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# High versus low energy administration in the early phase of acute pancreatitis (GOULASH): A multicentre randomized double-blind clinical trial

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# High versus low energy administration in the early phase of acute pancreatitis (GOULASH trial): A multicentre randomized double-blind clinical trial

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## ABSTRACT

**Introduction**. Acute pancreatitis (AP) is an inflammatory disease with no specific therapy Mitochondrial injury followed by ATP depletion in both acinar and ductal cells is a recently discovered early event in the pathogenesis. Importantly, preclinical research showed that intracellular ATP delivery restores the physiological function of the cells and protects from cell injury suggesting that restoration of energy levels in the pancreas is therapeutically beneficial. Despite several, high quality and experimental observations in this area, no randomized trials have been conducted to date to address the requirements for energy intake in the early phase of AP.

**Methods/Design.** This is a randomized, controlled two-arms double-blind multicentre trial. Patients suffering from AP will be randomly asigned to groups A (30kcal/kg/day energy administration starting within 24h of hospital admission) or B (no energy administration in the first 24h of hospital admission). Energy will be delivered with nasoenteric tube feeding with additional intravenous glucose supplementation or total parenteral nutrition if necessary. A combination of multi organ failure for more than 48h and mortality is defined as primary endpoint, whereas several secondary endpoints such as length of hospitalization or pain will be determined to elucidate more detailed differences between the groups. The general feasibility, safety and quality checks required for high quality evidence will be adhered to.

**Discussion**. This study will provide evidence whether early high-energy nutritional support is beneficial in the clinical management of AP.

**Trial registration**: The trial has been registered at the ISRCTN (ISRTCN 63827758).

**Keywords:** acute pancreatitis, energy administration, enteral feeding, randomised clinical trial

## BACKGROUND

Acute pancreatitis (AP) is an inflammatory disease of the exocrine pancreas, which is life threatening in its severe form. Unfortunately, while the overall mortality of AP is around 2-5%, and in its severe form 25-57%, no specific therapy is available. Besides the limited interest of pharmacological companies the main reasons are (i) the small number of research teams in the field and (ii) the lack of collaborations between basic and clinical scientists. Importantly, many new therapeutic targets have been identified in the last decade with clear translational merits [1-8]. One of the main highlights among them is the discovery of energy depletion in the early phase of AP [1, 3-5, 7-17].

It has been shown that almost independently of the etiological factors: bile acids, ethanol, fatty acids and the latter's metabolite fatty acid ethyl esters, a common mechanism is mitochondrial damage and ATP depletion in pancreatic ductal and acinar cells driving the cells to death and causing pancreatic necrosis [1, 3, 4, 10-14, 18-31]. Very importantly, restoration of ATP levels in both cell types prevented cell death and at least partially restored their function [1, 9]. In experimental pancreatitis models the same observations have been revealed [10-21]. Although these experimental observations clearly suggest that restoration of energy level could be a therapeutic tool in AP, this has not been translated into clinical trials.

One of the best and most physiological way of delivering energy to a patient is enteral nutrition (EN). Not surprisingly, besides fluid resuscitation this is almost the only way to significantly reduce mortality in AP [22-33]. Recent analyses of prospectively collected data from 600 patients suffering from severe AP showed that mortality is 27% with EN, versus 57% without EN [34]. Importantly EN not only decrease mortality, but also reduces the frequency of multi-organ failure and the necessity of interventions in patients suffering from severe AP (SAP) [35]. No data are available on whether early or on demand nutrition/energy

supply is beneficial in SAP. The recently published Dutch PYTHON study suggests that there is no difference on early versus on demand enteral tube feeding in SAP but patients may have received insufficient amount of energy at the early phase of the disease [36, 37]. In the early EN group patients received over 20 kcal/kg/day only from the third day onwards whereas in the on demand group they received energy supplementation only from the day six [37]. In mild and moderate AP (MAP) much less information is available concerning the usefulness of EN. There is a large variety of protocols on EN in MAP. Immediate oral feeding [38], nasojejunal feeding [39-41] and nasogastric feeding [42][43] were all used. Notably immediate oral feeding significantly decreased the length of hospital stay (LOH) [38]. Early (within 24h) nasogastric EN was not only well tolerated but reduced the intensity and duration of abdominal pain decreased the necessity for opiates and almost completely eliminated the risk of oral food intolerance [42]. In order to obtain higher evidence of the usefulness of early EN in MAP and SAP we performed a systematic review and meta-analysis which showed that early EN can be beneficial in both, MAP and SAP [35]. However, we also realized the lack of multicentre randomized control trials addressing energy intake in the early phase of AP.

The main objective of this trial is to understand whether early energy supplementation to patients suffering from acute pancreatitis is beneficial.

## METHODS

### 1. Design

This is a randomised controlled two-arms double-blind multicentre trial. Patients suffering from acute pancreatitis will be randomly asigned to groups A (high energy administration starting within 24h of hospital admission) and B (low energy administration after 24h of hospital admission).

## 2. Trial organization, committees and boards

GOULASH is designed and coordinated by the Centre for Translational Medicine at the University of Pécs and the Hungarian Pancreatic Study Group (HPSG). HPSG was established in 2011 in order to stimulate research in pancreatic diseases. Until now HPSG published the relevant guidelines of pancreatic diseases in order to improve patient care in the field of pancreatology [44-47] and has initiated four prospective clinical trials (EASY, PREPAST, APPLE and PINEAPPLE) [48-51].

The following committees and boards will be involved:

Steering committee (SC): The committee will be led by PH (gastroenterologist, internal medicine specialist). The members will be KM (medical doctor, full time employee on the project), ÁV (gastroenterologist, internal medicine specialist), ZM (intensive care specialist), TM (clinical research specialist) AS (multidisciplinary unit specialist), MP (gastroenterologist, internal medicine specialist), NF (radiologist), DK (surgeon), IB (interventional radiologist). SC will make decisions concerning all relevant questions including the drop outs during the study.

International translational advisory board (ITAB): The committee will include gastroenterologist (MML), surgeon (JPN) and basic scientists (MST, OHP). ITAB will continuously monitor the progress of the study and will give advice to the SC.

The study was designed by SC and ITAB. The study is financially sponsored by the University of Pécs, the Hungarian Academy of Sciences, and the National Research, Development and Innovation Office. Neither sponsors was involved in the design of the study, and they will have no access for the database management or to the randomisation code.

### 3. Study population

All patients diagnosed with AP will be informed on the possibility of taking part in the GOULASH study. After the consent form is signed, patients will be randomized by a computer using a block randomisation protocol. Figure 1 shows the flow chart of participants according to CONSORT2010 guideline [53].

**Inclusion criteria:** (1) Patients over 18y of age, (2) diagnosed AP on the base of the "2 out of 3" criteria of the IAP/APA guideline [52]: (a) upper abdominal pain; (b) serum amylase or lipase >3x upper limit of normal range; (c) characteristic findings on pancreatic imaging; however those patients without abdominal pain will be excluded because the onset of AP cannot be determined, (3) written informed consent form is signed.

**Exclusion criteria**: (1) Hospitalization 72 hours before admission, (2) abdominal pain >120 hours (5 days), (3) delirium tremens, (4) Child-Pugh C stage liver cirrhosis, (5) AP due to malignancy, (6) already on artificial nutrition (EN or PN), (7) pregnancy, (8) BMI above 40 or below 18, (9) age above 80, (10) ketoacidosis, (11) whenever CT with contrast is contraindicated.

**Sample size:** Sample size calculation was based on the National Hungarian Registry operated by the Hungarian Pancreatic Study Group. Our recent analyses indicated that MOF (multi organ failure) existing more than 48h arises in 9%, whereas mortality is in 2.8% of all patient suffering from AP [34]. Altogether they represent around 10% of all AP patients. In order to detect a treatment effect of at least 50% of the early treatment a sample size of 957 subjects will be necessary to be recruited using a 10% drop-out rate, 80% power and 95% significance level. The calculation was performed by the Independent data-management and biostatistics provider company (IDMB, Adware Research LTD, Balatonfüred, Hungary).

**Randomisation:** In each centre participants will be divided in 2 groups receiving one of the two study treatments. The allocation of participants to the different groups will be carried out based on predefined randomisation lists created separately for each recruiting centre. The randomisation lists will be prepared with a block size of 4 and with an allocation ratio of 1:1.

4. **Duration**

The planned starting date of the study is: 1 January, 2017, and the planned finishing date of the study is: 1 January, 2020

**5. Blinding**

The medical staff (e.g., taking the measurements such as blood pressure, examining health records for events such as abdominal pain, reviewing and interpreting examination results such as X-ray or CT) and the patient receiving the intervention will be blinded to knowledge of treatment assignment. The person providing the intervention cannot be blinded in this study.

**6. Intervention**

Based on the currently available guidelines enteral feeding can be started at any time for the patients suffering from AP. In addition no calorie restriction/order has been described. Therefore both groups can be regarded as being treated within accepted practice recommendations.

In this study, early high energy administration will be the intervention. Patients will be randomised to group A or B: see flowchart.

**Groups:** In **group A,** high energy will be delivered after admission. Patients will receive a 10 Ch nasogastric (NG) or nasojejunal (NJ) feeding tube on admission. EN will immediately started as follows: On Day 0 (from admission until the start of EN (can be vary from 2-24 h)): calorie intake will be 0 kcal/kg/day. From Day 1 high energy enteral tube feed 30 kcal/kg/day will be provided until the oral feeding starts. In **group B,** low energy administration after hospital admission. Patients will receive a NG or NJ feeding tube at admission as described above. On Day 0 (from admission until the start of EN): calorie intake will be 0 kcal/kg/day. On day 1 0 kcal/kg/day, on day 2 10 kcal/kg/day, on day 3 20 kcal/kg/day and from day 4 30 kcal/kg/day calorie will be delivered until the oral feeding starts. However, between groups A and B only the amount of calories administered will be different. Patients will receive the same amount of fluid and ions during EN (see below).

**Ingredients of enteral tube feed: High Energy Enteral Tube Feed (100ml):**

**Energy**: 150 kcal (630 KJ), **Protein** 6g (16%E), **Carbohydrate**: 18.3g (49%E), **Fat**: 5.8g (35%E) + **Minerals**: 134mg Sodium, 201mg Potassium, 108mg Calcium, 108mg Phosphorus, 34mg Magnesium, 100mg Chloride (0%E). In this study we will use Nutrison Energy (Numil Ltd, Budapest, Hungary), which is a registered product in Hungary (reg. number: 1217).

**Zero Energy Enteral Tube Feed (100ml):**

**Energy**: 0 kcal (0 KJ), **Protein** 0g, **Carbohydrate**: 0g, Fat: 0g + **Minerals**: 134mg Sodium, 201mg Potassium, 108mg Calcium, 108mg Phosphorus, 34mg Magnesium, 5.562g Chloride (0%E) (in this study the local institutional pharmacy will provide it in accordance with the Hungarian regulations). Whenever 10 or 20 kcal/kg/day calories will be delivered, the mixture of the above mentioned two solution will be used.

**Type of enteral tube:** Patients neither vomiting nor having gastric fluid retention >250 ml will receive primarily NG tube. Patients either vomiting or having gastric fluid retention >250 ml will receive NJ tube (placement will be done either endoscopically or radiologically). In

case of GCS 14 or lower in a patient who is not intubated, NG tube will be replaced by NJ tube (risk of aspiration). Abdominal X-ray will be used to check the tube's position.

**Start of mixed feeding** (around 2620 kcal): Mixed feeding (1000 ml tap water distributed for 24 h and 300 g (around 1900 kcal) biscuits/toasts/low fat meal (at least 75% CHO containing ones) orally plus enteral tube feed (440ml, 720 kcal/day) will be started on the day when: (1) abdominal pain has been ceased for at least 6 h before the new day started, (2) CRP level has started decreasing and are below 100 mg/L and (3) amylase or lipase level has started decreasing

**Start of total feeding** (around 2000 kcal): If the patients have no symptoms during the mixed oral/enteral feeding and the CRP, amylase or lipase levels are not rising again. Total feeding (according to local policy) can be started.

**Other issues:** The speed of EN will be different for the patients (depends on the body weight), however, the maximum speed of EN cannot exceed 65ml/h. In case of difficulties reaching the 30 kcal/kg/day calories intake (if the patients body weight is above 75 kg) additional intravenous calorie will be added using Sterofundin G. Maximum of 2000 ml (= 400 kcal) can be delivered in this way. If NG feeding is not tolerated, NG tube will be replaced to NJ tube as described above. If NJ feeding is not tolerated, EN will be reduced by 50% and increased again gradually until tolerated. If the re-increasing process is still not tolerated TPN will be started to reach the required energy target. In case of severe AP, TPN has to be delivered via central venous catheter.

### 11. Other treatment of subjects

General treatment indicated by the IAP/APA guideline will to be utilized [52].

### 12. Discharge of patients

Uniformisation of length of hospital stay is necessary to avoid bias concerning LOH. Re-admission within one week after discharge has to be considered as the same hospital admission. Patients has to be counted as discharged from hospital/from the study when (1) the total feeding was tolerated for 24h, (2) no amylase/lipase level are elevated after total enteral feeding, (3) CRP level is less than 50 mg/L, (4) abdominal pain has completely resolved (5) no other pancreatitis-related complication requiring hospitalization is detected.

### 13. Endpoints

The following primary endpoints will be calculated: A combination of Multi Organ Failure more than 48h and Mortality. The following secondary endpoints will be analysed: (1) pancreatic necrosis, (2) nutrition related complications: diarrhoea, aspiration pneumonia, pneumothorax due to central TPN catheter placement, (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 feeding, (6) use of antibiotics, (7) pain relapse, (8) CRP, (9) WBC, (10) PCT, (11) infection, (12) length of hospital stay, (13) need for ICU admission, (14) length of ICU therapy, (15) organ failure, (16) complications, (17) costs calculation.

### 14. Monitored parameters during hospitalization

There will be a large variety of parameters monitored during the study (e.g. medical history, physical examination, laboratory tests, diagnostic imaging, therapy, interventions). Form A will contain the parameters collected on admission. Form B will contain parameters collected every day during hospitalization. Form C will contain parameters collected 1 month after hospital discharge. For details see supplementary materials or web page (http://www.pancreas.hu/en/studies/goulash), which will be available from February 2017.

Data collection on the case report form (CRF) will be done electronically (see data management)

## 15. Data management and statistical analyses

**Data handling:** Data will be handled by IDMB. Electronic CRF will be used. The Investigator will ensure that the data in the eCRF are accurate, complete and legible. Detailed data flow will be described in Data Management Plan (DMP). Data from completed eCRFs will be validated under the direction of the Data Manager at IDMB according to Data Cleaning Plan (DCP). Any missing, implausible, or inconsistent recordings in the eCRFs will be referred back to the Investigator using a data query form (DQF), and be documented for each individual subject before clean file status is declared. All changes to eCRF will be recorded. Before Data Base Lock Data Review Meeting will decide and document necessary steps related to any issue in the database and define the analysis sets. Member of the data review meeting are delegated investigator, biostatistician and data manager. AEs will be coded using MedDRA. AdWare Research Ltd., who will act as IDMB, works according to GCP, GLP, FDA 21CFR PART11 and other relevant regulatory requirements. AdWare Ltd. has GLP and ISO 9001 certificates.

**Study populations:**

Three analysis populations will be defined:

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| Safety Analysis Set (SAS): | all patients enrolled to the study. |
| Per Protocol Set (PPS): | all enrolled patients who finished the study conforming to the requirements of the Study Protocol. |
| Intention to Treat (ITT) | all randomised participants who start on a treatment, excluding consent withdrawals. |

**Withdrawal of a subject from PPS:** Any participants/investigators and IDMB can submit recommendation for dropouts from the PPS group with reasons given to SC. All recommendations will be filed. SC will discuss all the information and if the alteration in the protocol would be expected to have any bearing on the interventions and outcomes of the study, the patient will not be included in the final per-protocol analysis. Automatic dropout from the per-protocol group shall be ordered if: (1) any of the exclusion criteria diagnosed during the course of AP, (2) at least 50% of the energy requirement is not achieved on any days during the study, (3) parameters required for answering the primary endpoints are missing or (4) serious medical reasons not related to pancreatitis (i.e. accidents, stroke) occur.

**Applied softwares:** Statistical analysis will be performed using SAS 9.2 or SPSS 19 (or later) statistical packages; Microsoft MSWord will be used for reporting.

**Statistical Methods:** Baseline patient and disease characteristics will be analysed by using descriptive analysis. Demographic and baseline characteristics will be summarized for the overall study population. Continuous variables will be described by mean, median, standard deviation, and ranges and categorical variables will be described by absolute and relative frequencies. A graphical presentation of efficacy variables will be prepared, if applicable. Descriptive statistics for both of the primary and secondary parameters will be analysed similarly. Mean changes (and their 95% CI) from baseline to end-of-study visit will be presented as well. Chi-squared tests will be applied to compare proportions between the different groups. Mortality/extended M0F will be investigated using the Kaplan-Meier analysis method; while subgroup comparisons will be performed using the Chi-squared or

Fisher's exact test, as appropriate. For safety data, descriptive statistics and individual listings of adverse events will be also presented.

**Subgroups:** The following subgroups will be made during statistical analyses: (1) ages (under 40y, 40y-60y, 60y-80y), (2) BMI (below 20, 20-25, 25-30, 30-35, above 35), (3) the start of abdominal pain before admission (≤24h, ≤48h, ≥48h), (4) severity of the disease SAP and MAP. All subgroup analyses, (5) etiologies will be done descriptively. No confirmatory statistical testing will be applied. Hence, statistical tests and the p-values attached to them will be regarded as descriptive and not as tests of hypotheses.

Details of the applied statistical tests will be described in the Statistical Analysis Plan.

### 16. Early quality assessment.

Early quality assessment check will be performed after the first 100 patients. IDMB (AdWare Ltd.) will perform an independent assessment of the trial related documents and activities, with the aim of ensuring the respect of subjects' right, safety and well-being and to guarantee the plausibility of clinical data. Similarity of groups at baseline will be also checked. IDMB will report to SC. SC will discuss all the information and if the differences would be expected to have any bearing on the interventions and outcomes of the study or the overall dropout rate from PPS is above 20 percent of all participants who were randomized or allocated into each group or the differential dropout rate is above 15 percent between the arms, the study needs to be reassessed and IDMB will make recommendations regarding either reevaluation of power calculation, extension of recruitment period, extension of number of study centers or termination of trial.

### 17. Interim analyses and premature termination of the study.

IDMB can also recommend to stop the trial early for ethical reasons if one of the groups clearly shows evidence of a significant benefit. An interim-analysis will be performed on the primary endpoint when 50% of patients have been randomised and discharged from hospital. The interim-analysis will be performed by the IDMB. IDMB will report to SC.

The Haybittle–Peto boundary approach will be used. If interim analysis shows a probability of equal to, or less than 0.001 that a difference as extreme between the treatments is found, given that the null hypothesis is true, then the trial will be stopped early.

