised clinical trial

Katalin Márta,[1] Marie Anne Engh,[2] Áron Vincze,[3] Bálint Erőss,[1,2,4] Péter J Hegyi,[1,2] Alexandra Mikó,[4,5] Ferenc Izbéki,[6] Mária Papp,[7] Péter Mátrai,[4] Zsolt Abonyi-Tóth,[4,8] Nándor Faluhelyi,[9] Andrea Szentesi,[4] Péter Hegyi ,[1,2,4,10] the Goulash Trial Group

► Additional supplemental material is published online only. To view, please visit the journal online (https://doi.org/10.1136/gutjnl-2025-335970).

For numbered affiliations see end of article.

Correspondence to
Professor Péter Hegyi;
hegyi2009@gmail.com

KM and MAE contributed equally.

Received 28 May 2025
Accepted 21 February 2026

To cite: Márta K, Engh MA, Vincze Á, *et al*. *Gut* Epub ahead of print: [*please include* Day Month Year]. doi:10.1136/gutjnl-2025-335970

ABSTRACT

Background Acute pancreatitis (AP) is among the most common gastrointestinal diseases requiring hospitalisation, often with severe outcomes and no disease-specific therapy. Nutritional support has been proven to improve outcome, but little is known regarding optimal timing and composition.

Objective This clinical trial aimed to compare high (30 kcal/kg/day, high energy (HE)) versus gradually increasing energy (0 increased to 30 kcal/kg/day over 4 days, low energy (LE)) strategies for enteral nutritional support in AP.

Design This was a multicentric, double-blind, randomised clinical trial, enrolling patients with AP regardless of predicted severity (January 2017 to April 2023). The primary outcome was a combination of mortality and severe acute pancreatitis (Revised Atlanta Criteria); secondary outcomes included severity, rate of infection, organ failure and pain relapse. Interim analysis was planned after 50% enrolment. The Benjamini-Hochberg false discovery rate (FDR) method was used to correct p value for multiple testing.

Results The trial was stopped early after enrolling 636 patients. Interim analysis showed that the primary outcome showed no difference between groups in the modified intention-to-treat (mITT) population (HE: 28/312, 9.0% vs LE: 18/307, 5.7%, p(uncorrected/corrected)=0.19/0.42). Secondary outcomes showed no difference in the mITT analysis. Without correction for multiplicity testing, results favoured a low gradual energy strategy in terms of organ failure (HE: 52/312, 16.7% vs LE: 28/307, 9.1%, p(uncorrected)=0.007) and pain relapse (80/312, 27.1% vs 54/307, 19.0% p(uncorrected)=0.03) but showed no differences between groups after correction for multiple testing (p=0.13 and p=0.23, respectively). It was determined that the superiority of the intervention would not be shown even with an increased sample size, and thus the trial was terminated based on a post hoc decision on ethics and futility.

Conclusion Based on this early terminated trial, a high-energy strategy for early nutrition in pancreatitis does not decrease mortality/severity, but potentially increases organ failure and pain relapse rate.

Trial registration number ISRCTN63827758.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Nutritional support can improve outcomes after acute pancreatitis, including reducing severity and mortality.

WHAT THIS STUDY ADDS

⇒ This study investigates two different approaches to early nutritional support (gradual implementation vs immediate high energy delivery) and shows that high energy delivery does not improve outcomes, and potentially worsens them.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ Based on the findings of this study, there is no justification to use a high energy approach to early nutrition, and gradual implementation of energy delivery is preferred.

INTRODUCTION

Acute pancreatitis (AP) is an inflammatory condition of the exocrine pancreas, with around 3 million cases annually worldwide[1] and a mortality rate ranging from 0.3% to 28.3% in its mild and severe forms, respectively.[2] Currently, no specific treatment exists; however, guidelines suggest fluid therapy, nutritional support and, in selected cases, interventions.[3]

Historically, a nil-per-os regimen was applied for patients with pancreatitis. However, the benefits of nutritional support in AP have a strong basis in pathophysiological and basic research. In vitro and in vivo studies have shown the important role of ATP depletion in virtually all aetiologies of pancreatitis, with the combination of energy deficiency and mitochondrial damage being a key driver of pancreatic injury.[4–7] Based on this theoretical background, studies have aimed to investigate the benefits of nutritional support, including systematic reviews and meta-analyses that showed a clear benefit to nutritional support in adult and paediatric populations—not only in severe acute pancreatitis (SAP) but also potentially in mild AP.[8–10]

As a result, nutritional support and early reintroduction of feeding have become a cornerstone

of the treatment of AP. Current guidelines recommend starting oral feeding when abdominal pain subsides and to prefer enteral nutrition (EN) if nutritional support is needed, by either nasojejunal or nasogastric tube. Parenteral nutrition is indicated if enteral nutrition is not tolerated. The guidelines do not elaborate on the ideal energy content of enteral nutrition.[3 11] Meanwhile, approximately 70% of pancreatology specialists and 60% of surgeons start some form of oral nutrition within the first 2 days of AP, while around 30% follow an early onset tube feeding strategy in moderate and severe AP. However, there is a divide between the caloric target of enteric feeding, with 40% of pancreatologists attempting to reach >25 kcal/kg/day within 24 hours, and 60% starting with <10 kcal/kg and escalating over 3–4 days.[12]

To address this gap in the guidelines, this study aimed to further elaborate the ideal protocol for nutritional support.[13] In view of a profound deficit in ATP early in the course of AP,[5] and improvement with enteral nutritional support in animal models,[4] we hypothesised that immediate high-energy support would provide clinical benefits by protecting against cell death and systemic inflammation.

To achieve this aim, we designed a multicentre, double-blind, randomised clinical trial comparing a high versus a gradually increasing energy delivery approach in patients with AP, aiming to reduce the primary outcome, a composite outcome of mortality and SAP.

METHODS

Trial design

This was a parallel group, randomised, controlled, two-arm, double-blind, multicentre trial in Hungary, with a 1:1 allocation ratio. The protocol was previously published[13] and registered at the ISRCTN registry (ISRCTN63827758). The complete protocol in its original version is available in the online supplemental appendix. We report the trial in accordance with the CONSORT (Consolidated Standards of Reporting Trials) statement.[14]

Ethics statement

This trial is conducted according to the principles of the Declaration of Helsinki, and ethical approval was obtained from the Scientific and Research Ethics Committee of the Hungarian Medical Research Council (55961-2/2016/EKU).