## 18. Centres

The trial will start in two centres (University of Debrecen and University of Pécs), after which the study is open for other centres. In all cases IDMB will make an audit of the centre and will report to the SC. SC keeps the right to decide whether the centre meets the required quality to join the study. Compulsory requirements for a centres: (1) it needs to treat at least 50 AP patients a year, (2) it needs to have all the equipment required for the study, (3) besides the regular medical team the centre has to appoint at least one doctor and one nurse/administrator fully available for the trial with no additional commitments which can interfere with her/his duty when her/his availability is required, (4) the blinding described above can be fully utilized, (5) all persons need to attend a preliminary meeting where all the details concerning the studies are discussed fully and have qualified as investigators in a GCP course. Centres wish to join needs to send a letter of intent to the corresponding author by e-mail.

## 19. Publication policy

Centres providing more than 25 patients can provide two authors to the authorship list. Every additional 25 patients will give the opportunity to nominate an additional author.

### 20. Feasibility

As a general protocol for the treatment of AP at the Centre for Translational Medicine at the University of Pécs, patients suffering from AP receive early EN (using nasogastric tube). Patients receive 50 ml Nutrison Energy per hour starting immediately when they arrive to the ward from the Emergency Department. Patients data between the period of 1 January – 31 May 2016 were analysed and the following observations were noted: (1) In 85% of all AP admission early EN could have been started within 24 h. In 15% of the cases it was not achievable due to the delayed transfer of the patients to the ward or vomiting. In these cases patients received NG tube later or they received NJ tube whenever X-ray assistance was available. (2) around 80% of NG-fed patients tolerated NG feeding without any complications. The rest of the patients who had gastric retention or vomiting NG feeding was stopped and they received NJ tube whenever X-ray assistance was available. (3) Comparing the outcome (rate of severity, mortality, necrosis, intervention, etc.) of this treatment protocol with the nil per os protocol utilized in most of the Hungarian hospitals revealed that patients enjoy benefits with no risk of early enteral feeding which data confirm the literature data described in the introduction. Concerning the number of patients. At the University of Pécs around 250 and at the University of Debrecen around 150 patients are admitted annually. Therefore, if no other Institution would join the study it can be completed within 3 years.

### 21. Safety

Since no unknown drugs/therapy are used in the study no adverse and serious adverse events are expected/interpretable that would be attributable to the intervention during the trial. In this trial IDMB will examine safety variables after every 16 patients have completed. Moreover, investigators will report AE or SAE via a separate form which has to be sent to IDMB and

SC. SC will discuss and if the adverse effect is confirmed it will be reported to the relevant institutional and national ethical committee http://www.ett.hu/tukeb.htm.

### 22. Additional information and future plan.

Blood samples (serum and plasma) will be stored from all patients in order to study laboratory parameters later if required (e.g. the laboratory could not measure it), and in order to build up a biobank for later clinical studies to which all participants will given informed consent. The samples will be stored on -80$^{o}$C. A follow-up study (called GOULASH PLUS) is under preparation in order to follow the patients for up to 5 years after the study. The study protocol will also be published.

## DISCUSSION

Here we report the protocol of a prospective double-blind RCT to study the effects of early energy restoration in AP. The pre-clinical studies [ 1, 9] and meta-analyses [35] suggest that energy supplementation should be beneficial. Our main hypothesis is that elevating the energy level of acinar and ductal cells will prevent these cells from injury, therefore, it will decrease the extent of necrosis during AP. Since both the local and systemic complications (immune response) are largely depend on the extent of the necrosis we propose that this intervention will reduce multi-organ failure and mortality in AP.

## CONCLUSION

This study provides the first and type A evidence concerning the necessity of energy intake for patients suffering from AP.

## List of abbreviations

AP – acute pancreatitis

CRP – C-reactive Protein

DCP – data cleaning plan

DMP – data management plan

DQF – data query form

eCRF – electronic clinical research form

EN – enteral nutrition

GOULASH – name of the study: general utilization of early energy administration in acute pancreatitis.

HPSG – Hungarian Pancreatic Study Group

ICU – intensive care unit

ITAB – International Translational Advisory Board

LOH – length of hospital stay

MAP – mild and moderate AP

MOF – multi organ failure

NG – nasogastric

NJ – nasojejunal

PCT – procalcitonin

PN – parenteral nutrition

PPS – Per Protocol Set

SAS – Safety Analysis Set

SAP – severe AP

SC – Streering Commitee

TPN – total parenteral nutrition

WBC – white blood cell count

**Declarations**

The trial is registered at the ISRCTN registry (ISRCTN63827758) and got the relevant ethical approval with the reference number of 55961-2/2016/EKU issued by The Scientific and Research Ethics Committee of the Medical Research Council.

**Availability of data and materials**

Not applicable, because the trial have not completed patient recruitment.

**Competing interest**

The authors declare that they have no competing interests.

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**Authors' contributions**

All authors were involved in the study design, edited the manuscript, read and approved the final manuscript. During the study KM, ANS, DP and PV are going to randomize the patients and ensure the blinding. AM, KS, JB, SG, MP, PS, ZVand TT are going to manage the treatment of the patients. ÁV will be responsible for the organization, quality and timing of the endoscopic treatments, ZM and RH for the intensive care, NF and IB for the imaging and interventional radiology, DK and RP for the surgical treatment if needed. PAV and EL will

prepare the nutritional solutions. ML, JN, MST and OP are members of ITAB. TM and AS will be members of SC. PH and KM drafted the manuscript.

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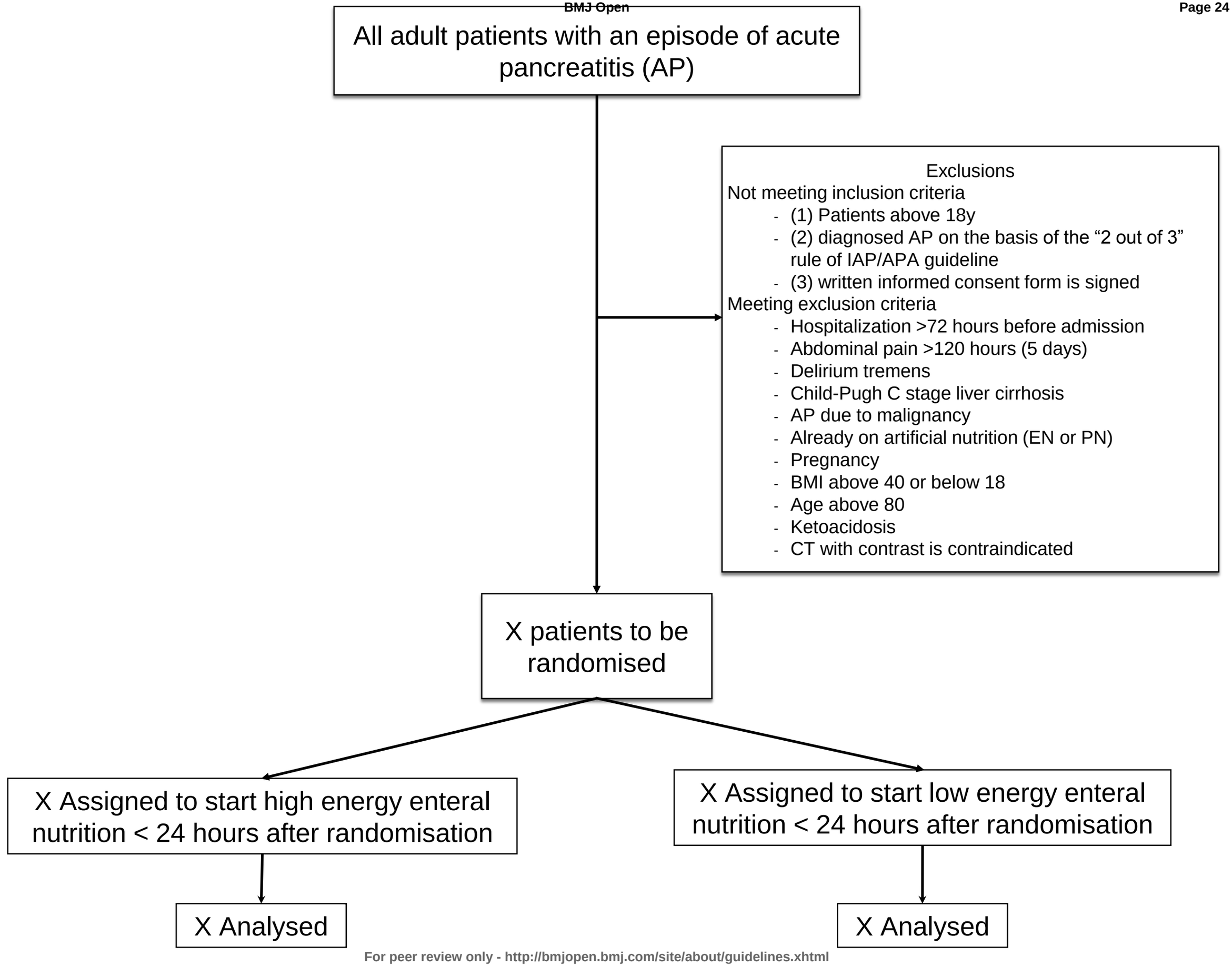
All adult patients with an episode of acute pancreatitis (AP)
Exclusions
Not meeting inclusion criteria
- (1) Patients above 18y
- (2) diagnosed AP on the basis of the “2 out of 3” rule of IAP/APA guideline
- (3) written informed consent form is signed
Meeting exclusion criteria
- Hospitalization >72 hours before admission
- Abdominal pain >120 hours (5 days)
- Delirium tremens
- Child-Pugh C stage liver cirrhosis
- AP due to malignancy
- Already on artificial nutrition (EN or PN)
- Pregnancy
- BMI above 40 or below 18
- Age above 80
- Ketoacidosis
- CT with contrast is contraindicated
X patients to be randomised
X Assigned to start high energy enteral nutrition < 24 hours after randomisation
X Assigned to start low energy enteral nutrition < 24 hours after randomisation
X Analysed
X Analysed

# FORM-A Acute Pancreatitis

Early Enteral Nutrition

GOULASH

***The physical examination has to be done ON ADMISSION!***
***The blood for laboratory parameters has to be drawn ON ADMISSION!***
***This form has to be filled ON ADMISSION!***

## *Questionnaire*

| |
|---|
| **Country:** |
| **Town:** |
| **Hospital:** |
| **Doctor:** |
| **Patient No:** |

## 1. Patient personal details

**Insurance number:**.....
**First name:**.....
**Last name:** .....
**Date of birth:**.....
**Gender:** female male
**Ethnicity/Race:** White / Black / Asian-Indian Not known

## 2. Details from the medical history

**Alcohol consumption**: yes / no
if yes: frequency: occasionally/monthly/weekly/dayly
amount (g/day):.....
since when? (years):.....
Alcohol consumption in the last 2 weeks: .....

if not:
Did you drink alcohol earlier? yes/no
if yes: frequency: occasionally/monthly/weekly/daily
amount (g/occasion):.....
For how many years?.....
How long ago did you stop drinking alcohol?.....

*Guide for estimation of the amount:*
*1 dl beer (4.5 vol. %) = ~3.5 g alcohol*
*1 dl wine (12.5 vol. %) = ~10 g alcohol*
*1 dl hard drink (50 vol. %) = ~40 g alcohol*

**Smoking**: yes / no
if yes: amount (cigarettes/day):.....
For how many years? .....
if not:
Did you smoke earlier? yes/no
if yes: amount (pcs/occasion):.....
For how many years?.....
How long ago did you stop smoking? .....

**Drug abuse**: yes / no *Prescribed medication should not be included here.*
if yes: type of drug:..... amount:.....
since when (year):.....
*(if there are more drugs, please describe them in the NOTES section at the end)*

**Diabetes mellitus**: yes / no
if yes: type: Type I. / Type II./Type III. c / MODY
since when (year):.....



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# FORM-A Acute Pancreatitis GOULASH

**Lipid metabolism disorder:** yes / no
if yes: type: ..... since when (year):.....

**Any disease of the pancreas:** yes / no *Not counting the current episode.*
if yes: acute pancreatitis/ chronic pancreatitis/ autoimmune pancreatitis/ tumor/ other
if other: please describe:.....
<u>If the patient had ACUTE PANCREATITIS in the history:</u>
How many times did the patient have acute episodes before this episode:.....
When did the patient have the first acute episode (year):.....

<u>If the patient has CHRONIC/AUTOIMMUNE PANCREATITIS:</u>
When was it diagnosed?.....
How many times did the patient have acute episodes before this episode:.....
When did the patient have the first acute episode (year):.....

<u>If the patient has PANCREATIC CANCER::</u>
When was it diagnosed?.....
Was the patient diagnosed with chronic pancreatitis? yes / no
If yes, when was it diagnosed?.....
How many times did the patient have acute episodes before this episode?:.....
When did the patient have the first acute episode (year):.....

Other information:
.....

**Pancreas disorders in family history:**
acute pancreatitis: yes / no if yes: relationship to patient:.....
chronic pancreatitis yes / no if yes: relationship to patient:.....
autoimmune pancreatitis: yes / no if yes: relationship to patient:.....
pancreas tumor: yes / no if yes: relationship to patient:.....
other (please describe):.....relationship to patient:.....
.....

**Congenital Anatomical Malformation of the pancreas:** yes / no / no data
if yes: please describe:.....

**Other illnesses:** yes / no
if yes: please list/describe them:.....

**Medications taken regularly:** yes / no *Please specify the name of the active substance (e.g. "acetylsalicylic acid"). Please specify the amount using the International System of Units –SI (e.g. milligram, gram)*
if yes:
name:.....active substance:.....dose(gram,milligram, etc.).....
if fluid, concentration (e.g. 10%, 1g/2ml, etc.).....how many times per day (e.g. 3)
type of administration:.....other notes: .....

name:.....active substance:.....dose(gram,milligram, etc.).....
if fluid, concentration (e.g. 10%, 1g/2ml, etc.).....how many times per day (e.g. 3)
type of administration:.....other notes: .....


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# FORM-A Acute Pancreatitis

Early Enteral Nutrition

GOULASH

name:.....active substance:.....dose(gram,milligram, etc.).....
if fluid, concentration (e.g. 10%, 1g/2ml, etc.).....how many times per day (e.g. 3)
type of administration:.....other notes: .....

name:.....active substance:.....dose(gram,milligram, etc.).....
if fluid, concentration (e.g. 10%, 1g/2ml, etc.).....how many times per day (e.g. 3)
type of administration:.....other notes: .....

**Diet:** yes / no
if yes: please describe:.....

## 3. Etiology

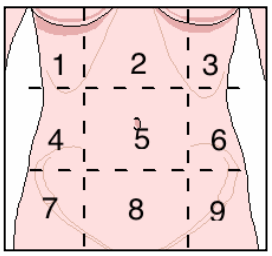
*The answer is "yes" if the etiological factor is proved, the answer is "no" if the etiological factor can be ruled out, the answer is "no data" if the etiological factor was not examined. Please answer "yes" to " Idiopathic" if etiological factor was not identified.*

| | | | |
|---|---|---|---|
| Biliary | yes | no | no data |
| Alcohol | yes | no | no data |
| Virus infection | yes | no | no data |
| Trauma | yes | no | no data |
| Drug-induced | yes | no | no data |
| Congenital anatomical malformation | yes | no | no data |
| Cystic fibrosis | yes | no | no data |
| Gluten-sensitive enteropathy | yes | no | no data |
| Hypertrigliceridaemia | yes | no | no data |
| Genetic | yes | no | has not been tested yet |
| Idiopathic | yes | no | |
| Other | yes | no | |

if yes: please describe:.....

## 4. Complains, symptoms

**Abdominal pain:** yes / no
if yes: since when (hours):.....
type: cramping / dull / sharp
intensity (1-10):.....
location: diffuse / localized
Please mark the location!
radiation:.....




**Nausea:** yes / no

**Vomiting:** yes / no
if yes: how many times:.....
contents of cast:.....

**Subfebrility/fever:** yes / no
if yes: since when:.....
degree (°C):.....

**Appetite:** good / retained / bad

**Weight loss:** yes / no
if yes: how much (kg):.....
How long did it take? (weeks):.....

**Jaundice:** yes / no
if yes: for how long:.....

**Stool:** normal / diarrhea / constipation / fatty / putrid / undigested food/bloody/mucus
*Please refer to the period just before your symptoms has started.*

## 5. Admission details and state

**Blood pressure (Hgmm):**..... **Heart rate (/minute):**.....
**Body weight (kg):**..... **Body height (cm):**.....
**Respiratory rate (/minute):**..... **Body temperature (°C):** .....
axillary/rectal

**Oxygen saturation (%):** ..... Previous O2 therapy: yes/no

**Abdominal tenderness :** yes / no **Abdominal guarding:** yes / no

**Jaundice:** yes / no

**Glasgow Coma Scale (GCS):**.....

**Glasgow Coma Scale:**
**Eye response**
4 points: Spontaneous eye opening
3 points: Eye opening in response any speech
2 points: Opening to response to pain
1 point: No eye opening

**Verbal Response**
5 points: Orientated
4 points: Confused conversation
3 points: Inappropriate speech
2 points: Incomprehensible speech
1 point: No verbal response.

**Motor Response**
6 points: Obeying command
5 points: Localizing response to pain
4 points: Withdraws to pain
3 points: Decorticate posture
2 points: Decerebrate posture
1 point: No response to pain

# FORM-A Acute Pancreatitis

Early Enteral Nutrition

GOULASH

## 6. Laboratory parameters on admission

**OBLIGATORY PARAMETERS:**

| | |
|---|---|
| Amylase (U/l) | |
| Lipase (U/l) | |
| White blood cell (WBC) count (G/l) | |
| Red blood cell (RBC) count (T/l) | |
| Hemoglobin (g/l) | |
| Hematocrit (%) | |
| Thrombocyte (G/l) | |
| Serum glucose (mmol/l) | |
| Hemoglobin A1C (%) | |
| Blood urea nitrogen (mmol/l) | |
| Creatinine (umol/l) | |
| eGFR | |
| C-reactive protein (mg/l) | |
| ASAT/GOT (U/l) | |
| Lactate dehydrogenase LDH (U/l) | |
| Calcium (mmol/l) | |
| Sodium (mmol/l) | |
| Potassium (mmol/l) | |
| Total protein (g/l) | |
| Albumin (g/l) | |
| Cholesterol (mmol/l) | |
| Triglyceride (mmol/l) | |
| ALAT/GPT (U/l) | |
| Gamma GT (U/l) | |
| Total bilirubin (umol/l) | |
| Direct/Conjugated bilirubin (umol/l) | |
| Alkaline phosphatase (U/l) | |
| Procalcitonin (ng/ml) | |

**OTHER PARAMETERS (if measured):**

| | |
|---|---|
| IgA (g/l) | |
| IgM (g/l) | |
| IgG (g/l) | |
| IgG4 (g/l) | |
| CA 19-9 (U/ml) | |
| $PaO_2$ (Hgmm) | |
| $HCO_3$ (mmol/l) | |
| $sO_2$ (%) | |
| sweat chloride (mmol/l) | |
| urine amylase | |
| uirne lipase | |
| urine creatinine | |
| (other) | |

Virus serology: yes / no Which viruses?..... results:.....

## 7. Imaging examinations on admission

Does the patient have pleural fluid? yes no N/A
Does the patient have lung infiltrate? yes no N/A
Does the patient have abnormal pancreatic structure? yes no N/A
If yes: hypoechoic/hyperechoic/peripancreatic fluid/irregular and blurred contours/Wirsung dilatation (above 1mm)/ascites/calcification/cyst

**Abdominal X-ray:** yes no
Description:
.....
.....

**Chest X-ray:** yes no
Description:
.....
.....

**Chest Computed Tomography:** yes no
Description:
.....
.....

**Abdominal Computed Tomography:**
Modified CTSI Score: .....0-10.....
*Please NOTE! Abdominal CT is compulsory on admission*

**CTSI Score: (I)** Normal pancreas 0 point, intrinsic pancreatic abnormalities with or without inflammatory changes in peripancreatic fat 2 points, Pancreatic or peripancreatic fluid collection or peripancreatic fat necrosis 4 points **(II)** Necrosis absent 0 Points, < 30% necrosis 2 Points, > 30% necrosis 4 points **(III)** presence of extrapancreatic findings 2 points.
MAXIMUM OF: 10 points

- **CTSI:**

**I. Pancreas**

- Normal pancreas
- Intrinsic pancreatic abnormalities with or without inflammatory changes in peripancreatic fat
- pancreatic or peripancreatic fluid collection or peripancreatic fat necrosis

**II. Size of Necrosis**

- Necrosis absent
- < 30% necrosis
- > 30% necrosis
- > 60% necrosis

**III. Extrapancreatic findings**

- presence of extrapancreatic findings

**DETAILED REPORT**

- **Pancreas Size:**
  - Normal
  - Partially enlarged (body AP diameter is over 2 cm and/or head AP diameter is over 2,5 cm, none exceeds 3 cm)
  - Definitely enlarged (any part over 3 cm AP diameter)
- Largest diameter of peripancreatic **fat infiltration**: …… cm

- **Peripancreatic fluid:**
  - none
  - present
  - Large pseudocyst(s)
- Size of peripancreatic fluid or pseudocyst: …… cm

- **Necrotizing area** (nonenchancement):
  - Largest diameter of necrosis area: …… cm
  - Location of necrosis: ……
  - Type: patchy / full width
  - Estimated necrosis: 0% , < 30% , 30% - 60%, above 60%

- **Wirsung** dilatation: YES / NO (yes, diameter: …… mm)

- Distant **abdominal fluid**:
  - Small amount (hard to see, less than 2 cm in lesser pelvis, less than 1 cm around liver/spleen)
  - Moderate amount (easy to see, but without pelvic or abdominal distension)
  - Large amount with abdominal/pelvic distension





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- **Pleural effusion:**
  - none
  - one sided:……. (AP diameter: …… cm)
  - Both sides, L - …… cm, R - …… cm

- **Extrapancreatic findings**:
  - Inflammation (Cholecystitis, Duodenitis, etc.) location: ……
  - Cholecystolithiasis
  - Choledocholithiais
  - Signs of bowel ischaemia
  - Bowel distension, ileus
  - Venous thrombosis
  - Pseudoaneurysm
  - Parenchymal organ involvement, define: ……

Other Description:
……
……

## 8. Genetic testing

Has it been performed earlier? yes no
if yes: please describe:

……
……
……

## 9.a Intravenious fluid in the early period

**Intravenious fluid in the early period……ml**

*To be counted from the first moment (including ambulance car) until the start of the early enteral nutrition. 5–10 ml/kg/h should be given in the first 2h. It has to be continued until: heart rate <120/min, mean arterial pressure between 65 and 85 mmHg (8.7–11.3 kPa), and urinary output >0.5–1 ml/kg/h*

## 9.b Immediate therapy on admission

**Intravenous fluid** **yes** **no**
if yes: type of fluid……
amount (ml)……

*If not contraindicated the type of fluid has to be Ringer Lactate. No glucose should be given if it is not compulsory due to hypoglycaemia*

**Pain management:** **yes** **no**
if yes:
name:……active substance:……dose(gram,milligram, etc.)……
if fluid, concentration (e.g. 10%, 1g/2ml, etc.)……how many times per day (e.g. 3)
type of administration:……other notes: ……

name:.....active substance:.....dose(gram,milligram, etc.).....
if fluid, concentration (e.g. 10%, 1g/2ml, etc.).....how many times per day (e.g. 3)
type of administration:.....other notes: .....

name:.....active substance:.....dose(gram,milligram, etc.).....
if fluid, concentration (e.g. 10%, 1g/2ml, etc.).....how many times per day (e.g. 3)
type of administration:.....other notes: .....

**Insulin:** **yes** **no**
if yes: name of the medication:.....
total dose of medication:.....

**Intensive care:** **yes** **no**
if yes: namely (ventilation, vasopressor therapy):.....

**Other:**
if yes: please describe:.....
.....

## 10. Interventions, endoscopic treatment: yes no

if yes: ERCP-EST/endobiliary stent/Wirsung stent/cysta drainage
Stent: 1 plastic stent/more plastic stents/uncovered metal stent/covered metal stent
Early complications: none/bleeding/perforation
**ERCP:** yes no
if yes:

| | | | |
|---|---|---|---|
| Successful biliary cannulation: | yes | no | if yes: notes: ..... |
| Precut: | yes | no | if yes: needleknife/precut papillotomia |
| EST: | yes | no | if yes: biliary/pancreatic |
| Stone extraction: | yes | no | |
| Stent: | yes | no | if yes: metal/plastic<br>How many pcs? diameter(Fr)? length(cm)? |
| Pancreatic duct filling: | yes | no | if yes: notes: ..... |

## 11. Complications

*Please register pancreatic complication of fluid collection/pseudocyst/necrosis only if you had imaging proof on the day of admission, otherwise, please mark "no data".*

**Pancreatic:** yes no no data
if yes: fluid collections /pseudocyst / necrosis / diabetes

**Organ failure:** yes no
if yes:, lung /heart / kidney /other

**Death:** yes no
If yes: the exact time of death: ..... *e.g. 10.25 or 22.45*

# FORM-A Acute Pancreatitis GOULASH

## 12. Epicrisis *A short summary of the hospitalization (how the patient got to medical care, diagnosis, most important facts and events of the hospitalization, what happened with the patient after the hospitalization, any recommended control examinations, surgery).*

……

……

**NOTES**

……

……

**DATE:**

YEAR: …… MONTH: …… DAY: …… HOUR …… MIN: ……

THE TOTAL TIME SPENT THE PATIENT ON ADMISSION: HOUR …… MIN: ……

**NAME OF THE DOCTOR MADE THE RANDOMIZATION:** ……**SIGNATURE:** ……

*Please NOTE! The doctor made the randomization MUST NOT involved in the treatment of patients any longer. She/He has to keep the information secretly from the patients and medical team involved in the treatment.*

**NAME OF THE DOCTOR EXAMINED/TREATED THE PATIENT:** ……**SIGNATURE:** ……

# FORM-B Acute Pancreatitis

Early Enteral Nutrition

GOULASH

*PLEASE FILL IN EVERY DAY DURING THE HOSPITAL STAY*

**Day No:**
**Date** (+hour, min)

**GOULASH No:**

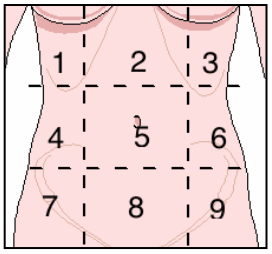
**(Automatically generated)**

## 1. Patient personal details

**First name:**.....

**Last name:** .....

## 2. Complains, symptoms




**Abdominal pain:** yes / no
if yes: since when (hours):.....
type: cramping / dull / sharp
intensity (1-10):.....
location: diffuse / localized
Please mark the location!
radiation:.....

**Nausea:** yes / no
*If YES, retention measurement has to be performed.*
**Vomiting:** yes / no
*If YES, NG tube has to be replaced by NJ tube.*

**Subfebrility/fever:** yes / no
if yes: since when:.....
degree (°C):.....

**Appetite:** good / retained / bad

**Stool:** yes / no

if yes: normal / diarrhea / constipation / fatty / putrid / undigested food/bloody/mucus





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FORM-B Acute Pancreatitis GOULASH

## 3. Patient's state

**Blood pressure (Hgmm):**..... **Heart rate (/minute):**.....
**Body weight (kg):**.....
**Respiratory rate (/minute):**..... **Body temperature (°C):** .....
axillary/rectal

**Oxygen saturation (%):** ..... O2 therapy: yes/no

**Abdominal tenderness :** yes / no **Abdominal guarding:** yes / no

**Jaundice:** yes / no

**Glasgow Coma Scale (GCS):**.....

**Glasgow Coma Scale:**

**Eye response**
4 points: Spontaneous eye opening
3 points: Eye opening in response any speech
2 points: Opening to response to pain
1 point: No eye opening

**Verbal Response**
5 points: Orientated
4 points: Confused conversation
3 points: Inappropriate speech
2 points: Incomprehensible speech
1 point: No verbal response.

**Motor Response**
6 points: Obeying command
5 points: Localizing response to pain
4 points: Withdraws to pain
3 points: Decorticate posture
2 points: Decerebrate posture
1 point: No response to pain

## 4. Laboratory parameters

**OBLIGATORY PARAMETERS**

| | |
|---|---|
| Amylase (U/l) | |
| Lipase (U/l) | |
| White blood cell (WBC) count (G/l) | |
| Red blood cell (RBC) count (T/l) | |
| Hemoglobin (g/l) | |
| Hematocrit (%) | |
| Thrombocyte (G/l) | |
| C-reactive protein (mg/l) | |





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# FORM-B Acute Pancreatitis

Early Enteral Nutrition GOULASH

**OTHER PARAMETERS (if measured):**

| | |
|---|---|
| Serum glucose (mmol/l) | |
| Blood urea nitrogen (mmol/l) | |
| Creatinine (umol/l) | |
| eGFR | |
| ASAT/GOT (U/l) | |
| Lactate dehydrogenase LDH (U/l) | |
| Calcium (mmol/l) | |
| Sodium (mmol/l) | |
| Potassium (mmol/l) | |
| Total protein (g/l) | |
| Albumin (g/l) | |
| Cholesterol (mmol/l) | |
| Triglyceride (mmol/l) | |
| ALAT/GPT (U/l) | |
| Gamma GT (U/l) | |
| Total bilirubin (umol/l) | |
| Direct/Conjugated bilirubin (umol/l) | |
| Alkaline phosphatase (U/l) | |
| Procalcitonin (ng/ml) | |
| IgA (g/l) | |
| IgM (g/l) | |
| IgG (g/l) | |
| IgG4 (g/l) | |
| CA 19-9 (U/ml) | |
| $PaO_2$ (Hgmm) | |
| $HCO_3$ (mmol/l) | |
| $sO_2$ (%) | |
| sweat chloride (mmol/l) | |
| urine amylase | |
| uirne lipase | |
| urine creatinine | |
| (other) | |

**Blood glucose (by finger stick test)** *Compulsory on the first day*:

| | | |
|---|---|---|
| 4h | mmol/l | amount of insulin if administered : …… IU |
| 8h | mmol/l | |
| 12h | mmol/l | |
| 16h | mmol/l | |
| 20h | mmol/l | |
| 24h | mmol/l | |





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# FORM-B Acute Pancreatitis GOULASH

## 5. Imaging (if performed)

yes no

**Abdominal ultrasonography:** yes no

*2 hours before the examination the enteral feeding has to be stopped. The amount of enteral feeding which was not given have to be administered additionally to the normal feeding in the next 10h. (for example: If the patient receive 45 ml/h and 90ml was not given due to the examination, the patient has to receive 54ml (45ml + 9ml) for the forthcoming 10h.*

- ***Visualization:***
  - Good, complete (head at least partially visualized, body and neck well visualized, tail: partially visualized)
  - Partially, incomplete (only body or only head visualized)
  - Poor, non-diagnostic
- **Size:**
  - Normal
  - Partially enlarged (body AP diameter is over 2 cm and/or head AP diameter is over 2,5 cm, none exceeds 3 cm)
  - Definitely enlarged (any part over 3 cm AP diameter)

- **Peripancreatic fluid:**
  - none
  - present
  - Large pseudocyst(s)
- Size of peripancreatic fluid or pseudocyst: …… cm

- **Pancreas homogeneity:**
  - Homogenous
  - Inhomogeneous, includes area(s) of low echogenicity
  - Inhomogeneous, includes calcifications

- In case of circumscribed low echogenicity area, it's size: …… cm

- **Wirsung** dilatation: YES / NO (yes, diameter: …… mm)

Other Description:

……

……

**Abdominal X-ray:** yes no

Description:

……

……

**Chest X-ray:** yes no

Description:

……

……

**Chest Computed Tomography:** yes no

Description:

……

……





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# FORM-B Acute Pancreatitis

Early Enteral Nutrition

GOULASH

**Abdominal Computed Tomography:** yes/no
Modified CTSI Score: ……0-10……
*Please NOTE! Abdominal CT is compulsory when the patient is discharged*

**CTSI Score: (I)** Normal pancreas 0 point, intrinsic pancreatic abnormalities with or without inflammatory changes in peripancreatic fat 2 points, Pancreatic or peripancreatic fluid collection or peripancreatic fat necrosis 4 points **(II)** Necrosis absent 0 Points, < 30% necrosis 2 Points, > 30% necrosis 4 points **(III)** presence of extrapancreatic findings 2 points.
MAXIMUM OF: 10 points

- **CTSI:**
  - **I. Pancreas**
  - Normal pancreas
  - Intrinsic pancreatic abnormalities with or without inflammatory changes in peripancreatic fat
  - pancreatic or peripancreatic fluid collection or peripancreatic fat necrosis
  - **II. Size of Necrosis**
  - Necrosis absent
  - < 30% necrosis
  - > 30% necrosis
  - > 60% necrosis
  - **III. Extrapancreatic findings**
  - presence of extrapancreatic findings
  -

**DETAILED REPORT**

- **Pancreas Size:**
  - Normal
  - Partially enlarged (body AP diameter is over 2 cm and/or head AP diameter is over 2,5 cm, none exceeds 3 cm)
  - Definitely enlarged (any part over 3 cm AP diameter)
- Largest diameter of peripancreatic **fat infiltration**: …… cm

- **Peripancreatic fluid:**
  - none
  - present
  - Large pseudocyst(s)
- Size of peripancreatic fluid or pseudocyst: …… cm

- **Necrotizing area** (nonenchancement):
  - Largest diameter of necrosis area: …… cm
  - Location of necrosis: ……
  - Type: patchy / full width
  - Estimated necrosis: 0% , < 30% , 30% - 60%, above 60%

- **Wirsung** dilatation: YES / NO (yes, diameter: …… mm)



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- Distant **abdominal fluid**:
  - Small amount (hard to see, less than 2 cm in lesser pelvis, less than 1 cm around liver/spleen)
  - Moderate amount (easy to see, but without pelvic or abdominal distension)
  - Large amount with abdominal/pelvic distension

- **Pleural effusion:**
  - none
  - one sided:……. (AP diameter: …… cm)
  - Both sides, L - …… cm, R - …… cm

- **Extrapancreatic findings**:
  - Inflammation (Cholecystitis, Duodenitis, etc.) location: ……
  - Cholecystolithiasis
  - Choledocholithiais
  - Signs of bowel ischaemia
  - Bowel distension, ileus
  - Venous thrombosis
  - Pseudoaneurysm
  - Parenchymal organ involvement, define: ……

Other Description:
……
……

## 6. Microbiology examination

Biological sample collection yes no
If yes: place: /blood, urine, airway, pancreas, other/
result: ……




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## 7. Therapy

**Total oral feeding** yes no

**CHO reach oral feeding** yes no

**Intravenous fluid** yes no

if yes, type of fluid……
amount (ml)……

type of fluid……
amount (ml)……

**Enteral feeding** yes no

if yes, naso-gastric / naso-jejunal
formula: ……
amount:…… (ml)
speed of the pump:…… ml/h

**Gastric retention measurement** *Compulsory on the first day*

amount:…… (ml)

**Did the patient need change in EN from NG to NJ feeding?** yes no

if yes, type of fluid……
amount (ml)……
speed of the pump:…… ml/h

**TPN** yes no

if yes, type of TPN……
amount (ml)……

type of TPN……
amount (ml)……

**NOTES FOR ENTERAL FEEDING**

……
……

**Total delivered calorie on the day?** …… kcal, ……kcal/kg

Calorie delivery by NGF: …… kcal
Calorie delivery by NJF: …… kcal
Calorie delivery by iv glucose: …… kcal
Calorie delivery by TPN: …… kcal
Calorie delivery by mixed oral feeding: …… kcal
Calorie delivery by total oral feeding: …… kcal





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# FORM-B Acute Pancreatitis GOULASH

**Pain management:** yes no

if yes:

name:.....active substance:.....dose(gram,milligram, etc.).....

if fluid, concentration (e.g. 10%, 1g/2ml, etc.).....how many times per day (e.g. 3)

type of administration:.....other notes: .....

name:.....active substance:.....dose(gram,milligram, etc.).....

if fluid, concentration (e.g. 10%, 1g/2ml, etc.).....how many times per day (e.g. 3)

type of administration:.....other notes: .....

name:.....active substance:.....dose(gram,milligram, etc.).....

if fluid, concentration (e.g. 10%, 1g/2ml, etc.).....how many times per day (e.g. 3)

type of administration:.....other notes: .....

**Antibiotic therapy:** yes no

if yes:

name:.....active substance:.....dose(gram,milligram, etc.).....

if fluid, concentration (e.g. 10%, 1g/2ml, etc.).....how many times per day (e.g. 3)

type of administration:.....other notes: .....

name:.....active substance:.....dose(gram,milligram, etc.).....

if fluid, concentration (e.g. 10%, 1g/2ml, etc.).....how many times per day (e.g. 3)

type of administration:.....other notes: .....

name:.....active substance:.....dose(gram,milligram, etc.).....

if fluid, concentration (e.g. 10%, 1g/2ml, etc.).....how many times per day (e.g. 3)

type of administration:.....other notes: .....

**Insulin:** yes no

if yes, name of the medication:.....

dosage:.....

**Intensive care:** yes no

if yes, namely (ventilation, vasopressor therapy):.....

**Other:**

if yes, please describe:.....

.....

.....