Patient and public involvement

Participants of our patient club were invited to attend our annual conference organised by the Hungarian Pancreatic Study Group, where we shared updates on our ongoing and planned clinical studies. Their feedback was actively sought on various aspects of the research project, as we highly value their perspective and experiences.

Our patient club is built around the idea of creating supportive communities for individuals living with chronic illnesses or recovering from acute conditions. These clubs provide comprehensive, reliable information to help members understand and manage their health, while also ensuring their voices are heard and represented.

Due to the nature of the trial, which did not require significant differences to standard treatment employed at the department beyond a change in nutritional composition, no major objections were raised.

Settings and locations

Five clinical centres in Hungary participated in the trial.

Trial oversight

The trial was designed and coordinated by the Institute for Translational Medicine at the University of Pécs in collaboration with the Hungarian Pancreatic Study Group.

All decisions concerning relevant questions, including drop-outs during the trial, were made by the steering committee (SC), assisted and monitored by the international trial advisory board, which also participated in the design of the study. Their details can be found in the online supplemental appendix.

Patient enrolment

Patients were eligible for inclusion if they (1) were over 18 years of age; (2) had diagnosed AP based on the '2 out of 3' criteria of the International Association of Pancreatology/American Pancreatic Association (IAP/APA) guideline: (a) upper abdominal pain; (b) serum amylase or lipase >3 × the upper limit of normal range; (c) characteristic findings on pancreatic imaging; and (3) had signed a written informed consent form.

Exclusion criteria were: (1) any prior hospitalisation within 72 hours before admission to our hospital; (2) abdominal pain >120 hours (5 days) or lack of abdominal pain (because onset of AP could not be determined); (3) delirium tremens; (4) Child-Pugh C stage liver cirrhosis; (5) AP due to malignancy; (6) already on artificial nutrition (EN or parenteral nutrition) at admission; (7) pregnancy; (8) body mass index (BMI) >40 or <18; (9) age >80 years; (10) ketoacidosis; and (11) whenever intravenous CT contrast agent administration is contraindicated.

All patients diagnosed with AP were informed of the possibility of taking part in the trial. When a patient was admitted to the emergency department with a diagnosis of acute pancreatitis, the on-call physician responsible for the studies (10–15 physicians per shift) was notified via a hotline. The on-call physician performed the inclusion test and informed the patient about the possibility of participation. If the patient expressed his/her consent in writing, patients were randomised and assigned to either Group A ('High Energy', high-energy administration starting within 24 hours of hospital admission) or Group B ('Gradual Energy', gradually increasing energy administration after hospital admission).

Randomisation

Predefined randomisation lists were used for randomisation, each created separately for each recruiting centre. The lists were prepared with a block size of 4 and an allocation ratio of 1:1 by an independent data management and biostatistics provider company (IDMB, Adware Research, Balatonfüred, Hungary). No stratification was applied. Once the allocation sequence was generated, the primary investigator (KM) sealed the allocation one-by-one in an envelope. The randomisation ID was written on the envelope. The allocation sequence was concealed by sealed envelopes, and nutritional support equipment was covered during the first 3 days.

Interventions

After enrolment, on admission, patients received a Ch 10 feeding tube. Patients with vomiting or gastric fluid retention >250 mL or a Glasgow Coma Scale score of 14 or lower without intubation received a nasojejunal (NJ) tube. All others received a nasogastric (NG) tube.

High-energy group
Immediately after randomisation (day 1), patients received 30/kcal/kg/day, which was continued until the start of oral feeding.

Gradual-energy group
Patients received 0 kcal/kg/day on day 1. Energy was increased daily by 10 kcal/kg/day, reaching 30 kcal/kg/day by day 4.

Composition and delivery of nutrition
To achieve calorie intakes of 0–30 kcal/kg/day, two types of enteral tube feeds (zero-energy and high-energy tube feeds) were used and mixed to achieve 10 and 20 kcal/kg/day. The amount of fluid and electrolytes administered per day was the same in both study arms. Exact composition and details of delivery can be found in the online supplemental appendix.

Introduction of oral feeding
Induction of oral feeding was protocolised to ensure consistency. The requirements and procedures for starting oral feeding can be found in the online supplemental appendix.

Additional therapies
Patients received the standard of care for AP following IAP/APA guidelines.[11]

Patient discharge
Patient discharge was protocolised[15] to minimise the risk of bias for the length of hospitalisation (LOH), see online supplemental appendix.

Endpoints
The primary endpoint was a composite of (1) severe acute pancreatitis, defined as a combination of organ (including cardiovascular, pulmonary and renal) failure persisting for more than 48 hours with AP,[16] and (2) mortality. Secondary endpoints were according to the protocol: (1) pancreatic necrosis; (2) nutrition-related complications (diarrhoea, aspiration pneumonia, pneumothorax caused by total peripheral nutrition (TPN)); (3) need for conversion from NG to NJ feeding tube; (4) need for conversion from EN to TPN; (5) days until the start of total per os feeding; (6) need for antibiotic treatment; (7) pain relapse after start of mixed/total per os feeding; (8) highest C-reactive protein (CRP); (9) highest white blood cell (WBC) count; (10) highest procalcitonin; (11) microbiologically confirmed infection of any kind; (12) LOH; (13) need for intensive care unit (ICU) admission; (14) duration of ICU treatment; (15) organ failure of any duration (cardiovascular, pulmonary, renal and pancreatic); (16) local complications; (17) cost calculations based on the duration of hospital stay, the need for medication, duration of ICU stay and interventions. Due to the early termination of the trial, the lack of benefit of the intervention and the lack of differences in the outcomes that were to be considered for our planned cost-benefit analysis, it was omitted.

Laboratory values were collected during the morning visit, while other clinical outcomes were entered into the data entry system after the morning visit. The severity was evaluated on the day of discharge and uploaded at that point. All patients underwent a CT scan before randomisation and were re-assessed at least once again, on discharge.