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## 8. Interventions, endoscopic treatment: yes no

if yes: ERCP-EST/endobiliary stent/Wirsung stent/cysta drainage
Stent: 1 plastic stent/more plastic stents/uncovered metal stent/covered metal stent
Early complications: none/bleeding/perforation

**ERCP:** yes no
if yes:

| | | | |
|---|---|---|---|
| Successful biliary cannulation: | yes | no | if yes: notes: …… |
| Precut: | yes | no | if yes: needleknife/precut papillotomia |
| EST: | yes | no | if yes: biliary/pancreatic |
| Stone extraction: | yes | no | |
| Stent: | yes | no | if yes: metal/plastic |
| | | | How many pcs? diameter(Fr)? length(cm)? |
| Pancreatic duct filling: | yes | no | if yes: notes: …… |

## 9. Complications

Pancreatic: yes no no data
if yes, fluid collections / pseudocyst / necrosis / diabetes
Organ failure: yes no
if yes, lung / heart / kidney /other
Duration of organ failure: <48 hours >48 hours
Death: yes no
if yes: the exact time of death: …… *e.g. 10.25 or 22.45*

**NOTES**

……
……
……

**DATE:**
YEAR: …… MONTH: …… DAY: ……

**NAME OF THE DOCTOR:** ……**SIGNATURE:** ……

**NAME OF THE NURSE:** ……**SIGNATURE:** ……

**NAME OF THE SCIENCE ADMINISTRATOR:** ……**SIGNATURE:** ……





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# FORM-C Acute Pancreatitis GOULASH

## Questionnaire

**GOULASH No:**

**(Automatically generated)**

### 1. Patient personal details

**First name:**.....

**Last name:** .....

### 2. Details from the medical history (in the last month)

**Alcohol consumption**: yes / no
if yes: frequency: occasionally/monthly/weekly/daily
amount (g/day):.....

*Guide for estimation of the amount:*
*1 dl beer (4.5 vol. %) = ~3.5 g alcohol*
*1 dl wine (12.5 vol. %) = ~10 g alcohol*
*1 dl hard drink (50 vol. %) = ~40 g alcohol*

**Smoking**: yes / no
if yes: amount (cigarettes/day):.....

**Drug abuse**: yes / no *Prescribed medication should not be included here.*
if yes: type of drug:..... amount:.....
*(if there are more drugs, please describe them in the NOTES section at the end)*

**Any re-hospitalization?:** yes / no

if yes: cholecystectomy: yes no
recurrent AP: yes no
other: .....

**Medications taken regularly in the last month:** yes / no
*Please specify the name of the active substance (e.g. "acetylsalicylic acid"). Please specify the amount using the International System of Units –SI (e.g. milligram, gram)*
if yes:
name:.....active substance:.....dose(gram,milligram, etc.).....
if fluid, concentration (e.g. 10%, 1g/2ml, etc.).....how many times per day (e.g. 3)
type of administration:.....other notes: .....

name:.....active substance:.....dose(gram,milligram, etc.).....
if fluid, concentration (e.g. 10%, 1g/2ml, etc.).....how many times per day (e.g. 3)
type of administration:.....other notes: .....

name:.....active substance:.....dose(gram,milligram, etc.).....
if fluid, concentration (e.g. 10%, 1g/2ml, etc.).....how many times per day (e.g. 3)
type of administration:.....other notes: .....

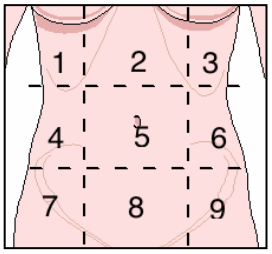
# FORM-C Acute Pancreatitis

Early Enteral Nutrition

GOULASH

**Diet:** yes / no
if yes: please describe:.....

## 3. Complains, symptoms




**Abdominal pain:** yes / no
if yes: since when (hours):.....
type: cramping / dull / sharp
intensity (1-10):.....
location: diffuse / localized
Please mark the location!
radiation:.....

**Nausea:** yes / no

**Vomiting:** yes / no
if yes: how many times:.....
contents of cast:.....

**Subfebrility/fever:** yes / no
if yes: since when:.....
degree (°C):.....

**Appetite:** good / retained / bad

**Weight loss:** yes / no
if yes: how much (kg):.....
How long did it take? (weeks):.....

**Jaundice:** yes / no
if yes: for how long:.....

**Stool:** normal / diarrhea / constipation / fatty / putrid / undigested food/bloody/mucus

## 4. Laboratory parameters

**OBLIGATORY PARAMETERS**

| | |
|---|---|
| Amylase (U/l) | |
| Lipase (U/l) | |
| White blood cell (WBC) count (G/l) | |
| Red blood cell (RBC) count (T/l) | |
| Hemoglobin (g/l) | |
| Hematocrit (%) | |
| Thrombocyte (G/l) | |
| C-reactive protein (mg/l) | |

**OTHER PARAMETERS (if measured):**

| | |
|---|---|
| Serum glucose (mmol/l) | |
| Blood urea nitrogen (mmol/l) | |
| Creatinine (umol/l) | |
| eGFR | |
| ASAT/GOT (U/l) | |
| Lactate dehydrogenase LDH (U/l) | |
| Calcium (mmol/l) | |
| Sodium (mmol/l) | |
| Potassium (mmol/l) | |
| Total protein (g/l) | |
| Albumin (g/l) | |
| Cholesterol (mmol/l) | |
| Triglyceride (mmol/l) | |
| ALAT/GPT (U/l) | |
| Gamma GT (U/l) | |
| Total bilirubin (umol/l) | |
| Direct/Conjugated bilirubin (umol/l) | |
| Alkaline phosphatase (U/l) | |

**5. Imaging examination**

**Abdominal ultrasonography:** yes no
Description:

**Ultrasound:**

- *Visualization:*
  - Good, complete (head at least partially visualized, body and neck well visualized, tail: partially visualized)
  - Partially, incomplete (only body or only head visualized)
  - Poor, non-diagnostic
- **Size:**
  - Normal
  - Partially enlarged (body AP diameter is over 2 cm and/or head AP diameter is over 2,5 cm, none exceeds 3 cm)
  - Definitely enlarged (any part over 3 cm AP diameter)
- **Peripancreatic fluid:**
  - none
  - present
  - Large pseudocyst(s)

- Size of peripancreatic fluid or pseudocyst: …… cm

- **Pancreas homogeneity:**
  - Homogenous
  - Inhomogeneous, includes area(s) of low echogenicity
  - Inhomogeneous, includes calcifications

- In case of circumscribed low echogenicity area, it's size: …… cm

- **Wirsung** dilatation: YES / NO (yes, diameter: …….. mm)

Other Description:

……
……

**Abdominal Computed Tomography:** yes no
Modified CTSI Score: ……0-10……

*Please NOTE! Abdominal CT is compulsory if*
*- Abdominal ultrasonography is not fully completed **OR***
*- There is any alteration on abdominal ultrasonography*

**CTSI Score: (I)** Normal pancreas 0 point, intrinsic pancreatic abnormalities with or without inflammatory changes in peripancreatic fat 2 points, Pancreatic or peripancreatic fluid collection or peripancreatic fat necrosis 4 points **(II)** Necrosis absent 0 Points, < 30% necrosis 2 Points, > 30% necrosis 4 points **(III)** presence of extrapancreatic findings 2 points.
MAXIMUM OF: 10 points

- **CTSI:**

**I. Pancreas**
- Normal pancreas
- Intrinsic pancreatic abnormalities with or without inflammatory changes in peripancreatic fat
- pancreatic or peripancreatic fluid collection or peripancreatic fat necrosis

**II. Size of Necrosis**
- Necrosis absent
- < 30% necrosis
- > 30% necrosis
- > 60% necrosis

**III. Extrapancreatic findings**
- presence of extrapancreatic findings

**DETAILED REPORT**

- **Pancreas Size:**
  - Normal
  - Partially enlarged (body AP diameter is over 2 cm and/or head AP diameter is over 2,5 cm, none exceeds 3 cm)

- Definitely enlarged (any part over 3 cm AP diameter)

- Largest diameter of peripancreatic **fat infiltration**: ..... cm

- **Peripancreatic fluid:**
  - none
  - present
  - Large pseudocyst(s)
- Size of peripancreatic fluid or pseudocyst: ..... cm

- **Necrotizing area** (nonenchancement):
  - Largest diameter of necrosis area: ..... cm
  - Location of necrosis: .....
  - Type: patchy / full width
  - Estimated necrosis: 0% , < 30% , 30% - 60%, above 60%

- **Wirsung** dilatation: YES / NO (yes, diameter: ..... mm)

- Distant **abdominal fluid**:
  - Small amount (hard to see, less than 2 cm in lesser pelvis, less than 1 cm around liver/spleen)
  - Moderate amount (easy to see, but without pelvic or abdominal distension)
  - Large amount with abdominal/pelvic distension

- **Pleural effusion:**
  - none
  - one sided:..... (AP diameter: ..... cm)
  - Both sides, L - ..... cm, R - ..... cm

- **Extrapancreatic findings**:
  - Inflammation (Cholecystitis, Duodenitis, etc.) location: .....
  - Cholecystolithiasis
  - Choledocholithiais
  - Signs of bowel ischaemia
  - Bowel distension, ileus
  - Venous thrombosis
  - Pseudoaneurysm
  - Parenchymal organ involvement, define: .....

Other Description:
.....
.....

# FORM-C Acute Pancreatitis

Early Enteral Nutrition

GOULASH

## 6. Complications

*Please register pancreatic complication of fluid collection/pseudocyst/necrosis only if you had imaging proof on the day of admission, otherwise, please mark "no data".*

**Pancreatic:** yes no no data
if yes: fluid collections /pseudocyst / necrosis / diabetes

**Organ failure:** yes no
if yes:, lung /heart / kidney /other

**Death:** yes no
If yes: the exact date of death: ..... *e.g. 10.25 or 22.45*

## 7. Epicrisis

*A short summary (what happened with the patient after the hospitalization, any recommended control examinations, surgery).*

.....
.....

**DATE:**
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**NAME OF THE DOCTOR : .....SIGNATURE:** .....

# CONSORT 2010 checklist of information to include when reporting a randomised trial*

| Section/Topic | Item No | Checklist item | Reported on page No |
|---|---|---|---|
| **Title and abstract** | | | |
| | 1a | Identification as a randomised trial in the title | 1 |
| | 1b | Structured summary of trial design, methods, results, and conclusions (for specific guidance see CONSORT for abstracts) | 2 |
| **Introduction** | | | |
| Background and objectives | 2a | Scientific background and explanation of rationale | 3-4 |
| | 2b | Specific objectives or hypotheses | 3,4 |
| **Methods** | | | |
| Trial design | 3a | Description of trial design (such as parallel, factorial) including allocation ratio | 4, 7 |
| | 3b | Important changes to methods after trial commencement (such as eligibility criteria), with reasons | |
| Participants | 4a | Eligibility criteria for participants | 6 |
| | 4b | Settings and locations where the data were collected | 14, 11 |
| Interventions | 5 | The interventions for each group with sufficient details to allow replication, including how and when they were actually administered | 7-9 |
| Outcomes | 6a | Completely defined pre-specified primary and secondary outcome measures, including how and when they were assessed | 10 |
| | 6b | Any changes to trial outcomes after the trial commenced, with reasons | |
| Sample size | 7a | How sample size was determined | 6 |
| | 7b | When applicable, explanation of any interim analyses and stopping guidelines | 13-14 |
| Randomisation: | | | |
| Sequence generation | 8a | Method used to generate the random allocation sequence | 6-7 |
| | 8b | Type of randomisation; details of any restriction (such as blocking and block size) | 6 |
| Allocation concealment mechanism | 9 | Mechanism used to implement the random allocation sequence (such as sequentially numbered containers), describing any steps taken to conceal the sequence until interventions were assigned | 11-12 |
| Implementation | 10 | Who generated the random allocation sequence, who enrolled participants, and who assigned participants to interventions | 18 |
| Blinding | 11a | If done, who was blinded after assignment to interventions (for example, participants, care providers, those | 18, 7 |

| | | | |
|---|---|---|---|
| | | assessing outcomes) and how | |
| | 11b | If relevant, description of the similarity of interventions | 7-8 |
| Statistical methods | 12a | Statistical methods used to compare groups for primary and secondary outcomes | 12 |
| | 12b | Methods for additional analyses, such as subgroup analyses and adjusted analyses | 12-13 |
| **Results** | | | |
| Participant flow (a diagram is strongly recommended) | 13a | For each group, the numbers of participants who were randomly assigned, received intended treatment, and were analysed for the primary outcome | 6-7 |
| | 13b | For each group, losses and exclusions after randomisation, together with reasons | |
| Recruitment | 14a | Dates defining the periods of recruitment and follow-up | 7,16 |
| | 14b | Why the trial ended or was stopped | |
| Baseline data | 15 | A table showing baseline demographic and clinical characteristics for each group | |
| Numbers analysed | 16 | For each group, number of participants (denominator) included in each analysis and whether the analysis was by original assigned groups | |
| Outcomes and estimation | 17a | For each primary and secondary outcome, results for each group, and the estimated effect size and its precision (such as 95% confidence interval) | |
| | 17b | For binary outcomes, presentation of both absolute and relative effect sizes is recommended | |
| Ancillary analyses | 18 | Results of any other analyses performed, including subgroup analyses and adjusted analyses, distinguishing pre-specified from exploratory | |
| Harms | 19 | All important harms or unintended effects in each group (for specific guidance see CONSORT for harms) | |
| **Discussion** | | | |
| Limitations | 20 | Trial limitations, addressing sources of potential bias, imprecision, and, if relevant, multiplicity of analyses | |
| Generalisability | 21 | Generalisability (external validity, applicability) of the trial findings | |
| Interpretation | 22 | Interpretation consistent with results, balancing benefits and harms, and considering other relevant evidence | |
| **Other information** | | | |
| Registration | 23 | Registration number and name of trial registry | 2,18, 1 |
| Protocol | 24 | Where the full trial protocol can be accessed, if available | 16 |
| Funding | 25 | Sources of funding and other support (such as supply of drugs), role of funders | 18 |

*We strongly recommend reading this statement in conjunction with the CONSORT 2010 Explanation and Elaboration for important clarifications on all the items. If relevant, we also recommend reading CONSORT extensions for cluster randomised trials, non-inferiority and equivalence trials, non-pharmacological treatments, herbal interventions, and pragmatic trials. Additional extensions are forthcoming: for those and for up to date references relevant to this checklist, see www.consort-statement.org.

BMJ Open

# High versus low energy administration in the early phase of acute pancreatitis (GOULASH): Protocol of a multicentre randomized double-blind clinical trial



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# High versus low energy administration in the early phase of acute pancreatitis (GOULASH trial): Protocol of a multicentre randomized double-blind clinical trial

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## ABSTRACT

**Introduction**. Acute pancreatitis (AP) is an inflammatory disease with no specific therapy. Mitochondrial injury followed by ATP depletion in both acinar and ductal cells is a recently discovered early event in the pathogenesis. Importantly, preclinical research showed that intracellular ATP delivery restores the physiological function of the cells and protects from cell injury suggesting that restoration of energy levels in the pancreas is therapeutically beneficial. Despite several, high quality and experimental observations in this area, no randomized trials have been conducted to date to address the requirements for energy intake in the early phase of AP.

**Methods/Design.** This is a randomized, controlled two-arms double-blind multicentre trial. Patients suffering from AP will be randomly assigned to groups A (30 kcal/kg/day energy administration starting within 24h of hospital admission) or B (low energy administration during the first 72h of hospital admission). Energy will be delivered with nasoenteric tube feeding with additional intravenous glucose supplementation or total parenteral nutrition if necessary. A combination of multi organ failure for more than 48h and mortality is defined as the primary endpoint, whereas several secondary endpoints such as length of hospitalization or pain will be determined to elucidate more detailed differences between the groups. The general feasibility, safety and quality checks required for high quality evidence will be adhered to.

**Discussion**. This study will provide evidence whether early high-energy nutritional support is beneficial in the clinical management of AP. The results of this trial will be published in an open access way and disseminated among medical doctors.

**Ethical Approval:** The study has been approved by the relevant organization, The Scientific and Research Ethics Committee of the Hungarian Medical Research Council (55961-2/2016/EKU).

**Trial registration**: The trial has been registered at the ISRCTN (ISRTCN 63827758).

**Keywords:** acute pancreatitis, energy administration, enteral feeding, randomized clinical trial

## BACKGROUND

Acute pancreatitis (AP) is an inflammatory disease of the exocrine pancreas, which is life threatening in its severe form. Unfortunately, while the overall mortality of AP is around 2-5%, and in its severe form 25-57%, no specific therapy is available. Besides the limited interest of pharmacological companies the main reasons are (i) the small number of research teams in the field and (ii) the lack of collaborations between basic and clinical scientists. Importantly, many new therapeutic targets were identified in the last decade with clear translational merits [1-8]. One of the main highlights among them is the discovery of energy depletion in the early phase of AP [1, 3-5, 7-17].

It has been shown that almost independently of the etiological factors the early phase of AP is almost the same. Bile acids, ethanol, fatty acids and the latter's metabolite fatty acid ethyl esters cause mitochondrial damage and ATP depletion in pancreatic ductal and acinar cells driving the cells to death and causing pancreatic necrosis [1, 3, 4, 10-14, 18-31]. Very importantly, restoration of ATP levels in both cell types prevented cell death and at least partially restored their function [1, 9]. In experimental pancreatitis models the same observations have been revealed [10-21]. Although these experimental observations clearly suggest that restoration of energy level could be a therapeutic tool in AP, this has not been translated into clinical trials.

One of the best and most physiological way of delivering energy to a patient is enteral nutrition (EN). Not surprisingly, besides fluid resuscitation this is almost the only way to significantly reduce mortality in AP [22-33]. Recent analyses of prospectively collected data from 600 patients suffering from severe AP (SAP) showed that mortality is 27% with EN, versus57% without EN [34]. Importantly EN not only decreases mortality but also reduces the frequency of multi-organ failure and the necessity of interventions in patients suffering from SAP [35]. No data are available on whether early or on demand nutrition/energy supply is beneficial in SAP. The recently published Dutch PYTHON study suggests that there is no difference on early versus on demand enteral tube

feeding in SAP but patients may have received an insufficient amount of energy at the early phase of the disease [36, 37]. In the early EN group patients received over 20 kcal/kg/day only from the third day onwards whereas in the on demand group they received energy supplementation only from day six[37]. In mild and moderate AP (MAP) much less information is available concerning the usefulness of EN. There are a large variety of protocols on EN in MAP. Immediate oral feeding [38], nasojejunal feeding [39-41] and nasogastric feeding [42][43] were all used. Notably immediate oral feeding significantly decreased the length of hospital stay (LOH) [38]. Early (within 24h) nasogastric EN was not only well tolerated but reduced the intensity and duration of abdominal pain, decreased the necessity for opiates and almost completely eliminated the risk of oral food intolerance [42]. In order to obtain higher evidence of the usefulness of early EN in MAP and SAP we performed a systematic review and meta-analysis which showed that early EN can be beneficial in both, MAP and SAP [35]. However, we also realized the lack of multicentre randomized control trials addressing energy intake in the early phase of AP.

The main objective of this trial is to understand whether early energy supplementation to patients suffering from AP is beneficial. Our hypothesis is that early energy supplementation will prevent the cells from death or decrease the size of necrosis if occur. This will decrease systemic immune response that will be ended in lower frequency of multi organ failure (MOF) and mortality. To prove this concept a randomized clinical trial involving all AP patients must be organized.

## METHODS

### 1. Design

This is a randomized controlled two-arms double-blind multicentre trial. Patients suffering from acute pancreatitis will be randomly assigned to groups A (high energy administration starting within 24h of hospital admission) and B (no energy administration after 24h of hospital admission).

### 2. Trial organization, committees and boards

GOULASH is designed and coordinated by the Centre for Translational Medicine at the University of Pécs and the Hungarian Pancreatic Study Group (HPSG). HPSG was established in 2011 in order to stimulate research in pancreatic diseases. Until now HPSG published the relevant guidelines of pancreatic diseases in order to improve patient care in the field of pancreatology [44-47] and has initiated four prospective clinical trials (EASY, PREPAST, APPLE and PINEAPPLE) [48-51].

The following committees and boards will be involved:

Steering committee (SC): The committee will be led by PH (gastroenterologist, internal medicine specialist). The members will be KM (medical doctor, full time employee on the project), ÁV (gastroenterologist, internal medicine specialist), ZM (intensive care specialist), TM (clinical research specialist) AS (multidisciplinary unit specialist), MP (gastroenterologist, internal medicine specialist), NF (radiologist), DK (surgeon), IB (interventional radiologist). SC will make decisions concerning all relevant questions including the drop outs during the study.

International translational advisory board (ITAB): The committee will include gastroenterologist (MML), surgeon (JPN) and basic scientists (MST, OHP). ITAB will continuously monitor the progress of the study and will give advice to the SC.

The study was designed by SC and ITAB. The study is financially sponsored by the University of Pécs, the Hungarian Academy of Sciences, and the National Research, Development and Innovation Office. Neither sponsors were involved in the design of the study, and they will have no access to the database management or to the randomization code.

### 3. Study population

All patients diagnosed with AP will be informed of the possibility of taking part in the GOULASH study. After the consent form is signed, a computer using a block randomization protocol will

randomize the patients. Figure 1 shows the flow chart of participants according to SPIRIT 2013 statement[52].

**Inclusion criteria:** (1) Patients over 18y of age, (2) diagnosed AP on the base of the "2 out of 3" criteria of the IAP/APA guideline[53] : (a) upper abdominal pain; (b) serum amylase or lipase >3x upper limit of normal range; (c) characteristic findings on pancreatic imaging; however those patients without abdominal pain will be excluded because the onset of AP cannot be determined, (3) written informed consent form is signed.

**Exclusion criteria**: (1) Hospitalization 72 hours before admission, (2) abdominal pain >120 hours (5 days), (3) delirium tremens, (4) Child-Pugh C stage liver cirrhosis, (5) AP due to malignancy, (6) already on artificial nutrition (EN or PN), (7) pregnancy, (8) BMI above 40 or below 18, (9) age above 80, (10) ketoacidosis, (11) whenever CT with contrast is contraindicated.

**Sample size:** Sample size calculation was based on the National Hungarian Registry operated by the Hungarian Pancreatic Study Group. Our recent analyses indicated that MOF existing more than 48h arises in 9%, whereas mortality is in 2.8% of all patient suffering from AP [34]. Altogether they represent around 10% of all AP patients. In order to detect a treatment effect of at least 50% of the early treatment a sample size of 957 subjects will be necessary to be recruited using a 10% drop-out rate, 80% power and 95% significance level. The calculation was performed by the Independent data management and biostatistics provider company (IDMB, Adware Research LTD, Balatonfüred, Hungary).

**Randomization:** In each centre participants will be divided into 2 groups receiving one of the two study treatments. The allocation of participants to the different groups will be carried out based on predefined randomization lists created separately for each recruiting centre. The randomization lists will be prepared with a block size of 4 and with an allocation ratio of 1:1.

4. **Duration**

The planned starting date of the study is; 1 January 2017, and the planned finishing date of the study is; 1 January2020.

### 5. Blinding

The medical staff (e.g., taking the measurements such as blood pressure, examining health records for events such as abdominal pain, reviewing and interpreting examination results such as X-ray or CT) and the patient receiving the intervention will be blinded to knowledge of treatment assignment. The person providing the intervention cannot be blinded in this study. Sealed envelopes ensure the allocation sequence. Nutritional support equipment will be covered until the fourth day to ensure that only who made the randomization will know which group the patient was enrolled into.

### 6. Intervention

Based on the currently available guidelines enteral feeding can be started at any time for the patients suffering from AP. In addition, no calorie restriction/order has been described. Therefore both groups can be regarded as being treated within accepted practice recommendations.

In this study, early high energy administration will be the intervention. Patients will be randomized to group A or B: see Figure 2.

**Groups:** In **group A,** high energy will be delivered after admission. Patients will receive a 10 Ch nasogastric (NG) or nasojejunal (NJ) feeding tube on admission. EN will be immediately started as follows: On Day 0 (from admission until the start of EN (can vary from 2-24 h)): calorie intake will be 0 kcal/kg/day. From Day 1 high energy enteral tube feed 30 kcal/kg/day will be provided until the oral feeding starts. In **group B,** low energy administration after hospital admission. Patients will receive a NG or NJ feeding tube at admission as described above. On Day 0 (from admission until the start of EN): calorie intake will be 0 kcal/kg/day. On day 1 0 kcal/kg/day, on day 2 10 kcal/kg/day, on day 3 20 kcal/kg/day and from day 4 30 kcal/kg/day calorie will be delivered until the oral feeding starts. However, between groups A and B only the amount of calories administered will be different. Patients will receive the same amount of fluid and ions during EN (see below).

**Ingredients of enteral tube feed: High Energy Enteral Tube Feed (100ml):**

**Energy**: 150 kcal (630 KJ), **Protein** 6g (16%E), **Carbohydrate**: 18.3g (49%E), **Fat**: 5.8g (35%E) + **Minerals**: 134mg Sodium, 201mg Potassium, 108mg Calcium, 108mg Phosphorus, 34mg Magnesium, 100mg Chloride (0%E). In this study we will use Nutrison Energy (Numil Ltd, Budapest, Hungary), which is a registered product in Hungary (reg. number: 1217).

**Zero Energy Enteral Tube Feed (100ml):**

**Energy**: 0 kcal (0 KJ), **Protein** 0g, **Carbohydrate**: 0g, Fat: 0g + **Minerals**: 134mg Sodium, 201mg Potassium, 108mg Calcium, 108mg Phosphorus, 34mg Magnesium, 5.562g Chloride (0%E) (in this study the local institutional pharmacy will provide it in accordance with the Hungarian regulations). Whenever 10 or 20 kcal/kg/day calories will be delivered, the mixture of the above-mentioned two solutions will be used.

**Type of enteral tube:** Patients neither vomiting nor having gastric fluid retention >250 ml will receive primarily NG tube. Patients either vomiting or having gastric fluid retention >250 ml will receive NJ tube (placement will be done either endoscopically or radiologically). In case of GCS 14 or lower in a patient who is not intubated, NG tube will be replaced by NJ tube (risk of aspiration). Abdominal X-ray will be used to check the tube's position.

**Start of mixed feeding** (around 2620 kcal): Mixed feeding (1000 ml tap water distributed for 24 h and 300 g (around 1900 kcal) biscuits/toasts/low fat meal (at least 75% CHO containing ones) orally plus enteral tube feed (440ml, 720 kcal/day) will be started on the day when: (1) abdominal pain has been ceased for at least 6 h before the new day started, (2) CRP level has started decreasing and are below 100 mg/L and (3) amylase or lipase level has started decreasing

**Start of total feeding** (around 2000kcal): If the patients have no symptoms during the mixed oral/enteral feeding and the CRP, amylase or lipase levels are not rising again. Total feeding (according to local policy) can be started.

**Other issues:** The speed of EN will be different for the patients (depends on the body weight), however, the maximum speed of EN cannot exceed 65ml/h. In case of difficulties reaching the 30

kcal/kg/day calories intake (if the patient's body weight is above 75 kg) additional intravenous calorie will be added using Sterofundin G. Maximum of 2000 ml (= 400 kcal) can be delivered in this way. If NG feeding is not tolerated, NG tube will be replaced to NJ tube as described above. If NJ feeding is not tolerated, EN will be reduced by 50% and increased again gradually until tolerated. If the re-increasing process is still not tolerated total parenteral nutrition (TPN) will be started to reach the required energy target. In case of SAP, TPN has to be delivered via central venous catheter.

### 11. Other treatment of subjects

General treatment indicated by the IAP/APA guideline will be utilized[53].

### 12. Discharge of patients

Uniformization of the length of hospital stay is necessary to avoid bias concerning LOH. Re-admission within one week after discharge has to be considered as the same hospital admission. Patients has to be counted as discharged from hospital/from the study when (1) the total feeding was tolerated for 24h, (2) no amylase/lipase level are elevated after total enteral feeding, (3) CRP level is less than 50 mg/L, (4) abdominal pain has completely resolved (5) no other pancreatitis-related complication requiring hospitalization is detected.

### 13. Endpoints

The following primary endpoints will be calculated: A combination of MOF more than 48h and Mortality. The following secondary endpoints will be analyzed: (1) pancreatic necrosis, (2) nutrition related complications: diarrhoea, aspiration pneumonia, pneumothorax due to central TPN catheter placement, (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 feeding, (6) use of antibiotics, (7) pain relapse, (8) CRP, (9) WBC, (10) PCT, (11) infection, (12) length of hospital stay, (13) need for ICU admission, (14) length of ICU therapy, (15) organ failure, (16) complications, (17) costs calculation. Notably,

only direct costs will be calculated that include all medications, services, salaries of healthcare professionals, equipment and day care costs.

### 14. Monitored parameters during hospitalization

There will be a large variety of parameters monitored during the study (e.g. medical history, physical examination, laboratory tests, diagnostic imaging, therapy, interventions). Form A will contain the parameters collected on admission. Form B will contain parameters collected every day during hospitalization. Form C will contain parameters collected 1 month after hospital discharge. For details see supplementary materials or web page (http://www.pancreas.hu/en/studies/goulash), which will be available from February 2017. Data collection on the case report form (CRF) will be done electronically (see data management).

### 15. Data management and statistical analyses

**Data handling:** Data will be handled by IDMB. Electronic CRF (eCRF) will be used. The Investigator will ensure that the data in the eCRF are accurate, complete and legible. Detailed data flow will be described in Data Management Plan (DMP). Data from completed eCRFs will be validated under the direction of the Data Manager at IDMB according to Data Cleaning Plan (DCP). Any missing, implausible, or inconsistent recordings in the eCRFs will be referred back to the Investigator using a data query form (DQF), and be documented for each individual subject before clean file status is declared. All changes to eCRF will be recorded. Before Data Base Lock Data Review Meeting will decide and document necessary steps related to any issue in the database and define the analysis sets. Member of the data review meeting are delegated investigator, biostatistician and data manager. Adverse events (AEs) will be coded using MedDRA. AdWare Research Ltd., who will act as IDMB, works according to GCP, GLP, FDA 21CFR PART11 and other relevant regulatory requirements. AdWare Ltd. has GLP and ISO 9001 certificates.

**Study populations:**

Three analysis populations will be defined:

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| Safety Analysis Set (SAS): | all patients enrolled in the study. |
| Per Protocol Set (PPS): | all enrolled patients who finished the study conforming to the requirements of the Study Protocol. |
| Intention to Treat (ITT) | all randomized participants who start on a treatment, excluding consent withdrawals. |

**Withdrawal of a subject from PPS:** Any participants/investigators and IDMB can submit recommendation for dropouts from the PPS group with reasons given to SC. All recommendations will be filed. SC will discuss all the information and if the alteration in the protocol would be expected to have any bearing on the interventions and outcomes of the study, the patient will not be included in the final per-protocol analysis. Automatic dropout from the per-protocol group shall be ordered if: (1) any of the exclusion criteria diagnosed during the course of AP, (2) at least 50% of the energy requirement is not achieved on any days during the study, (3) parameters required for answering the primary endpoints are missing or (4) serious medical reasons not related to pancreatitis (i.e. accidents, stroke) occur.

**Applied softwares:** Statistical analysis will be performed using SAS 9.2 or SPSS 19 (or later) statistical packages; Microsoft MSWord will be used for reporting.

**Statistical Methods:** Baseline patient and disease characteristics will be analyzed by using descriptive analysis. Demographic and baseline characteristics will be summarized for the overall study population. Continuous variables will be described by mean, median, standard deviation, and ranges and categorical variables will be described by absolute and relative frequencies. A graphical presentation of efficacy variables will be prepared, if applicable. Descriptive statistics for both of the primary and secondary parameters will be analyzed similarly. Mean changes (and their 95% CI) from baseline to end-of-study visit will be presented as well. Chi-squared tests will be applied to

compare proportions between the different groups. Mortality/extended MOF will be investigated using the Kaplan-Meier analysis method; while subgroup comparisons will be performed using the Chi-squared or Fisher's exact test, as appropriate. For safety data, descriptive statistics and individual listings of adverse events will be also presented.

**Subgroups:** The following subgroups will be made during statistical analyses: (1) ages (under 40y, 40y-59y, 60y-80y), (2) BMI (below 20, 20-24, 25-29, 30-35, above 35), (3) the start of abdominal pain before admission (≤24h, 24-48h, ≥48h), (4) severity of the disease SAP and MAP. All subgroup analyses, (5) etiologies will be done descriptively. No confirmatory statistical testing will be applied. Hence, statistical tests and the p-values attached to them will be regarded as descriptive and not as tests of hypotheses.

Details of the applied statistical tests will be described in the Statistical Analysis Plan.

### 16. Early quality assessment.

Early quality assessment check will be performed on the first 100 patients. IDMB (AdWare Ltd.) will perform an independent assessment of the trial related documents and activities, with the aim of ensuring the respect of subject's right, safety and well-being and to guarantee the plausibility of clinical data. The similarity of groups at baseline will be also checked. IDMB will report to SC. SC will discuss all the information and if the differences would be expected to have any bearing on the interventions and outcomes of the study or the overall dropout rate from PPS is above 20 percent of all participants who were randomized or allocated into each group or the differential dropout rate is above 15 percent between the arms, the study needs to be reassessed and IDMB will make recommendations regarding either reevaluation of power calculation, extension of recruitment period, extension of number of study centers or termination of trial.

### 17. Interim analyses and premature termination of the study.

IDMB can also recommend to stop the trial early for ethical reasons if one of the groups clearly shows evidence of a significant benefit. An interim analysis will be performed on the primary endpoint when 50% of patients have been randomized and discharged from the hospital. The interim analysis will be performed by the IDMB. IDMB will report to SC.

The Haybittle–Peto boundary approach will be used. If the interim analysis shows a probability of equal to, or less than 0.001 that a difference as extreme between the treatments is found, given that the null hypothesis is true, then the trial will be stopped early.

## 18. Centres

The trial will start in two centres (University of Debrecen and University of Pécs), after which the study is open for other centres. In all cases IDMB will make an audit of the centre and will report to the SC. SC keeps the right to decide whether the centre meets the required quality to join the study. Compulsory requirements for a centres: (1) it needs to treat at least 50 AP patients a year, (2) it needs to have all the equipment required for the study, (3) besides the regular medical team the centre has to appoint at least one doctor and one nurse/administrator fully available for the trial with no additional commitments which can interfere with her/his duty when her/his availability is required, (4) the blinding described above can be fully utilized, (5) all persons need to attend a preliminary meeting where all the details concerning the studies are discussed fully and have qualified as investigators in a GCP course. Centres wish to join need to send a letter of intent to the corresponding author by e-mail.

## 19. Publication policy

Centres providing more than 25 patients can provide two authors to the authorship list. Every additional 25 patients will give the opportunity to nominate an additional author.

## 20. Feasibility

As a general protocol for the treatment of AP at the Centre for Translational Medicine at the University of Pécs, patients suffering from AP receive early EN (using nasogastric tube). Patients receive 50 ml Nutrison Energy per hour starting immediately when they arrive to the ward from the Emergency Department. Patients data between the period of 1 January – 31 May 2016 were analyzed and the following observations were noted: (1) In 85% of all AP admission early EN could have been started within 24 h. In 15% of the cases it was not achievable due to the delayed transfer of the patients to the ward or vomiting. In these cases patients received NG tube later or they received NJ tube whenever X-ray assistance was available. (2) around 80% of NG-fed patients tolerated NG feeding without any complications. The rest of the patients who had gastric retention or vomiting NG feeding was stopped and they received NJ tube whenever X-ray assistance was available. (3) Comparing the outcome (rate of severity, mortality, necrosis, intervention, etc.) of this treatment protocol with the nil per os protocol utilized in most of the Hungarian hospitals revealed that patients enjoy benefits with no risk of early enteral feeding which data confirm the literature data described in the introduction. Concerning the number of patients at the University of Pécs around 250 and at the University of Debrecen around 150 patients are admitted annually. Therefore, if no other Institution would join the study it can be completed within 3 years.

## 21. Safety

Since no unknown drugs/therapy are used in the study no adverse and serious adverse events (SAE) are expected/interpretable that would be attributable to the intervention during the trial. In this trial IDMB will examine safety variables after every 16 patients have completed. Moreover, investigators will report AE or SAE via a separate form which has to be sent to IDMB and SC. SC will discuss and if the adverse effect is confirmed it will be reported to the relevant institutional and national ethical committee http://www.ett.hu/tukeb.htm.

## 22. Additional information and future plan.

Blood samples (serum and plasma) will be stored from all patients in order to study laboratory parameters later if required (e.g. the laboratory could not measure it), and in order to build up a biobank for later clinical studies to which all participants will be given informed consent. The samples will be stored on -80°C. A follow-up study (called GOULASH PLUS) is under preparation in order to follow the patients for up to 5 years after the study. The study protocol will also be published.

## DISCUSSION

Here we report the protocol of a prospective double-blind RCT to study the effects of early energy restoration in AP. The pre-clinical studies [1, 9] and meta-analyses suggest that early energy supplementation should be beneficial. Our main hypothesis is that elevating the energy level of acinar and ductal cells will prevent these cells from injury, therefore, it will decrease the extent of necrosis during AP. Since both the local and systemic complications (immune response) largely depend on the extent of the necrosis we propose that this intervention will reduce multi-organ failure and mortality in AP as well. Although nutritional interventions for patients with mild pancreatitis are probably not needed, we must involve all AP patients into the study. It has to be highlighted that the main aim of the study is not to find new treatments in MAP or SAP, but to prevent the development of SAP. This is the reason why severity cannot be a selection criteria but has to be the primary endpoint. Concerning ethical issues, this study has very low risk for patients. The enteral solution (Nutrison Energy) used in this study is widely used in several diseases related malnutrition in patients and has almost no contraindications, therefore no adverse events are expected during the trial. It is almost needless to say that at the end of the project we will disseminate our results in the medical community. We will publish our results in an open access way.

## CONCLUSION

This study provides the first and type A evidence concerning the necessity of energy intake for patients suffering from AP.

## List of abbreviations

AE – adverse event

AP – acute pancreatitis

BMI – body mass index

CRF – case report file

CRP – C-reactive Protein

DCP – data cleaning plan

DMP – data management plan

DQF – data query form

eCRF – electronic clinical report form

EN – enteral nutrition

GOULASH – name of the study: general utilization of early energy administration in acute pancreatitis.

HPSG – Hungarian Pancreatic Study Group

ICU – intensive care unit

IDMB – Independent data management and biostatistics provider company

ITAB – International Translational Advisory Board

ITT – Intention to Treat

LOH – length of hospital stay/hospitalization

MAP – mild and moderate AP

MOF – multi organ failure

NG – nasogastric

NJ – nasojejunal

PCT – procalcitonin

PN – parenteral nutrition

PPS – Per Protocol Set

SAE – severe adverse event

SAS – Safety Analysis Set

SAP – severe AP

SC – Steering Committee

TPN – total parenteral nutrition

WBC – white blood cell count

**Declarations**

The trial is registered at the ISRCTN registry (ISRCTN63827758) and got the relevant ethical approval with the reference number of 55961-2/2016/EKU issued by The Scientific and Research Ethics Committee of the Medical Research Council.