Sample size calculations
The sample size was calculated by an IDMB (Adware Research, Balatonfüred, Hungary). In recent analyses, multiorgan failure (MOF) of over 48 hours and mortality occurred in about 9% and 2.8% of patients with AP, respectively.[2] The overall event rate of mortality and MOF thus made up approximately 10% of patients with AP. Applying Fleiss χ^2 test for superiority and assuming a 10% drop-out rate, 80% power, a 95% significance level and a desire to detect a treatment effect of at least 50% of early treatment,[17] the sample size for this trial was set at 957 subjects.

Blinding
The patient and the clinical staff administering general care to the patient, as well as outcome assessors, were blinded to the treatment assignment of the patient. Only the dedicated person, a medical doctor in PhD training in clinical sciences, who delivered the intervention was aware of group allocation and ensured that nutritional support equipment was covered all the way until the patient nose. Covering was maintained until day 4, after which both groups received the same composition of feed. Only nutritional content differed between groups; the volume and speed of delivery was equal in both arms.

Data management
The IDMB handled the data and safety analysis.

Interim assessments
An early quality assessment was planned after the first 100 patients, was performed and did not show a significant difference in the primary outcome between the two groups (p=0.398). The distribution of subjects by gender in the two groups was similar. The parameters of aetiology were not significantly different between the two groups. Most of the obligatory parameters were not significantly different between the two groups. Only the value of amylase was statistically significant (p=0.048). The results of the abdominal CT scans were similar for the two groups, with no significant difference in the CT severity indexes.

An interim analysis was planned after 50% of patients were randomised, performed by the IDMB and reported to the SC. An a priori stopping rule was set that a probability of <0.001 to reject the null hypothesis would allow the trial to be stopped early. The trial was paused after 50% of patients had been discharged from hospital and their data had been through all steps of data verification. No further patients were enrolled from that stage and interim analysis was performed with available data. Although the conditions set out in the a priori rules did not apply, the interim analysis showed that regardless of sample size, superiority would not be shown. Based on the apparent futility of the trial and out of ethical considerations for patient safety, patient enrolment was terminated. Data collection and verification were completed for patients already enrolled in the trial, and the complete dataset forms the basis of this analysis.

Statistical methods
R V.4.4.2 was used for the analysis. Both a modified intention-to-treat (mITT) and a per-protocol (PP) analysis was performed. The mITT analysis included all patients randomised and eligible according to eligibility criteria that had started the allocated intervention. The PP analysis included only patients who received the allocated caloric intake in the first 24 hours. We provided descriptive statistics for the baseline parameters: mean and SD, median and IQR for the numerical variables, case numbers and percentages for the categorical ones. Due to the homogeneity of the baseline values, it was not necessary to adjust for them. We reported the number of missing values as well.

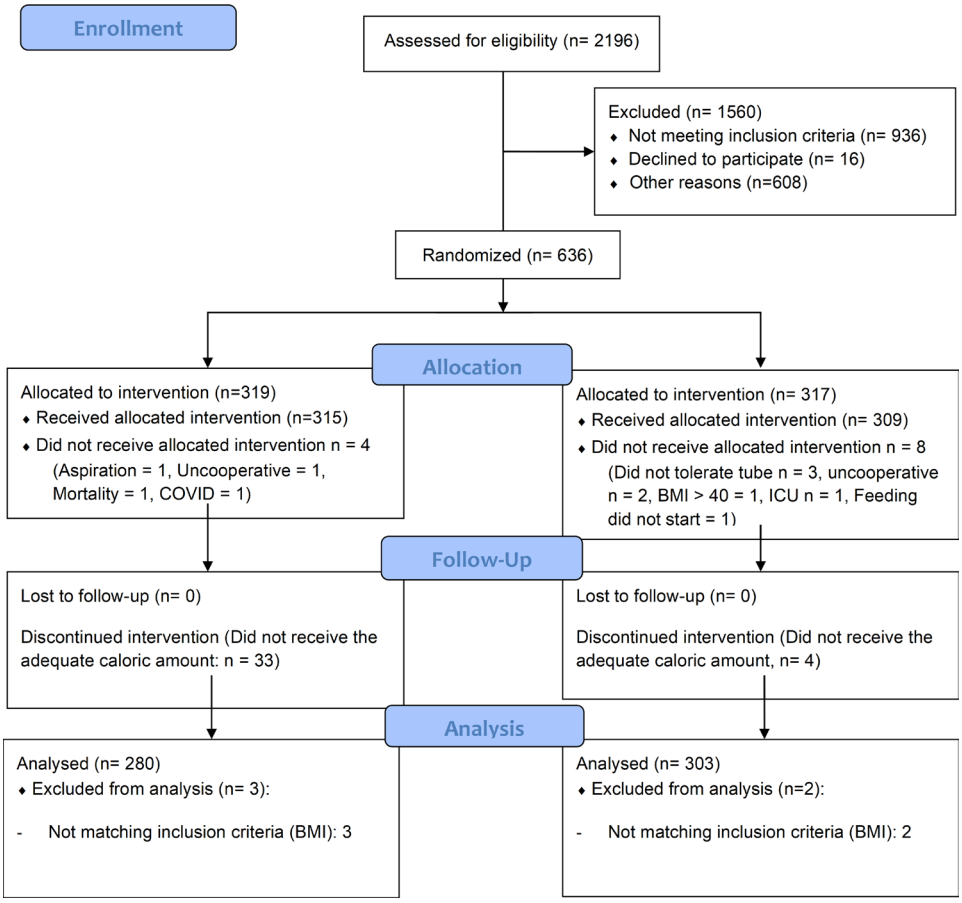

Figure 1 CONSORT flowchart detailing patient enrolment. CONSORT, Consolidated Standards of Reporting Trials; BMI, body mass index; ICU, intensive care unit.

Risk ratios (RR) and mean differences (MD) with 95% CI were calculated for comparisons.

We used the Welch test to compare numerical variables and Pearson's χ^2 test to compare relative frequencies. The explanatory variable was the treatment arm in both mITT and PP analysis. P values were adjusted using the Benjamini-Hochberg FDR method. In the mITT and the PP analysis, 17 statistical tests were performed. In the subgroup analysis, Bonferroni-Holm correction was applied across both mITT and PP values for each subgroup analysis.