This protocol is the first version of the trial completed on 24th May 2017.

**Availability of data and materials**

Not applicable, because the trial has not completed patient recruitment.

**Competing interest**

The authors declare that they have no competing interests.

**Funding**

Centre costs (IT, biostatistics, trial organization, etc) are covered by the University of Pécs, Momentum Grant of the Hungarian Academy of Sciences (LP2014-10/2014); and Economic Development and Innovation Operative Programme Grant of the National Research, Development and Innovation Office (GINOP-2.3.2-15-2016-00015). Since no additional treatment is necessary for the study, the general healthcare costs are covered by the National Healthcare System.

**Authors' contributions**

All authors were involved in the study design, edited the manuscript, read and approved the final manuscript. During the study KM, ANS, DP and PV are going to randomize the patients, obtain the consent form and ensure the blinding. AM, KS, JB, SG, MP, PS, ZV and TT are going to manage the treatment of the patients. ÁV will be responsible for the organization, quality and timing of the endoscopic treatments, ZM and RH for the intensive care, NF and IB for the imaging and interventional radiology, DK and RP for the surgical treatment if needed. PAV and EL will prepare the nutritional solutions. ML, JN, MST and OP are members of ITAB. TM and AS will be members of SC. PH and KM drafted the manuscript.

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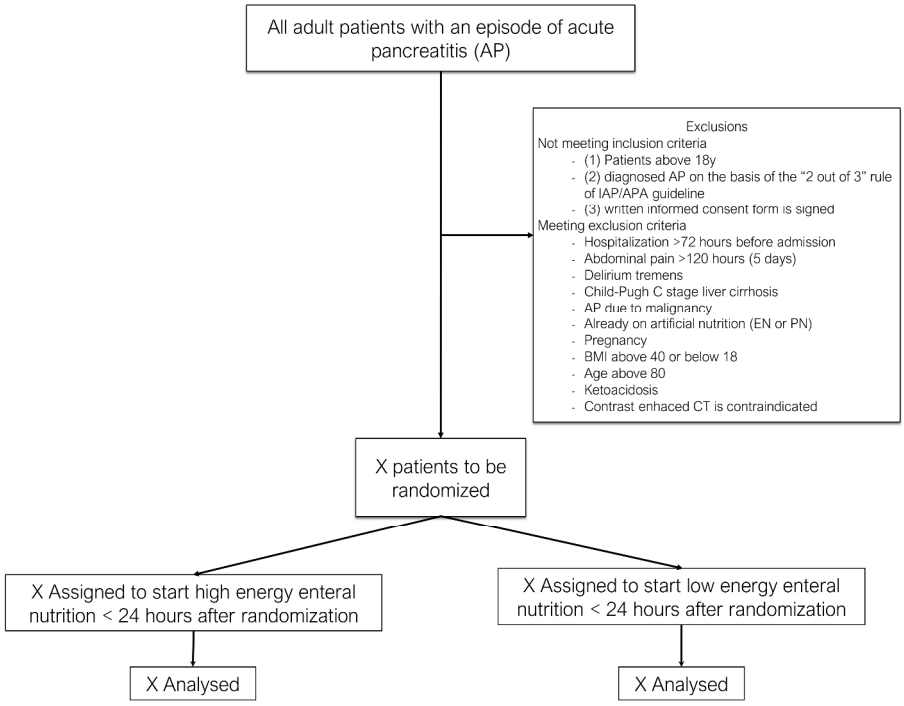


Flow of participants

361x270mm (300 x 300 DPI)

| | STUDY PERIOD | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | Enrolment | Allocation | Post-allocation | | | | | Close-out |
| TIMEPOINT** | *<24h* | 0 | *day1* | *day2* | *day3* | *dayx* | *discharge* | *1m after discharge* |
| ENROLMENT: | | | | | | | | |
| Eligibility screen | X | | | | | | | |
| Informed consent | X | | | | | | | |
| *Laboratory test* | X | | | | | | | |
| *CT examination* | X | | | | | | | |
| Allocation | | X | | | | | | |
| INTERVENTIONS: | | | | | | | | |
| *High energy administration* | | | ♦ | — | — | ♦ | | |
| *Low energy administration* | | | ♦ | — | — | ♦ | | |
| ASSESSMENTS: | | | | | | | | |
| *Questionnaire A* | | X | | | | | | |
| *Questionnaire B* | | | X | X | X | X | X | |
| *Questionnaire C* | | | | | | | | X |

Intervention. Patients will be randomized to group A (high energy) or B (low energy)

194x169mm (300 x 300 DPI)

# FORM-A Acute Pancreatitis GOULASH

***The physical examination has to be done ON ADMISSION!***
***The blood for laboratory parameters has to be drawn ON ADMISSION!***
***This form has to be filled ON ADMISSION!***

## *Questionnaire*

| |
|---|
| **Country:** |
| **Town:** |
| **Hospital:** |
| **Doctor:** |
| **Patient No:** |

## 1. Patient personal details

**Insurance number:**.....
**First name:**.....
**Last name:** .....
**Date of birth:**.....
**Gender:** female male
**Ethnicity/Race:** White / Black / Asian-Indian Not known

## 2. Details from the medical history

**Alcohol consumption**: yes / no
if yes: frequency: occasionally/monthly/weekly/dayly
amount (g/day):.....
since when? (years):.....
Alcohol consumption in the last 2 weeks: .....

if not:
Did you drink alcohol earlier? yes/no
if yes: frequency: occasionally/monthly/weekly/daily
amount (g/occasion):.....
For how many years?.....
How long ago did you stop drinking alcohol?.....

*Guide for estimation of the amount:*
*1 dl beer (4.5 vol. %) = ~3.5 g alcohol*
*1 dl wine (12.5 vol. %) = ~10 g alcohol*
*1 dl hard drink (50 vol. %) = ~40 g alcohol*

**Smoking**: yes / no
if yes: amount (cigarettes/day):.....
For how many years? .....
if not:
Did you smoke earlier? yes/no
if yes: amount (pcs/occasion):.....
For how many years?.....
How long ago did you stop smoking? .....

**Drug abuse**: yes / no *Prescribed medication should not be included here.*
if yes: type of drug:..... amount:.....
since when (year):.....
*(if there are more drugs, please describe them in the NOTES section at the end)*

**Diabetes mellitus**: yes / no
if yes: type: Type I. / Type II./Type III. c / MODY
since when (year):.....



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# FORM-A Acute Pancreatitis

Early Enteral Nutrition

GOULASH

**Lipid metabolism disorder:** yes / no
if yes: type: ..... since when (year):.....

**Any disease of the pancreas:** yes / no *Not counting the current episode.*
if yes: acute pancreatitis/ chronic pancreatitis/ autoimmune pancreatitis/ tumor/ other
if other: please describe:.....
<u>If the patient had ACUTE PANCREATITIS in the history:</u>
How many times did the patient have acute episodes before this episode:.....
When did the patient have the first acute episode (year):.....

<u>If the patient has CHRONIC/AUTOIMMUNE PANCREATITIS:</u>
When was it diagnosed?.....
How many times did the patient have acute episodes before this episode:.....
When did the patient have the first acute episode (year):.....

<u>If the patient has PANCREATIC CANCER::</u>
When was it diagnosed?.....
Was the patient diagnosed with chronic pancreatitis? yes / no
If yes, when was it diagnosed?.....
How many times did the patient have acute episodes before this episode?:.....
When did the patient have the first acute episode (year):.....

Other information:
.....

**Pancreas disorders in family history:**
acute pancreatitis: yes / no if yes: relationship to patient:.....
chronic pancreatitis yes / no if yes: relationship to patient:.....
autoimmune pancreatitis: yes / no if yes: relationship to patient:.....
pancreas tumor: yes / no if yes: relationship to patient:.....
other (please describe):.....relationship to patient:.....
.....

**Congenital Anatomical Malformation of the pancreas:** yes / no / no data
if yes: please describe:.....

**Other illnesses:** yes / no
if yes: please list/describe them:.....

**Medications taken regularly:** yes / no *Please specify the name of the active substance (e.g. "acetylsalicylic acid"). Please specify the amount using the International System of Units –SI (e.g. milligram, gram)*
if yes:
name:.....active substance:.....dose(gram,milligram, etc.).....
if fluid, concentration (e.g. 10%, 1g/2ml, etc.).....how many times per day (e.g. 3)
type of administration:.....other notes: .....

name:.....active substance:.....dose(gram,milligram, etc.).....
if fluid, concentration (e.g. 10%, 1g/2ml, etc.).....how many times per day (e.g. 3)
type of administration:.....other notes: .....

# FORM-A Acute Pancreatitis GOULASH

name:.....active substance:.....dose(gram,milligram, etc.).....
if fluid, concentration (e.g. 10%, 1g/2ml, etc.).....how many times per day (e.g. 3)
type of administration:.....other notes: .....

name:.....active substance:.....dose(gram,milligram, etc.).....
if fluid, concentration (e.g. 10%, 1g/2ml, etc.).....how many times per day (e.g. 3)
type of administration:.....other notes: .....

**Diet:** yes / no
if yes: please describe:.....

## 3. Etiology

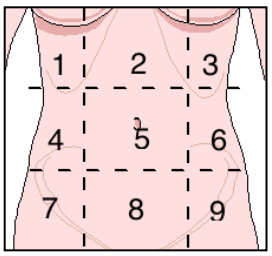
*The answer is "yes" if the etiological factor is proved, the answer is "no" if the etiological factor can be ruled out, the answer is "no data" if the etiological factor was not examined. Please answer "yes" to " Idiopathic" if etiological factor was not identified.*

| | | | |
|---|---|---|---|
| Biliary | yes | no | no data |
| Alcohol | yes | no | no data |
| Virus infection | yes | no | no data |
| Trauma | yes | no | no data |
| Drug-induced | yes | no | no data |
| Congenital anatomical malformation | yes | no | no data |
| Cystic fibrosis | yes | no | no data |
| Gluten-sensitive enteropathy | yes | no | no data |
| Hypertrigliceridaemia | yes | no | no data |
| Genetic | yes | no | has not been tested yet |
| Idiopathic | yes | no | |
| Other | yes | no | |

if yes: please describe:.....

## 4. Complains, symptoms

**Abdominal pain:** yes / no
if yes: since when (hours):.....
type: cramping / dull / sharp
intensity (1-10):.....
location: diffuse / localized
Please mark the location!
radiation:.....




**Nausea:** yes / no

**Vomiting:** yes / no
if yes: how many times:.....
contents of cast:.....

# FORM-A Acute Pancreatitis

Early Enteral Nutrition

GOULASH

**Subfebrility/fever:** yes / no
if yes: since when:.....
degree (°C):.....

**Appetite:** good / retained / bad

**Weight loss:** yes / no
if yes: how much (kg):.....
How long did it take? (weeks):.....

**Jaundice:** yes / no
if yes: for how long:.....

**Stool:** normal / diarrhea / constipation / fatty / putrid / undigested food/bloody/mucus
*Please refer to the period just before your symptoms has started.*

## 5. Admission details and state

**Blood pressure (Hgmm):**..... **Heart rate (/minute):**.....
**Body weight (kg):**..... **Body height (cm):**.....
**Respiratory rate (/minute):**..... **Body temperature (°C):** .....
axillary/rectal

**Oxygen saturation (%):** ..... Previous O2 therapy: yes/no

**Abdominal tenderness :** yes / no **Abdominal guarding:** yes / no

**Jaundice:** yes / no

**Glasgow Coma Scale (GCS):**.....

**Glasgow Coma Scale:**
**Eye response**
4 points: Spontaneous eye opening
3 points: Eye opening in response any speech
2 points: Opening to response to pain
1 point: No eye opening

**Verbal Response**
5 points: Orientated
4 points: Confused conversation
3 points: Inappropriate speech
2 points: Incomprehensible speech
1 point: No verbal response.

**Motor Response**
6 points: Obeying command
5 points: Localizing response to pain
4 points: Withdraws to pain
3 points: Decorticate posture
2 points: Decerebrate posture
1 point: No response to pain

FORM-A Acute Pancreatitis GOULASH

## 6. Laboratory parameters on admission

**OBLIGATORY PARAMETERS:**

| | |
|---|---|
| Amylase (U/l) | |
| Lipase (U/l) | |
| White blood cell (WBC) count (G/l) | |
| Red blood cell (RBC) count (T/l) | |
| Hemoglobin (g/l) | |
| Hematocrit (%) | |
| Thrombocyte (G/l) | |
| Serum glucose (mmol/l) | |
| Hemoglobin A1C (%) | |
| Blood urea nitrogen (mmol/l) | |
| Creatinine (umol/l) | |
| eGFR | |
| C-reactive protein (mg/l) | |
| ASAT/GOT (U/l) | |
| Lactate dehydrogenase LDH (U/l) | |
| Calcium (mmol/l) | |
| Sodium (mmol/l) | |
| Potassium (mmol/l) | |
| Total protein (g/l) | |
| Albumin (g/l) | |
| Cholesterol (mmol/l) | |
| Triglyceride (mmol/l) | |
| ALAT/GPT (U/l) | |
| Gamma GT (U/l) | |
| Total bilirubin (umol/l) | |
| Direct/Conjugated bilirubin (umol/l) | |
| Alkaline phosphatase (U/l) | |
| Procalcitonin (ng/ml) | |

# FORM-A Acute Pancreatitis

Early Enteral Nutrition

GOULASH

**OTHER PARAMETERS (if measured):**

| | |
|---|---|
| IgA (g/l) | |
| IgM (g/l) | |
| IgG (g/l) | |
| IgG4 (g/l) | |
| CA 19-9 (U/ml) | |
| $PaO_2$ (Hgmm) | |
| $HCO_3$ (mmol/l) | |
| $sO_2$ (%) | |
| sweat chloride (mmol/l) | |
| urine amylase | |
| uirne lipase | |
| urine creatinine | |
| (other) | |

Virus serology: yes / no Which viruses?..... results:.....

## 7. Imaging examinations on admission

Does the patient have pleural fluid? yes no N/A
Does the patient have lung infiltrate? yes no N/A
Does the patient have abnormal pancreatic structure? yes no N/A
If yes: hypoechoic/hyperechoic/peripancreatic fluid/irregular and blurred contours/Wirsung dilatation (above 1mm)/ascites/calcification/cyst

**Abdominal X-ray:** yes no
Description:
.....
.....

**Chest X-ray:** yes no
Description:
.....
.....

**Chest Computed Tomography:** yes no
Description:
.....
.....

**Abdominal Computed Tomography:**
Modified CTSI Score: .....0-10.....
*Please NOTE! Abdominal CT is compulsory on admission*

**CTSI Score: (I)** Normal pancreas 0 point, intrinsic pancreatic abnormalities with or without inflammatory changes in peripancreatic fat 2 points, Pancreatic or peripancreatic fluid collection or peripancreatic fat necrosis 4 points **(II)** Necrosis absent 0 Points, < 30% necrosis 2 Points, > 30% necrosis 4 points **(III)** presence of extrapancreatic findings 2 points.
MAXIMUM OF: 10 points

- **CTSI:**

**I. Pancreas**
- Normal pancreas
- Intrinsic pancreatic abnormalities with or without inflammatory changes in peripancreatic fat
- pancreatic or peripancreatic fluid collection or peripancreatic fat necrosis

**II. Size of Necrosis**
- Necrosis absent
- < 30% necrosis
- > 30% necrosis
- > 60% necrosis

**III. Extrapancreatic findings**
- presence of extrapancreatic findings

**DETAILED REPORT**

- **Pancreas Size:**
  - Normal
  - Partially enlarged (body AP diameter is over 2 cm and/or head AP diameter is over 2,5 cm, none exceeds 3 cm)
  - Definitely enlarged (any part over 3 cm AP diameter)
- Largest diameter of peripancreatic **fat infiltration**: …… cm

- **Peripancreatic fluid:**
  - none
  - present
  - Large pseudocyst(s)
- Size of peripancreatic fluid or pseudocyst: …… cm

- **Necrotizing area** (nonenchancement):
  - Largest diameter of necrosis area: …… cm
  - Location of necrosis: ……
  - Type: patchy / full width
  - Estimated necrosis: 0% , < 30% , 30% - 60%, above 60%

- **Wirsung** dilatation: YES / NO (yes, diameter: …… mm)

- Distant **abdominal fluid**:
  - Small amount (hard to see, less than 2 cm in lesser pelvis, less than 1 cm around liver/spleen)
  - Moderate amount (easy to see, but without pelvic or abdominal distension)
  - Large amount with abdominal/pelvic distension

- **Pleural effusion:**
  - none
  - one sided:……. (AP diameter: …… cm)
  - Both sides, L - …… cm, R - …… cm

- **Extrapancreatic findings**:
  - Inflammation (Cholecystitis, Duodenitis, etc.) location: ……
  - Cholecystolithiasis
  - Choledocholithiais
  - Signs of bowel ischaemia
  - Bowel distension, ileus
  - Venous thrombosis
  - Pseudoaneurysm
  - Parenchymal organ involvement, define: ……

Other Description:

……

……

## 8. Genetic testing

Has it been performed earlier? yes no

if yes: please describe:

……

……

……

## 9.a Intravenious fluid in the early period

**Intravenious fluid in the early period……ml**

*To be counted from the first moment (including ambulance car) until the start of the early enteral nutrition. 5–10 ml/kg/h should be given in the first 2h. It has to be continued until: heart rate <120/min, mean arterial pressure between 65 and 85 mmHg (8.7–11.3 kPa), and urinary output >0.5–1 ml/kg/h*

## 9.b Immediate therapy on admission

**Intravenous fluid** **yes** **no**

if yes: type of fluid……

amount (ml)……

*If not contraindicated the type of fluid has to be Ringer Lactate. No glucose should be given if it is not compulsory due to hypoglycaemia*

**Pain management:** **yes** **no**

if yes:

name:……active substance:……dose(gram,milligram, etc.)……

if fluid, concentration (e.g. 10%, 1g/2ml, etc.)……how many times per day (e.g. 3)

type of administration:……other notes: ……

# FORM-A Acute Pancreatitis GOULASH

name:.....active substance:.....dose(gram,milligram, etc.).....
if fluid, concentration (e.g. 10%, 1g/2ml, etc.).....how many times per day (e.g. 3)
type of administration:.....other notes: .....

name:.....active substance:.....dose(gram,milligram, etc.).....
if fluid, concentration (e.g. 10%, 1g/2ml, etc.).....how many times per day (e.g. 3)
type of administration:.....other notes: .....