Missing values were excluded from the analysis.

RESULTS

Patient enrolment

Between January 2017 and April 2023, 636 patients were enrolled in the trial and randomised. Details of patient enrolment can be found in the CONSORT diagram (figure 1).

Patient characteristics

The study included a total of 619 patients in the mITT analysis, with 312 in the high-energy group and 307 in the gradual energy group. Their characteristics are summarised in table 1.

In the PP analysis, which included 583 patients (280 in the high-energy group and 303 in the gradual-energy group), the baseline characteristics remained consistent with the mITT population (online supplemental table S1).

Primary outcome: mortality and severity

Results are depicted in table 2.

The primary outcome, a composite of in-hospital mortality and SAP, did not differ significantly between the high-energy and gradual-energy groups in either mITT or PP analyses (table 2). In the mITT analysis, the composite outcome occurred in 28 patients (9.0%) in the high-energy group and 18 patients (5.9%) in the gradual-energy group (RR=1.53, 95% CI 0.86 to 2.71, p(uncorrected)=0.19/p(corrected)=0.42). The same result was observed in the PP analysis, with no difference in the primary outcome between the groups (RR=1.71, 95% CI 0.92 to 3.19, p(uncorrected)=0.56/p(corrected)=0.79).

Secondary outcomes

Results are depicted in table 2.

Pain relapse: pain relapse was significantly more common in the high-energy group compared with the gradual-energy group before correction for multiplicity. In the mITT analysis, relapse occurred in 27.1% of the high-energy group and 19.0% of the gradual-energy group (RR=1.43, 95% CI 1.06 to 1.94, p(uncorrected)=0.03, p(corrected)=0.23). The PP analysis demonstrated a similar difference, present only before correction, with relapse rates of 26.1% in the high-energy group versus 18.9% in the gradual-energy group (RR=1.39, 95% CI 1.01 to 1.90, p(uncorrected)=0.05, p(corrected)=0.32).

Organ failure: organ failure was significantly more frequent in the high-energy group compared with the gradual-energy group before correction for multiplicity. In the mITT analysis, organ failure occurred in 16.7% of the high-energy group and 9.1% of the gradual-energy group (RR=1.83, 95% CI 1.19 to 2.81, p(uncorrected)=0.007, p(corrected)=0.13). Similarly, the PP

Table 1 Baseline characteristics of included patients

mITT	High energy	Gradual energy	Missing values
Total	312	307	
Sex—N (%)			0
Female	131 (42)	118 (38.4)	
Male	181 (58)	189 (61.6)	
Age			0
Mean (SD)	54.79 (14.58)	53.6 (14.8)	
Median (IQR)	56 (44–67)	53 (43–65)	
BMI			19
Mean (SD)	28.48 (5.17)	28.47 (5.02)	
Median (IQR)	28.16 (24.84–31.52)	28.15 (24.81–32.14)	
Aetiology—N (%)			0
Alcohol	78 (25)	62 (20.2)	
Biliary	139 (44.6)	149 (48.5)	
Hypertriglyceridaemia	12 (3.9)	4 (1.3)	
Hypertriglyceridaemia+alcohol	9 (2.9)	19 (6.2)	
Idiopathic	45 (14.4)	28 (9.1)	
Multiple	6 (1.9)	12 (3.9)	
Other	23 (7.4)	33 (10.8)	
Abdominal pain at admission	309 (99)	306 (99.7)	0
Baseline WBC			13
Mean (SD)	13.09 (4.69)	13.77 (4.6)	
Median (IQR)	12.8 (9.5–16.04)	13.3 (10.54–16.28)	
Baseline PCT			63
Mean (SD)	0.97 (4.44)	1.04 (4.38)	
Median (IQR)	0.12 (0.04–0.37)	0.13 (0.05–0.41)	
Energy delivery in the first 4 days—mean (SD)			
kcal/bwkg	103.8 (20.3)	58.5 (17.3)	127
kcal	8401.7 (1520.7)	4699.3 (1225.6)	110
Energy delivery until total oral feeding—mean (SD)			
kcal/bwkg	114.3 (130.4)	55.5 (68.3)	34
kcal	9358.4 (9425.3)	4857.8 (7924.2)	10

BMI, body mass index; ITT, intention-to-treat; kcal/bwkg, kilocalories per body-weight kilogram; PCT, procalcitonin; WBC, white blood cell.

analysis reported rates of 14.3% in the high-energy group versus 8.6% in the gradual-energy group (RR=1.66, 95% CI 1.04 to 2.65, p(uncorrected)=0.04, p(corrected)=0.32).

Maximum CRP: in the PP analysis, maximum CRP levels were significantly lower in the high-energy group compared with the gradual-energy group before multiplicity testing (161.1±110.79 mg/L, 181.43±116.76 mg/L, MD=−20.33, 95% CI −40.01 to 0.65, p(uncorrected)=0.04, p(corrected)=0.32).

Other outcomes: no significant differences were observed between the high-energy and gradual-energy groups for other secondary outcomes, including the other inflammatory markers and other clinical complications.

Subgroup analyses

Subgroup analyses were conducted based on the time of onset of pain, age, BMI and severity. Results of the subgroup analysis can be found in the supplementary materials (online supplemental text and tables S2–S7).

DISCUSSION

This randomised clinical trial assessing the effect of early high-energy enteral administration in a setting of acute pancreatitis showed no benefits in the primary outcome, a composite outcome of mortality and severe AP. However, before correction for multiplicity, both the PP and the mITT analyses showed a higher rate of pain relapse and organ failure in the high-energy group. The PP analysis likewise revealed a lower maximum CRP in the high-energy group, while all other secondary outcomes showed no differences between the groups. Due to the lack of benefit shown during the interim analysis, the trial was terminated early.