**Insulin:** **yes** **no**
if yes: name of the medication:.....
total dose of medication:.....

**Intensive care:** **yes** **no**
if yes: namely (ventilation, vasopressor therapy):.....

**Other:**
if yes: please describe:.....
.....

## 10. Interventions, endoscopic treatment: yes no

if yes: ERCP-EST/endobiliary stent/Wirsung stent/cysta drainage
Stent: 1 plastic stent/more plastic stents/uncovered metal stent/covered metal stent
Early complications: none/bleeding/perforation
**ERCP:** yes no
if yes:

| | | | |
|---|---|---|---|
| Successful biliary cannulation: | yes | no | if yes: notes: ..... |
| Precut: | yes | no | if yes: needleknife/precut papillotomia |
| EST: | yes | no | if yes: biliary/pancreatic |
| Stone extraction: | yes | no | |
| Stent: | yes | no | if yes: metal/plastic<br>How many pcs? diameter(Fr)? length(cm)? |
| Pancreatic duct filling: | yes | no | if yes: notes: ..... |

## 11. Complications

*Please register pancreatic complication of fluid collection/pseudocyst/necrosis only if you had imaging proof on the day of admission, otherwise, please mark "no data".*

**Pancreatic:** yes no no data
if yes: fluid collections /pseudocyst / necrosis / diabetes

**Organ failure:** yes no
if yes:, lung /heart / kidney /other

**Death:** yes no
If yes: the exact time of death: ..... *e.g. 10.25 or 22.45*

# FORM-A Acute Pancreatitis

Early Enteral Nutrition

GOULASH

**12. Epicrisis** *A short summary of the hospitalization (how the patient got to medical care, diagnosis, most important facts and events of the hospitalization, what happened with the patient after the hospitalization, any recommended control examinations, surgery).*

……

……

**NOTES**

……

……

**DATE:**

YEAR: …… MONTH: …… DAY: …… HOUR …… MIN: ……

THE TOTAL TIME SPENT THE PATIENT ON ADMISSION: HOUR …… MIN: ……

**NAME OF THE DOCTOR MADE THE RANDOMIZATION:** ……**SIGNATURE:** ……

*Please NOTE! The doctor made the randomization MUST NOT involved in the treatment of patients any longer. She/He has to keep the information secretly from the patients and medical team involved in the treatment.*

**NAME OF THE DOCTOR EXAMINED/TREATED THE PATIENT:** ……**SIGNATURE:** ……

# FORM-B Acute Pancreatitis GOULASH

*PLEASE FILL IN EVERY DAY DURING THE HOSPITAL STAY*

**Day No:**
**Date (+hour, min)**

**GOULASH No:**

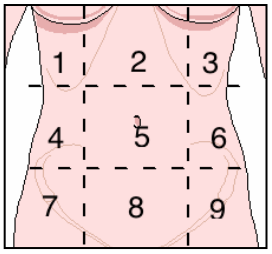
**(Automatically generated)**

## 1. Patient personal details

**First name:**.....

**Last name:** .....

## 2. Complains, symptoms




**Abdominal pain:** yes / no
if yes: since when (hours):.....
type: cramping / dull / sharp
intensity (1-10):.....
location: diffuse / localized
Please mark the location!
radiation:.....

**Nausea:** yes / no
*If YES, retention measurement has to be performed.*
**Vomiting:** yes / no
*If YES, NG tube has to be replaced by NJ tube.*

**Subfebrility/fever:** yes / no
if yes: since when:.....
degree (°C):.....

**Appetite:** good / retained / bad

**Stool:** yes / no

if yes: normal / diarrhea / constipation / fatty / putrid / undigested food/bloody/mucus





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## 3. Patient's state

**Blood pressure (Hgmm):**..... **Heart rate (/minute):**.....

**Body weight (kg):**.....

**Respiratory rate (/minute):**..... **Body temperature (°C):** .....
axillary/rectal

**Oxygen saturation (%):** ..... O2 therapy: yes/no

**Abdominal tenderness :** yes / no **Abdominal guarding:** yes / no

**Jaundice:** yes / no

**Glasgow Coma Scale (GCS):**.....

**Glasgow Coma Scale:**

**Eye response**
4 points: Spontaneous eye opening
3 points: Eye opening in response any speech
2 points: Opening to response to pain
1 point: No eye opening

**Verbal Response**
5 points: Orientated
4 points: Confused conversation
3 points: Inappropriate speech
2 points: Incomprehensible speech
1 point: No verbal response.

**Motor Response**
6 points: Obeying command
5 points: Localizing response to pain
4 points: Withdraws to pain
3 points: Decorticate posture
2 points: Decerebrate posture
1 point: No response to pain

## 4. Laboratory parameters

**OBLIGATORY PARAMETERS**

| | |
|---|---|
| Amylase (U/l) | |
| Lipase (U/l) | |
| White blood cell (WBC) count (G/l) | |
| Red blood cell (RBC) count (T/l) | |
| Hemoglobin (g/l) | |
| Hematocrit (%) | |
| Thrombocyte (G/l) | |
| C-reactive protein (mg/l) | |





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# FORM-B Acute Pancreatitis GOULASH

**OTHER PARAMETERS (if measured):**

| | |
|---|---|
| Serum glucose (mmol/l) | |
| Blood urea nitrogen (mmol/l) | |
| Creatinine (umol/l) | |
| eGFR | |
| ASAT/GOT (U/l) | |
| Lactate dehydrogenase LDH (U/l) | |
| Calcium (mmol/l) | |
| Sodium (mmol/l) | |
| Potassium (mmol/l) | |
| Total protein (g/l) | |
| Albumin (g/l) | |
| Cholesterol (mmol/l) | |
| Triglyceride (mmol/l) | |
| ALAT/GPT (U/l) | |
| Gamma GT (U/l) | |
| Total bilirubin (umol/l) | |
| Direct/Conjugated bilirubin (umol/l) | |
| Alkaline phosphatase (U/l) | |
| Procalcitonin (ng/ml) | |
| IgA (g/l) | |
| IgM (g/l) | |
| IgG (g/l) | |
| IgG4 (g/l) | |
| CA 19-9 (U/ml) | |
| $PaO_2$ (Hgmm) | |
| $HCO_3$ (mmol/l) | |
| $sO_2$ (%) | |
| sweat chloride (mmol/l) | |
| urine amylase | |
| uirne lipase | |
| urine creatinine | |
| (other) | |

**Blood glucose (by finger stick test)** *Compulsory on the first day*:

| | | |
|---|---|---|
| 4h | mmol/l | amount of insulin if administered : …… IU |
| 8h | mmol/l | |
| 12h | mmol/l | |
| 16h | mmol/l | |
| 20h | mmol/l | |
| 24h | mmol/l | |





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## 5. Imaging (if performed) yes no

**Abdominal ultrasonography:** yes no

*2 hours before the examination the enteral feeding has to be stopped. The amount of enteral feeding which was not given have to be administered additionally to the normal feeding in the next 10h. (for example: If the patient receive 45 ml/h and 90ml was not given due to the examination, the patient has to receive 54ml (45ml + 9ml) for the forthcoming 10h.*

- ***Visualization:***
  - Good, complete (head at least partially visualized, body and neck well visualized, tail: partially visualized)
  - Partially, incomplete (only body or only head visualized)
  - Poor, non-diagnostic
- **Size:**
  - Normal
  - Partially enlarged (body AP diameter is over 2 cm and/or head AP diameter is over 2,5 cm, none exceeds 3 cm)
  - Definitely enlarged (any part over 3 cm AP diameter)

- **Peripancreatic fluid:**
  - none
  - present
  - Large pseudocyst(s)
- Size of peripancreatic fluid or pseudocyst: …… cm

- **Pancreas homogeneity:**
  - Homogenous
  - Inhomogeneous, includes area(s) of low echogenicity
  - Inhomogeneous, includes calcifications

- In case of circumscribed low echogenicity area, it's size: …… cm

- **Wirsung** dilatation: YES / NO (yes, diameter: …… mm)

Other Description:

……

……

**Abdominal X-ray:** yes no

Description:

……

……

**Chest X-ray:** yes no

Description:

……

……

**Chest Computed Tomography:** yes no

Description:

……

……





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# FORM-B Acute Pancreatitis GOULASH

**Abdominal Computed Tomography:** yes/no
Modified CTSI Score: ……0-10……
*Please NOTE! Abdominal CT is compulsory when the patient is discharged*

**CTSI Score: (I)** Normal pancreas 0 point, intrinsic pancreatic abnormalities with or without inflammatory changes in peripancreatic fat 2 points, Pancreatic or peripancreatic fluid collection or peripancreatic fat necrosis 4 points **(II)** Necrosis absent 0 Points, < 30% necrosis 2 Points, > 30% necrosis 4 points **(III)** presence of extrapancreatic findings 2 points.
MAXIMUM OF: 10 points

- **CTSI:**
  - **I. Pancreas**
  - Normal pancreas
  - Intrinsic pancreatic abnormalities with or without inflammatory changes in peripancreatic fat
  - pancreatic or peripancreatic fluid collection or peripancreatic fat necrosis
  - **II. Size of Necrosis**
  - Necrosis absent
  - < 30% necrosis
  - > 30% necrosis
  - > 60% necrosis
  - **III. Extrapancreatic findings**
  - presence of extrapancreatic findings
  -

**DETAILED REPORT**

- **Pancreas Size:**
  - Normal
  - Partially enlarged (body AP diameter is over 2 cm and/or head AP diameter is over 2,5 cm, none exceeds 3 cm)
  - Definitely enlarged (any part over 3 cm AP diameter)
- Largest diameter of peripancreatic **fat infiltration**: …… cm

- **Peripancreatic fluid:**
  - none
  - present
  - Large pseudocyst(s)
- Size of peripancreatic fluid or pseudocyst: …… cm

- **Necrotizing area** (nonenchancement):
  - Largest diameter of necrosis area: …… cm
  - Location of necrosis: ……
  - Type: patchy / full width
  - Estimated necrosis: 0% , < 30% , 30% - 60%, above 60%

- **Wirsung** dilatation: YES / NO (yes, diameter: …… mm)



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- Distant **abdominal fluid**:
  - Small amount (hard to see, less than 2 cm in lesser pelvis, less than 1 cm around liver/spleen)
  - Moderate amount (easy to see, but without pelvic or abdominal distension)
  - Large amount with abdominal/pelvic distension

- **Pleural effusion:**
  - none
  - one sided:……. (AP diameter: …… cm)
  - Both sides, L - …… cm, R - …… cm

- **Extrapancreatic findings**:
  - Inflammation (Cholecystitis, Duodenitis, etc.) location: ……
  - Cholecystolithiasis
  - Choledocholithiais
  - Signs of bowel ischaemia
  - Bowel distension, ileus
  - Venous thrombosis
  - Pseudoaneurysm
  - Parenchymal organ involvement, define: ……

Other Description:
……
……

## 6. Microbiology examination

Biological sample collection yes no
If yes: place: /blood, urine, airway, pancreas, other/
result: ……





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# FORM-B Acute Pancreatitis GOULASH

## 7. Therapy

**Total oral feeding** yes no

**CHO reach oral feeding** yes no

**Intravenous fluid** yes no
if yes, type of fluid……
amount (ml)……

type of fluid……
amount (ml)……

**Enteral feeding** yes no
if yes, naso-gastric / naso-jejunal
formula: ……
amount:…… (ml)
speed of the pump:…… ml/h

**Gastric retention measurement** *Compulsory on the first day*

amount:…… (ml)

**Did the patient need change in EN from NG to NJ feeding?** yes no
if yes, type of fluid……
amount (ml)……
speed of the pump:…… ml/h

**TPN** yes no
if yes, type of TPN……
amount (ml)……

type of TPN……
amount (ml)……

**NOTES FOR ENTERAL FEEDING**
……
……

**Total delivered calorie on the day?** …… kcal, ……kcal/kg
Calorie delivery by NGF: …… kcal
Calorie delivery by NJF: …… kcal
Calorie delivery by iv glucose: …… kcal
Calorie delivery by TPN: …… kcal
Calorie delivery by mixed oral feeding: …… kcal
Calorie delivery by total oral feeding: …… kcal





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# FORM-B Acute Pancreatitis

Early Enteral Nutrition

GOULASH

**Pain management:** yes no

if yes:

name:.....active substance:.....dose(gram,milligram, etc.).....

if fluid, concentration (e.g. 10%, 1g/2ml, etc.).....how many times per day (e.g. 3)

type of administration:.....other notes: .....

name:.....active substance:.....dose(gram,milligram, etc.).....

if fluid, concentration (e.g. 10%, 1g/2ml, etc.).....how many times per day (e.g. 3)

type of administration:.....other notes: .....

name:.....active substance:.....dose(gram,milligram, etc.).....

if fluid, concentration (e.g. 10%, 1g/2ml, etc.).....how many times per day (e.g. 3)

type of administration:.....other notes: .....

**Antibiotic therapy:** yes no

if yes:

name:.....active substance:.....dose(gram,milligram, etc.).....

if fluid, concentration (e.g. 10%, 1g/2ml, etc.).....how many times per day (e.g. 3)

type of administration:.....other notes: .....

name:.....active substance:.....dose(gram,milligram, etc.).....

if fluid, concentration (e.g. 10%, 1g/2ml, etc.).....how many times per day (e.g. 3)

type of administration:.....other notes: .....

name:.....active substance:.....dose(gram,milligram, etc.).....

if fluid, concentration (e.g. 10%, 1g/2ml, etc.).....how many times per day (e.g. 3)

type of administration:.....other notes: .....

**Insulin:** yes no

if yes, name of the medication:.....

dosage:.....

**Intensive care:** yes no

if yes, namely (ventilation, vasopressor therapy):.....

**Other:**

if yes, please describe:.....

.....

.....





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## 8. Interventions, endoscopic treatment: yes no

if yes: ERCP-EST/endobiliary stent/Wirsung stent/cysta drainage
Stent: 1 plastic stent/more plastic stents/uncovered metal stent/covered metal stent
Early complications: none/bleeding/perforation

**ERCP:** yes no
if yes:

| | | | |
|---|---|---|---|
| Successful biliary cannulation: | yes | no | if yes: notes: …… |
| Precut: | yes | no | if yes: needleknife/precut papillotomia |
| EST: | yes | no | if yes: biliary/pancreatic |
| Stone extraction: | yes | no | |
| Stent: | yes | no | if yes: metal/plastic |
| | | | How many pcs? diameter(Fr)? length(cm)? |
| Pancreatic duct filling: | yes | no | if yes: notes: …… |

## 9. Complications

Pancreatic: yes no no data
if yes, fluid collections / pseudocyst / necrosis / diabetes
Organ failure: yes no
if yes, lung / heart / kidney /other
Duration of organ failure: <48 hours >48 hours
Death: yes no
if yes: the exact time of death: …… *e.g. 10.25 or 22.45*

**NOTES**

……
……
……

**DATE:**
YEAR: …… MONTH: …… DAY: ……

**NAME OF THE DOCTOR:** ……**SIGNATURE:** ……

**NAME OF THE NURSE:** ……**SIGNATURE:** ……

**NAME OF THE SCIENCE ADMINISTRATOR:** ……**SIGNATURE:** ……





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# FORM-C Acute Pancreatitis

Early Enteral Nutrition

GOULASH

## Questionnaire

### 1. Patient personal details

**GOULASH No:**

**(Automatically generated)**

**First name:**.....

**Last name:** .....

### 2. Details from the medical history (in the last month)

**Alcohol consumption**: yes / no
if yes: frequency: occasionally/monthly/weekly/daily
amount (g/day):.....

*Guide for estimation of the amount:*
*1 dl beer (4.5 vol. %) = ~3.5 g alcohol*
*1 dl wine (12.5 vol. %) = ~10 g alcohol*
*1 dl hard drink (50 vol. %) = ~40 g alcohol*

**Smoking**: yes / no
if yes: amount (cigarettes/day):.....

**Drug abuse**: yes / no *Prescribed medication should not be included here.*
if yes: type of drug:..... amount:.....
*(if there are more drugs, please describe them in the NOTES section at the end)*

**Any re-hospitalization?:** yes / no

if yes: cholecystectomy: yes no
recurrent AP: yes no
other: .....

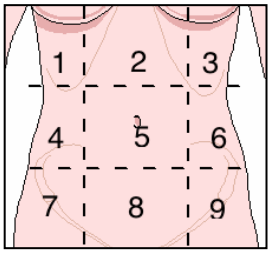
**Medications taken regularly in the last month:** yes / no
*Please specify the name of the active substance (e.g. "acetylsalicylic acid"). Please specify the amount using the International System of Units –SI (e.g. milligram, gram)*
if yes:
name:.....active substance:.....dose(gram,milligram, etc.).....
if fluid, concentration (e.g. 10%, 1g/2ml, etc.).....how many times per day (e.g. 3)
type of administration:.....other notes: .....

name:.....active substance:.....dose(gram,milligram, etc.).....
if fluid, concentration (e.g. 10%, 1g/2ml, etc.).....how many times per day (e.g. 3)
type of administration:.....other notes: .....

name:.....active substance:.....dose(gram,milligram, etc.).....
if fluid, concentration (e.g. 10%, 1g/2ml, etc.).....how many times per day (e.g. 3)
type of administration:.....other notes: .....

**Diet:** yes / no
if yes: please describe:.....

## 3. Complains, symptoms




**Abdominal pain:** yes / no
if yes: since when (hours):.....
type: cramping / dull / sharp
intensity (1-10):.....
location: diffuse / localized
Please mark the location!
radiation:.....