Outcomes showed no difference between the intervention and control groups. However, before correction for multiplicity, significant differences were found for organ failure, pain relapse and CRP. While these are no longer significant after the appropriate statistical approach, they may still represent important signals, particularly for consideration in future trials. The increased rate of organ failure observed was primarily driven by a higher incidence of respiratory failure, which might possibly be explained by a higher metabolic stress experienced by the patients with higher nutritional delivery.[16 17] Importantly, the rates of pneumonia, pneumothorax and conversion to TPN were equal among the groups, as were rates of vomiting and nausea.

It is important to note that the feeds were kept at equal speed of delivery, equal volume and equal electrolyte content. As fat, carbohydrates and protein were added to provide the caloric content, the composition differed not only in energy, but also in osmolarity (360 mOsmol/l vs 342.31 mOsmol/l). This may have accounted for some of the potential differences in outcomes.

The mean maximum CRP was found to be significantly lower in the high-energy nutrition group in the PP analysis. However, this difference was not seen in the mITT analysis and is likely an artefact of an unequal dropout rate.

The non-inferiority of early enteral feeding to nil-per-os or parenteral feeding was established by several key trials.[18–21] Since then, trials have been conducted to compare early versus on-demand tube feeding,[22] early oral refeeding versus usual oral refeeding and early nutrition to prevent adverse outcomes in obese individuals with pancreatitis.[23] These trials establish quite well the benefit of providing early enteral nutrition, including oral feeding as soon as possible, that is, once the patient is hungry and nausea has subsided, and form the basis of the current guidelines.[3 11] Our trial aimed to establish an ideal strategy for caloric content of early nutrition, positing that adequate calorie delivery is crucial to prevent breakdown of pancreas function, including cell death and systemic inflammation, thereby preventing worsening of pancreatitis. We failed to show any benefits of a high energy approach. Of interest, however, is that our subgroup analysis based on BMI showed that the high energy strategy was particularly unhelpful in morbidly obese (BMI >35) patients, a stark contrast to the trial by Jin *et al* investigating early enteral nutrition in obese patients.

During the conception and design of this trial, we decided to include patients regardless of predicted severity. This was in part based on a previous meta-analysis that had shown a benefit of nutritional support even in mild cases,[8] in part based on a desire to understand the potential benefits of the intervention for all patients. As the patient groups differ in their outcomes, we planned a subgrouping based on severity. However, the decision to include these patients may have contributed to obscuring the effects of the intervention. Outcomes of pancreatitis are quite good in patients with mild pancreatitis, and showing a difference between two groups may require a much larger sample size than feasible.

The ultimate aim of this trial was to bring the results of basic research into direct patient care in accordance with current priorities of translational medicine.[24 25] Our results support existing evidence that early enteral feeding should be initiated

Table 2 Primary and secondary outcomes, modified intention-to-treat (mITT) and per-protocol (PP)

mITT	High energy	Missing values	Gradual energy	Missing values	Total	P value	PP	High energy	Missing values	Gradual energy	Missing values	Total	P value
Total	312		307					280		303		583	
In-hospital mortality—n (%)	8 (2.6)	0	6 (2.0)	0	14 (2.3)	0.91		4 (1.4)	0	5 (1.7)	0	9 (1.5)	1
Severe pancreatitis+mortality n (%)	28 (9.0)	0	18 (5.9)	0		0.42		20 (7.1)	0	17 (5.6)	0	37 (6.4)	0.79
Severity—n (%)		0		0		0.71			0		0		0.91
Mild	161 (51.6)		168 (54.7)		331 (53.3)			145 (51.8)		167 (55.1)		312 (53.5)	
Moderate	126 (40.4)		121 (39.4)		247 (39.8)			117 (41.8)		119 (39.2)		236 (40.5)	
Severe	25 (8.0)		18 (5.9)		43 (6.9)			18 (6.4)		17 (5.6)		35 (6.0)	
NG to NJ—n (%)	47 (16.5)	27	32 (11.2)	20	79 (13.8)	0.36		37 (14.2)	20	32 (11.3)	19	69 (12.7)	0.76
EN to TPN—n (%)	20 (6.7)	13	10 (3.3)	6	30 (5.0)	0.36		16 (6.0)	12	8 (2.7)	6	24 (4.3)	0.39
Nutrition complications—n (%)	98 (31.4)	0	90 (29.3)	0	189 (30.0)	0.81		84 (30.0)	0	89 (29.4)	0	173 (29.7)	1
Need for antibiotics—n (%)	135 (44.0)	5	138 (45.4)	3	273 (44.5)	0.91		114 (41.3)	4	134 (44.7)	3	248 (43.1)	0.76
Pain relapse—n (%)	80 (27.1)	17	54 (19.0)	22	134 (23.1)	0.23		70 (26.1)	12	53 (18.9)	22	123 (22.4)	0.32
Need for ICU admission—n (%)	14 (4.5)	0	8 (2.6)	0	22 (3.5)	0.48		7 (2.5)	0	7 (2.3)	0	14 (2.4)	1
Organ failure—n (%)	52 (16.7)	0	28 (9.1)	0	80 (12.9)	0.13		40 (14.3)	0	26 (8.6)	0	66 (11.3)	0.32
Infection—n (%)	13 (4.4)	15	6 (2.1)	21	19 (3.2)	0.42		13 (4.9)	13	6 (2.1)	21	19 (3.5)	0.46
Necrosis—n (%)	64 (20.5)	0	54 (17.6)	0	118 (19.1)	0.62		57 (20.4)	0	53 (17.5)	0	110 (18.9)	0.76
Length of hospital stay (days)		1		0		0.48			1		0		0.76
Mean (SD)	8.9 (7.7)		8.2 (7.7)		8.5 (7.7)			8.6 (6.9)		8.1 (7.6)		8.4 (7.3)	
Median (IQR)	7 (5–9)		6 (5–8)		6 (5–9)			7 (5–9)		6 (5–8)		6 (5–8)	
Start of total oral feeding (days)		21		29		0.42			18		27		0.60
Mean (SD)	5.8 (5.4)		5.2 (4.3)		5.5 (4.9)			5.7 (4.7)		5.2 (4.3)		5.5 (4.5)	
Median (IQR)	5 (4–6)		5 (4–5)		5 (4–6)			5 (4–6)		5 (4–5)		5 (4–6)	
Maximum CRP		32		39		0.36			30		37		0.32
Mean (SD)	166.8 (114.2)		183.2 (118.5)		175.1 (116.5)			161.1 (110.8)		181.4 (116.8)		171.6 (114.3)	
Median (IQR)	158.1 (71.5–247.8)		161.9 (91.1–273.3)		160.6 (78.9–259.2)			154.6 (68.2–238.6)		161.2 (90.6–268.6)		157.9 (77.3–257.4)	
Maximum WBC		49		55		1.00			44		52		0.79
Mean (SD)	13.9 (6.0)		13.9 (5.5)		14.0 (5.8)			13.6 (5.5)		13.9 (5.5)		13.7 (5.5)	
Median (IQR)	12.7 (9.2–16.9)		12.85 (9.7–17.3)		12.8 (9.5–17.3)			12.7 (9.2–16.8)		12.8 (9.7–17.3)		12.7 (9.4–17.0)	
Maximum PCT		127		145		0.48			121		145		0.60
Mean (SD)	1.81 (5.54)		3.09 (13.79)		2.54 (10.40)			1.44 (4.99)		2.88 (13.82)		2.16 (10.39)	
Median (IQR)	0.27 (0.1–0.81)		0.31 (0.11–1.23)		0.29 (0.10–0.94)			0.25 (0.1–0.68)		0.3 (0.11–1.10)		0.27 (0.10–0.81)	
Length of ICU stay		298		299		0.91			0		0		0.99
Mean (SD)	21.4 (14.2)		22.9 (21.8)		20.5 (16.8)			23.3 (10.2)		21.1 (23.0)		22.2 (17.1)	
Median (IQR)	20 (10.8–31.8)		18 (2.8–38.3)		19.5 (4.5–33.5)			20 (19.5–25.5)		12 (2.5–36)		20 (10.5–27)	

The reported p values are adjusted using the Benjamini-Hochberg FDR method.
CRP, C-reactive protein; EN, enteral nutrition; FDR, false discovery rate; ICU, intensive care unit; NG, nasogastric; NJ, nasojejunal; TPN, total peripheral nutrition; WBC, white blood cell.

according to current guidelines, and that a step-up approach with on-demand tube feeding—consistent with the findings of the PYTHON trial[22]—remains the most effective strategy.

This trial had a significantly higher dropout rate in the intervention arm (27 vs 4 individuals), the majority failed to reach the necessary level of caloric intake in the first 24 hours. The unequal dropout rate may have introduced attrition bias in the PP population. Considering the clinical reality, however, this inability to administer high energy enteral feeding to a proportion of patients is likely a realistic clinical course for the disease/therapy of interest, and the ITT analysis should be considered the reality when assessing the efficacy of treatment.

Strengths and limitations

This clinical trial was a multicentre, randomised, double-blind trial, following the newest and strictest guidelines for trial design, and was developed based on experience from previous studies. The design used standard formulations and clear guidelines for clinical decision-making, ensuring that interventions delivered were as comparable as possible. It was stopped early based on a predetermined interim analysis, in adherence to ethical standards.

Among the limitations are the early termination, potentially resulting in an underpowered sample size for outcomes, and a high rate of missing data for some secondary outcomes (in particular procalcitonin).

Clinical implications

A high-energy strategy for early nutrition is not indicated and may be harmful in patients with acute pancreatitis.

CONCLUSIONS

Choosing a high-energy strategy for early nutrition in patients with acute pancreatitis does not reduce mortality or severity of the disease.

Author affiliations
[1]Institute of Pancreatic Diseases, Semmelweis University, Budapest, Hungary
[2]Centre for Translational Medicine, Semmelweis University, Budapest, Hungary
[3]Division of Gastroenterology, First Department of Medicine, Medical School, University of Pécs, Pécs, Hungary
[4]Institute for Translational Medicine, Mediacal School, University of Pécs, Pécs, Hungary
[5]Department of Medical Genetics, Medical School, University of Pécs, Pécs, Hungary
[6]Szent György Teaching Hospital of Fejér County, Székesfehérvár, Hungary
[7]Department of Gastroenterology, Institute of Internal Medicine, Faculty of Medicine, University of Debrecen, Debrecen, Hungary
[8]Department of Biostatistics, University of Veterinary Medicine, Budapest, Hungary
[9]Department of Medical Imaging, Medical School, University of Pécs, Pécs, Hungary
[10]Translational Pancreatology Research Group, Interdisciplinary Centre for Excellence for Research, Development and Innovation, University of Szeged, Szeged, Hungary

Acknowledgements The authors wish to express their gratitude to the following collaborators from the University of Pécs for their assistance in patient recruitment and data collection (patient inclusion under 10 at the University of Pécs): Marcell Imrei, Dóra Dohos, Fanni Dembrovszky, Bernadett Nagy, Bernadett Czibere and Péter Vén. The authors also thank the nursing staff and administrative personnel at each participating institution for their support, as well as the patients for their participation.

Collaborators The Goulash Trial Group: Miklós Sahin-Tóth (Department of Surgery, University of California Los Angeles, Los Angeles), Ole H Petersen (School of Biosciences, Cardiff University, Cardiff, UK), Markus M Lerch (Department of Medicine, Ludwig Maximilian University Hospital, Munich, Germany), John P Neoptolemos (Department of General, Visceral and Transplantation Surgery, Heidelberg University Hospital, Heidelberg, Germany), Kálmán Tóth, Erzsébet Lankó (First Department of Medicine, Medical School, University of Pécs, Pécs, Hungary), Péter Kanizsai (Department of Emergency Medicine, Medical School, University of Pécs, Pécs, Hungary), Vivien Vass (Institute for Translational Medicine, Medical School, University of Pécs, Pécs, Hungary), Szilárd Váncsa (Centre for Translational Medicine, Semmelweis University, Budapest, Hungary), Rita Nagy (Centre for Translational Medicine, Semmelweis University, Budapest, Hungary), Benedek Tinusz (Institute for Translational Medicine, Medical School, University of Pécs, Pécs, Hungary), Dániel Pécsi (Institute for Translational Medicine, Medical School, University of Pécs, Pécs, Hungary and Division of Gastroenterology, First Department of Medicine, Medical School, University of Pécs, Pécs, Hungary), Adrienn Erős, Zsolt Szakács, Péter Varjú, Anikó Nóra Szabó, Noémi Zádori, Lajos Szakó, Endre Csiki, Nóra Vörhendi (Institute for Translational Medicine, Medical School, University of Pécs, Pécs, Hungary), Márk Félix Juhász, Klementina Ocskay, Szabolcs Kiss, Mária Földi (Institute for Translational Medicine, Medical School, University of Pécs, Pécs, Hungary and Heim Pál National Pediatric Institute, Budapest, Hungary), Alexandra Bálint (Institute for Translational Medicine, Medical School, University of Pécs, Pécs, Hungary), Brigitta Teutsch (Institute for Translational Medicine, Medical School, University of Pécs, Pécs, Hungary and Centre for Translational Medicine, Semmelweis University, Budapest, Hungary and Medical Imaging Centre, Department of Radiology, Semmelweis University, Budapest, Hungary), Andrea Párniczky (Institute for Translational Medicine, Medical School, University of Pécs, Pécs, Hungary and Heim Pál National Pediatric Institute, Budapest, Hungary), Dóra Mosztbacher (Institute for Translational Medicine, Medical School, University of Pécs, Pécs, Hungary), Szilárd Gódi (Division of Gastroenterology, First Department of Medicine, Medical School, University of Pécs, Pécs, Hungary), Judit Bajor, Patrícia Sarlós, József Czimmer, Imre Szabó, Anita Illés, Gabriella Pár, Roland Hágendorn (Division of Gastroenterology, First Department of Medicine, Medical School, University of Pécs, Pécs, Hungary), Zsolt Márton (Intensive Care Unit, First Department of Medicine, Medical School, University of Pécs, Pécs, Hungary), Tamás Nagy (Department of Laboratory Medicine, Medical School, University of Pécs, Pécs, Hungary), Attila Miseta (Department of Laboratory Medicine, Medical School, University of Pécs, Pécs, Hungary), András Vereczkei, Dezső Kelemen (Department of Surgery, Medical School, University of Pécs, Pécs, Hungary), Veronika Dunás-Varga, László Gajdán, Adrienn Halász, Roland Fejes (Szent György Teaching Hospital of County Fejér, Székesfehérvár, Hungary), Zsuzsanna Vitális, Földi Ildikó, Krisztina Eszter Fehér, György Kovács (Department of Gastroenterology, Institute of Internal Medicine, Faculty of Medicine, University of Debrecen, Debrecen, Hungary), Tamás Miskolczi, Gábor Lakatos (Department of Medical Imaging, University of Debrecen, Debrecen, Hungary), János Novák, Stephan Crai (BVM Central Hospital/Pandy Kálmám Hospital, Department of Gastroenterology, Gyula, Hungary), Pál Maurovics-Horvát, Pál Ákos Deák (Medical Imaging Centre, Department of Radiology, Semmelweis University, Budapest, Hungary), Ibolya Kocsis, Barna Vásárhelyi (Institute of Laboratory Medicine, Semmelweis University, Budapest, Hungary), László Zubek, Zsolt Molnár (Department of Anesthesiology and Intensive Therapy, Semmelweis University, Budapest, Hungary), Fruzsina Petlickij (Institute for Translational Medicine, Medical School, University of Pécs, Pécs, Hungary and Institute of Pancreatic Diseases, Semmelweis University, Budapest, Hungary), Olga Julia Zahariev and Bettina Csilla Budai (Centre for Translational Medicine, Semmelweis University, Budapest, Hungary and Institute of Pancreatic Diseases, Semmelweis University, Budapest, Hungary), Luca Havelda (Institute of Pancreatic Diseases, Semmelweis University, Budapest, Hungary), Tamás Hussein, Zoltán Hajnády (Institute for Translational Medicine, Medical School, University of Pécs, Pécs, Hungary and Institute of Pancreatic Diseases, Semmelweis University, Budapest, Hungary), Balázs Lázár (Institute of Pancreatic Diseases, Semmelweis University, Budapest, Hungary), Péter Sahin, Tamás Tornai, Mónika Lipp, Dorottya Tarján, Emese Fürst (Institute of Pancreatic Diseases, Semmelweis University, Budapest, Hungary), Edina Tari (Centre for Translational Medicine, Semmelweis University, Budapest, Hungary and Szent György Teaching Hospital of County Fejér, Székesfehérvár, Hungary), Orsolya Eperjesi, Zoltán Bánfalvi, Boglárka Barna, Orsolya Urbán, Zita Kormos, Laura Tóth (Institute of Pancreatic Diseases, Semmelweis University, Budapest, Hungary), Andrea Harnos (Centre for Translational Medicine, Semmelweis University, Budapest, Hungary and Department of Biostatistics, University of Veterinary Medicine Budapest, Budapest, Hungary), and Nelli Farkas (Institute for Translational Medicine, Medical School, University of Pécs, Pécs, Hungary and Institute of Bioanalysis, Medical School, University of Pécs, Pécs, Hungary).

Contributors KM: Conceptualisation, Writing—Review and Editing, Project administration, Investigation, Data curation, Validation. MAE: Writing—Original Draft, Formal analysis, Data curation, Validation. AV: Writing—Review and Editing, Resources. BE: Writing—Review and Editing, Investigation. PJH: Writing—Review and Editing, Investigation. AM: Writing—Review and Editing, Investigation. FI: Writing—Review and Editing, Resources. MP: Writing—Review and Editing, Resources. PM: Writing—Review and Editing, Data Curation, Formal analysis. ZA-T, Writing—Review and Editing, Data Curation, Formal analysis. NF: Writing—Review and Editing, Investigation. AS: Writing—Review and Editing, Project administration, Validation. PH (guarantor): Conceptualisation, Supervision, Writing—Review and Editing, Resources, Funding acquisition.

Funding Funding was provided by the Ministry of Innovation and Technology of Hungary (TKP2021-EGA-23) and the Nemzeti Kutatási Fejlesztési és Innovációs Hivatal/National Office for Research Development and Innovation (A152891, GINOP-2.3.2-15-2016-00015, GINOP-2.3.2-15-2016-00020, K131996, K147265).

Competing interests None declared.

Patient and public involvement Patients and/or the public were involved in the design, or conduct, or reporting, or dissemination plans of this research. Refer to the Methods section for further details.

Patient consent for publication Not applicable.

Ethics approval This trial is conducted according to the principles of the declaration of Helsinki, and ethical approval was obtained from the Scientific and Research Ethics Committee of the Hungarian Medical Research Council (55961-2/2016/EKU). Participants gave informed consent to participate in the study before taking part.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data are available upon reasonable request. Data will be made available upon reasonable request to the corresponding author.

ORCID iD

Péter Hegyi https://orcid.org/0000-0003-0399-7259

REFERENCES

1 Li C, Jiang M, Pan C, *et al*. The global, regional, and national burden of acute pancreatitis in 204 countries and territories, 1990–2019. *BMC Gastroenterol* 2021;21:332.
2 Párniczky A, Kui B, Szentesi A, *et al*. Prospective, Multicentre, Nationwide Clinical Data from 600 Cases of Acute Pancreatitis. *PLoS One* 2016;11:e0165309.
3 IAP/APA/EPC/IPC/JPS Working Group. Electronic address: info@internationalpancreatology.org, IAP/APA/EPC/IPC/JPS Working Group. International Association of Pancreatology Revised Guidelines on Acute Pancreatitis 2025: Supported and Endorsed by the American Pancreatic Association, European Pancreatic Club, Indian Pancreas Club, and Japan Pancreas Society. *Pancreatology* 2025;25:770–814.
4 Maléth J, Hegyi P, Rakonczay Z, *et al*. Breakdown of bioenergetics evoked by mitochondrial damage in acute pancreatitis: Mechanisms and consequences. *Pancreatology* 2015;15:S18–22.
5 Maléth J, Rakonczay Z, Venglovecz V, *et al*. Central role of mitochondrial injury in the pathogenesis of acute pancreatitis. *Acta Physiol (Oxf)* 2013;207:226–35.
6 Maléth J, Venglovecz V, Rázga Z, *et al*. Non-conjugated chenodeoxycholate induces severe mitochondrial damage and inhibits bicarbonate transport in pancreatic duct cells. *Gut* 2011;60:136–8.
7 Petersen OH, Gerasimenko JV, Gerasimenko OV, *et al*. The roles of calcium and ATP in the physiology and pathology of the exocrine pancreas. *Physiol Rev* 2021;101:1691–744.
8 Márta K, Farkas N, Szabó I, *et al*. Meta-Analysis of Early Nutrition: The Benefits of Enteral Feeding Compared to a Nil Per Os Diet Not Only in Severe, but Also in Mild and Moderate Acute Pancreatitis. *Int J Mol Sci* 2016;17:1691.
9 Mosztbacher D, Farkas N, Solymár M, *et al*. Restoration of energy level in the early phase of acute pediatric pancreatitis. *World J Gastroenterol* 2017;23:957–63.
10 Petrov MS, Whelan K. Comparison of complications attributable to enteral and parenteral nutrition in predicted severe acute pancreatitis: a systematic review and meta-analysis. *Br J Nutr* 2010;103:1287–95.
11 IAP/APA evidence-based guidelines for the management of acute pancreatitis. *Pancreatology* 2013;13:e1–15.
12 Machicado JD, Wani S, Quingalahua E, *et al*. Practice patterns and adherence to nutrition guidelines in acute pancreatitis: An international physician survey. *Pancreatology* 2021;21:642–8.
13 Márta K, Szabó AN, Pécsi D, *et al*. High versus low energy administration in the early phase of acute pancreatitis (GOULASH trial): protocol of a multicentre randomised double-blind clinical trial. *BMJ Open* 2017;7:e015874.
14 Cuschieri S. The CONSORT statement. *Saudi J Anaesth* 2019;13:S27–30.
15 Nagy R, Ocskay K, Sipos Z, *et al*. Discharge protocol in acute pancreatitis: an international survey and cohort analysis. *Sci Rep* 2023;13:22109.
16 Banks PA, Bollen TL, Dervenis C, *et al*. Classification of acute pancreatitis--2012: revision of the Atlanta classification and definitions by international consensus. *Gut* 2013;62:102–11.
17 Weaver CS, Leonardi-Bee J, Bath-Hextall FJ, *et al*. Sample size calculations in acute stroke trials: a systematic review of their reporting, characteristics, and relationship with outcome. *Stroke* 2004;35:1216–24.
18 Kalfarentzos F, Kehagias J, Mead N, *et al*. Enteral nutrition is superior to parenteral nutrition in severe acute pancreatitis: results of a randomized prospective trial. *Br J Surg* 1997;84:1665–9.
19 Doley RP, Yadav TD, Wig JD, *et al*. Enteral nutrition in severe acute pancreatitis. *JOP* 2009;10:157–62.
20 McClave SA, Greene LM, Snider HL, *et al*. Comparison of the safety of early enteral vs parenteral nutrition in mild acute pancreatitis. *JPEN J Parenter Enteral Nutr* 1997;21:14–20.
21 Stimac D, Poropat G, Hauser G, *et al*. Early nasojejunal tube feeding versus nil-by-mouth in acute pancreatitis: A randomized clinical trial. *Pancreatology* 2016;16:523–8.
22 Bakker OJ, van Brunschot S, van Santvoort HC, *et al*. Early versus on-demand nasoenteric tube feeding in acute pancreatitis. *N Engl J Med* 2014;371:1983–93.
23 Jin Z, Wang Z, Wang J. Early Enteral Nutrition Prevent Acute Pancreatitis From Deteriorating in Obese Patients. *J Clin Gastroenterol* 2020;54:184–91.
24 Hegyi P, Petersen OH, Holgate S, *et al*. Academia Europaea Position Paper on Translational Medicine: The Cycle Model for Translating Scientific Results into Community Benefits. *J Clin Med* 2020;9:1532.
25 Hegyi P, Erőss B, Izbéki F, *et al*. Accelerating the translational medicine cycle: the Academia Europaea pilot. *Nat Med* 2021;27:1317–9.