**Nausea:** yes / no

**Vomiting:** yes / no
if yes: how many times:.....
contents of cast:.....

**Subfebrility/fever:** yes / no
if yes: since when:.....
degree (°C):.....

**Appetite:** good / retained / bad

**Weight loss:** yes / no
if yes: how much (kg):.....
How long did it take? (weeks):.....

**Jaundice:** yes / no
if yes: for how long:.....

**Stool:** normal / diarrhea / constipation / fatty / putrid / undigested food/bloody/mucus

## 4. Laboratory parameters

**OBLIGATORY PARAMETERS**

| | |
|---|---|
| Amylase (U/l) | |
| Lipase (U/l) | |
| White blood cell (WBC) count (G/l) | |
| Red blood cell (RBC) count (T/l) | |
| Hemoglobin (g/l) | |
| Hematocrit (%) | |
| Thrombocyte (G/l) | |
| C-reactive protein (mg/l) | |

**OTHER PARAMETERS (if measured):**

| | |
|---|---|
| Serum glucose (mmol/l) | |
| Blood urea nitrogen (mmol/l) | |
| Creatinine (umol/l) | |
| eGFR | |
| ASAT/GOT (U/l) | |
| Lactate dehydrogenase LDH (U/l) | |
| Calcium (mmol/l) | |
| Sodium (mmol/l) | |
| Potassium (mmol/l) | |
| Total protein (g/l) | |
| Albumin (g/l) | |
| Cholesterol (mmol/l) | |
| Triglyceride (mmol/l) | |
| ALAT/GPT (U/l) | |
| Gamma GT (U/l) | |
| Total bilirubin (umol/l) | |
| Direct/Conjugated bilirubin (umol/l) | |
| Alkaline phosphatase (U/l) | |

**5. Imaging examination**

**Abdominal ultrasonography:** yes no
Description:

**Ultrasound:**

- *Visualization:*
  - Good, complete (head at least partially visualized, body and neck well visualized, tail: partially visualized)
  - Partially, incomplete (only body or only head visualized)
  - Poor, non-diagnostic
- **Size:**
  - Normal
  - Partially enlarged (body AP diameter is over 2 cm and/or head AP diameter is over 2,5 cm, none exceeds 3 cm)
  - Definitely enlarged (any part over 3 cm AP diameter)
- **Peripancreatic fluid:**
  - none
  - present
  - Large pseudocyst(s)

- Size of peripancreatic fluid or pseudocyst: …… cm

- **Pancreas homogeneity:**
  - Homogenous
  - Inhomogeneous, includes area(s) of low echogenicity
  - Inhomogeneous, includes calcifications

- In case of circumscribed low echogenicity area, it's size: …… cm

- **Wirsung** dilatation: YES / NO (yes, diameter: …….. mm)

Other Description:

……
……

**Abdominal Computed Tomography:** yes no
Modified CTSI Score: ……0-10……

*Please NOTE! Abdominal CT is compulsory if*
*- Abdominal ultrasonography is not fully completed **OR***
*- There is any alteration on abdominal ultrasonography*

**CTSI Score: (I)** Normal pancreas 0 point, intrinsic pancreatic abnormalities with or without inflammatory changes in peripancreatic fat 2 points, Pancreatic or peripancreatic fluid collection or peripancreatic fat necrosis 4 points **(II)** Necrosis absent 0 Points, < 30% necrosis 2 Points, > 30% necrosis 4 points **(III)** presence of extrapancreatic findings 2 points.
MAXIMUM OF: 10 points

- **CTSI:**

**I. Pancreas**
  - Normal pancreas
  - Intrinsic pancreatic abnormalities with or without inflammatory changes in peripancreatic fat
  - pancreatic or peripancreatic fluid collection or peripancreatic fat necrosis

**II. Size of Necrosis**
  - Necrosis absent
  - < 30% necrosis
  - > 30% necrosis
  - > 60% necrosis

**III. Extrapancreatic findings**
  - presence of extrapancreatic findings

**DETAILED REPORT**

- **Pancreas Size:**
  - Normal
  - Partially enlarged (body AP diameter is over 2 cm and/or head AP diameter is over 2,5 cm, none exceeds 3 cm)

- Definitely enlarged (any part over 3 cm AP diameter)

- Largest diameter of peripancreatic **fat infiltration**: …… cm

- **Peripancreatic fluid:**
  - none
  - present
  - Large pseudocyst(s)
- Size of peripancreatic fluid or pseudocyst: …… cm

- **Necrotizing area** (nonenchancement):
  - Largest diameter of necrosis area: …… cm
  - Location of necrosis: ……
  - Type: patchy / full width
  - Estimated necrosis: 0% , < 30% , 30% - 60%, above 60%

- **Wirsung** dilatation: YES / NO (yes, diameter: …… mm)

- Distant **abdominal fluid**:
  - Small amount (hard to see, less than 2 cm in lesser pelvis, less than 1 cm around liver/spleen)
  - Moderate amount (easy to see, but without pelvic or abdominal distension)
  - Large amount with abdominal/pelvic distension

- **Pleural effusion:**
  - none
  - one sided:…… (AP diameter: …… cm)
  - Both sides, L - …… cm, R - …… cm

- **Extrapancreatic findings**:
  - Inflammation (Cholecystitis, Duodenitis, etc.) location: ……
  - Cholecystolithiasis
  - Choledocholithiais
  - Signs of bowel ischaemia
  - Bowel distension, ileus
  - Venous thrombosis
  - Pseudoaneurysm
  - Parenchymal organ involvement, define: ……

Other Description:
……
……

## 6. Complications

*Please register pancreatic complication of fluid collection/pseudocyst/necrosis only if you had imaging proof on the day of admission, otherwise, please mark "no data".*

**Pancreatic:** yes no no data
if yes: fluid collections /pseudocyst / necrosis / diabetes

**Organ failure:** yes no
if yes:, lung /heart / kidney /other

**Death:** yes no
If yes: the exact date of death: ..... *e.g. 10.25 or 22.45*

## 7. Epicrisis

*A short summary (what happened with the patient after the hospitalization, any recommended control examinations, surgery).*

.....
.....

**DATE:**
YEAR: ..... MONTH: ..... DAY: ..... HOUR ..... MIN: .....

**NAME OF THE DOCTOR : .....SIGNATURE:** .....


SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

| Section/item | Item No | Description | Addressed on page number |
|---|---|---|---|
| **Administrative information** | | | |
| Title | 1 | Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym | 1 |
| Trial registration | 2a | Trial identifier and registry name. If not yet registered, name of intended registry | 2,17 |
| | 2b | All items from the World Health Organization Trial Registration Data Set | 17 |
| Protocol version | 3 | Date and version identifier | 17 |
| Funding | 4 | Sources and types of financial, material, and other support | 17 |
| Roles and responsibilities | 5a | Names, affiliations, and roles of protocol contributors | 1,18 |
| | 5b | Name and contact information for the trial sponsor | 5 |
| | 5c | Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities | 5, 17 |
| | 5d | Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee) | 5, 12 13 |

| | | | |
|---|---|---|---|
| **Introduction** | | | |
| Background and rationale | 6a | Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention | 3, 4 15, 16 |
| | 6b | Explanation for choice of comparators | 4 |
| Objectives | 7 | Specific objectives or hypotheses | 4 |
| Trial design | 8 | Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory) | 4, 6 |
| **Methods: Participants, interventions, and outcomes** | | | |
| Study setting | 9 | Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained | 13, 10 |
| Eligibility criteria | 10 | Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists) | 6, 13 |
| Interventions | 11a | Interventions for each group with sufficient detail to allow replication, including how and when they will be administered | 7, 8, 9 |
| | 11b | Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease) | 9 |
| | 11c | Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests) | 14 |
| | 11d | Relevant concomitant care and interventions that are permitted or prohibited during the trial | 9 |
| Outcomes | 12 | Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended | 9, 10, 11, 14 |
| Participant timeline | 13 | Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure) | 7, 10 |

| | | | |
|---|---|---|---|
| Sample size | 14 | Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations | 6 |
| Recruitment | 15 | Strategies for achieving adequate participant enrolment to reach target sample size | 6 |
| **Methods: Assignment of interventions (for controlled trials)** | | | |
| Allocation: | | | |
| Sequence generation | 16a | Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions | 6, 7 |
| Allocation concealment mechanism | 16b | Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned | 7 |
| Implementation | 16c | Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions | 6, 18 |
| Blinding (masking) | 17a | Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how | 7 |
| | 17b | If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial | |
| **Methods: Data collection, management, and analysis** | | | |
| Data collection methods | 18a | Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol | 10, 11, 12, 13, 14, 15 |
| | 18b | Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols | 6, 10 |

| | | | |
|---|---|---|---|
| Data management | 19 | Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol | 10 |
| Statistical methods | 20a | Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol | 11, 12, 13 |
| | 20b | Methods for any additional analyses (eg, subgroup and adjusted analyses) | 12, 13 |
| | 20c | Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation) | 10, 11, 12 |
| **Methods: Monitoring** | | | |
| Data monitoring | 21a | Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed | 6, 10, 12 |
| | 21b | Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial | 13, 14 |
| Harms | 22 | Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct | 14 |
| Auditing | 23 | Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor | 14, 6, 10, 12 |
| **Ethics and dissemination** | | | |
| Research ethics approval | 24 | Plans for seeking research ethics committee/institutional review board (REC/IRB) approval | 2, 17 |
| Protocol amendments | 25 | Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators) | 14 |

| | | | |
|---|---|---|---|
| Consent or assent | 26a | Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32) | 6, _____ |
| | 26b | Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable | 15_____ |
| Confidentiality | 27 | How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial | 10_____ |
| Declaration of interests | 28 | Financial and other competing interests for principal investigators for the overall trial and each study site | 17_____ |
| Access to data | 29 | Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators | 2_____ |
| Ancillary and post-trial care | 30 | Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation | 14_____ |
| Dissemination policy | 31a | Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions | 2_____ |
| | 31b | Authorship eligibility guidelines and any intended use of professional writers | 13_____ |
| | 31c | Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code | 2_____ |
| **Appendices** | | | |
| Informed consent materials | 32 | Model consent form and other related documentation given to participants and authorised surrogates | _____ |
| Biological specimens | 33 | Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable | 15_____ |

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.

BMJ Open

# High versus low energy administration in the early phase of acute pancreatitis (GOULASH trial): Protocol of a multicentre randomized double-blind clinical trial

| | |
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| | |

# High versus low energy administration in the early phase of acute pancreatitis (GOULASH trial): Protocol of a multicentre randomized double-blind clinical trial

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## ABSTRACT

**Introduction**. Acute pancreatitis (AP) is an inflammatory disease with no specific therapy. Mitochondrial injury followed by ATP depletion in both acinar and ductal cells is a recently discovered early event in the pathogenesis. Importantly, preclinical research showed that intracellular ATP delivery restores the physiological function of the cells and protects from cell injury suggesting that restoration of energy levels in the pancreas is therapeutically beneficial. Despite several, high quality and experimental observations in this area, no randomized trials have been conducted to date to address the requirements for energy intake in the early phase of AP.

**Methods/Design.** This is a randomized, controlled two-arms double-blind multicentre trial. Patients suffering from AP will be randomly assigned to groups A (30 kcal/kg/day energy administration starting within 24h of hospital admission) or B (low energy administration during the first 72h of hospital admission). Energy will be delivered with nasoenteric tube feeding with additional intravenous glucose supplementation or total parenteral nutrition if necessary. A combination of multi organ failure for more than 48h and mortality is defined as the primary endpoint, whereas several secondary endpoints such as length of hospitalization or pain will be determined to elucidate more detailed differences between the groups. The general feasibility, safety and quality checks required for high quality evidence will be adhered to.

**Ethics and Dissemination.** The study has been approved by the relevant organization, The Scientific and Research Ethics Committee of the Hungarian Medical Research Council (55961-2/2016/EKU). This study will provide evidence whether early high-energy nutritional support is beneficial in the clinical management of AP. The results of this trial will be published in an open access way and disseminated among medical doctors.

**Trial registration**: The trial has been registered at the ISRCTN (ISRTCN 63827758).


**Keywords:** acute pancreatitis, energy administration, enteral feeding, randomized clinical trial

## ARTICLE SUMMARY

### Strengths and limitations of this study

- Strenght 1; This is a randomized controlled two-arms double-blind multicentre trial which provides the first type A evidence concerning the necessity of early energy intake for patients suffering from AP.
- Strenght 2; The study enjoys continuous support from an International Translational advisory board (ITAB) including several well established experts.
- Strenght 3; Data will be separately handled by an Indepemdent Data Management Board (IDMB).
- Strenght 4; There are no unknown drugs/therapy used in the study, therefore no adverse and serious adverse events are expected.

- Limitation 1; In order to detect a treatment effect of at least 50% of the early treatment, a sample size of 957 subjects will be necessary to be recruited which delay the final conclusion of the study.
- Limitation 2; The double-blind arrengement of the study requires many staff member working on the project which may limit the number of joining centres.

## BACKGROUND

Acute pancreatitis (AP) is an inflammatory disease of the exocrine pancreas, which is life threatening in its severe form. Unfortunately, while the overall mortality of AP is around 2-5%, and in its severe form 25-57%, no specific therapy is available. Besides the limited interest of pharmacological companies the main reasons are (i) the small number of research teams in the field and (ii) the lack of collaborations between basic and clinical scientists. Importantly, many new therapeutic targets were identified in the last decade with clear translational merits [1-8]. One of the main highlights among them is the discovery of energy depletion in the early phase of AP [1, 3-5, 7-17].

It has been shown that almost independently of the etiological factors the early phase of AP is almost the same. Bile acids, ethanol, fatty acids and the latter's metabolite fatty acid ethyl esters cause mitochondrial damage and ATP depletion in pancreatic ductal and acinar cells driving the cells to death and causing pancreatic necrosis [1, 3, 4, 10-14, 18-31]. Very importantly, restoration of ATP levels in both cell types prevented cell death and at least partially restored their function [1,

9]. In experimental pancreatitis models the same observations have been revealed [10-21]. Although these experimental observations clearly suggest that restoration of energy level could be a therapeutic tool in AP, this has not been translated into clinical trials.

One of the best and most physiological way of delivering energy to a patient is enteral nutrition (EN). Not surprisingly, besides fluid resuscitation this is almost the only way to significantly reduce mortality in AP [22-33]. Recent analyses of prospectively collected data from 600 patients suffering from AP showed that the mortality is 27% with EN, versus 57% without EN in the severe form (SAP) [34]. Importantly EN not only decreases mortality but also reduces the frequency of multi-organ failure and the necessity of interventions in patients suffering from SAP [35]. No data are available on whether early or on demand nutrition/energy supply is beneficial in SAP. The recently published Dutch PYTHON study suggests that there is no difference on early versus on demand enteral tube feeding in SAP but patients may have received an insufficient amount of energy at the early phase of the disease [36, 37]. In the early EN group patients received over 20 kcal/kg/day only from the third day onwards whereas in the on demand group they received energy supplementation only from day six[37]. In mild and moderate AP (MAP) much less information is available concerning the usefulness of EN. There are a large variety of protocols on EN in MAP. Immediate oral feeding [38], nasojejunal feeding [39-41] and nasogastric feeding [42][43] were all used. Notably immediate oral feeding significantly decreased the length of hospital stay (LOH) [38]. Early (within 24h) nasogastric EN was not only well tolerated but reduced the intensity and duration of abdominal pain, decreased the necessity for opiates and almost completely eliminated the risk of oral food intolerance [42]. In order to obtain higher evidence of the usefulness of early EN in MAP and SAP we performed a systematic review and meta-analysis which showed that early EN can be beneficial in both, MAP and SAP [35]. However, we also realized the lack of multicentre randomized control trials addressing energy intake in the early phase of AP.

The main objective of this trial is to understand whether early energy supplementation to patients suffering from AP is beneficial. Our hypothesis is that early energy supplementation will prevent

the cells from death or decrease the size of necrosis if occur. This will decrease systemic immune response that will be ended in lower frequency of multi organ failure (MOF) and mortality. To prove this concept a randomized clinical trial involving all AP patients must be organized.

## METHODS

### 1. Design

This is a randomized controlled two-arms double-blind multicentre trial. Patients suffering from acute pancreatitis will be randomly assigned to groups A (high energy administration starting within 24h of hospital admission) and B (no energy administration after 24h of hospital admission).

### 2. Trial organization, committees and boards

GOULASH is designed and coordinated by the Centre for Translational Medicine at the University of Pécs and the Hungarian Pancreatic Study Group (HPSG). HPSG was established in 2011 in order to stimulate research in pancreatic diseases. Until now HPSG published the relevant guidelines of pancreatic diseases in order to improve patient care in the field of pancreatology [44-47] and has initiated four prospective clinical trials (EASY, PREPAST, APPLE and PINEAPPLE) [48-51].

The following committees and boards will be involved:

Steering committee (SC): The committee will be led by PH (gastroenterologist, internal medicine specialist). The members will be KM (medical doctor, full time employee on the project), ÁV (gastroenterologist, internal medicine specialist), ZM (intensive care specialist), TM (clinical research specialist) AS (multidisciplinary unit specialist), MP (gastroenterologist, internal medicine specialist), NF (radiologist), DK (surgeon), IB (interventional radiologist). SC will make decisions concerning all relevant questions including the drop outs during the study.

International translational advisory board (ITAB): The committee will include gastroenterologist (MML), surgeon (JPN) and basic scientists (MST, OHP). ITAB will continuously monitor the progress of the study and will give advice to the SC.

The study was designed by SC and ITAB. The study is financially sponsored by the University of Pécs, the Hungarian Academy of Sciences, and the National Research, Development and Innovation Office. Neither sponsors were involved in the design of the study, and they will have no access to the database management or to the randomization code.

## 3. Study population

All patients diagnosed with AP will be informed of the possibility of taking part in the GOULASH study. After the consent form is signed, a computer using a block randomization protocol will randomize the patients (Figure 1).

**Inclusion criteria:** (1) Patients over 18y of age, (2) diagnosed AP on the base of the "2 out of 3" criteria of the IAP/APA guideline[53] : (a) upper abdominal pain; (b) serum amylase or lipase >3x upper limit of normal range; (c) characteristic findings on pancreatic imaging; however those patients without abdominal pain will be excluded because the onset of AP cannot be determined, (3) written informed consent form is signed.

**Exclusion criteria**: (1) Hospitalization 72 hours before admission, (2) abdominal pain >120 hours (5 days), (3) delirium tremens, (4) Child-Pugh C stage liver cirrhosis, (5) AP due to malignancy, (6) already on artificial nutrition (EN or PN), (7) pregnancy, (8) BMI above 40 or below 18, (9) age above 80, (10) ketoacidosis, (11) whenever CT with contrast is contraindicated.

**Sample size:** Sample size calculation was based on the National Hungarian Registry operated by the Hungarian Pancreatic Study Group. Our recent analyses indicated that MOF existing more than 48h arises in 9%, whereas mortality is in 2.8% of all patient suffering from AP [34]. Altogether they represent around 10% of all AP patients. In order to detect a treatment effect of at least 50% of

the early treatment a sample size of 957 subjects will be necessary to be recruited using a 10% drop-out rate, 80% power and 95% significance level. The calculation was performed by the Independent data management and biostatistics provider company (IDMB, Adware Research LTD, Balatonfüred, Hungary).

**Randomization:** In each centre participants will be divided into 2 groups receiving one of the two study treatments. The allocation of participants to the different groups will be carried out based on predefined randomization lists created separately for each recruiting centre. The randomization lists will be prepared with a block size of 4 and with an allocation ratio of 1:1.

## 4. Duration

The planned starting date of the study is; 1 January 2017, and the planned finishing date of the study is; 1 January 2020.

## 5. Blinding

The medical staff (e.g., taking the measurements such as blood pressure, examining health records for events such as abdominal pain, reviewing and interpreting examination results such as X-ray or CT) and the patient receiving the intervention will be blinded to knowledge of treatment assignment. The person providing the intervention cannot be blinded in this study. Sealed envelopes ensure the allocation sequence. Nutritional support equipment will be covered until the fourth day to ensure that only who made the randomization will know which group the patient was enrolled into.

## 6. Intervention

Based on the currently available guidelines enteral feeding can be started at any time for the patients suffering from AP. In addition, no calorie restriction/order has been described. Therefore both groups can be regarded as being treated within accepted practice recommendations.

In this study, early high energy administration will be the intervention. Patients will be randomized to group A or B: see Figure 2.

**Groups:** In **group A,** high energy will be delivered after admission. Patients will receive a 10 Ch nasogastric (NG) or nasojejunal (NJ) feeding tube on admission. EN will be immediately started as follows: On Day 0 (from admission until the start of EN (can vary from 2-24 h)): calorie intake will be 0 kcal/kg/day. From Day 1 high energy enteral tube feed 30 kcal/kg/day will be provided until the oral feeding starts. In **group B,** low energy administration after hospital admission. Patients will receive a NG or NJ feeding tube at admission as described above. On Day 0 (from admission until the start of EN): calorie intake will be 0 kcal/kg/day. On day 1 0 kcal/kg/day, on day 2 10 kcal/kg/day, on day 3 20 kcal/kg/day and from day 4 30 kcal/kg/day calorie will be delivered until the oral feeding starts. However, between groups A and B only the amount of calories administered will be different. Patients will receive the same amount of fluid and ions during EN (see below).

**Ingredients of enteral tube feed: High Energy Enteral Tube Feed (100ml):**

**Energy**: 150 kcal (630 KJ), **Protein** 6g (16%E), **Carbohydrate**: 18.3g (49%E), **Fat**: 5.8g (35%E) + **Minerals**: 134mg Sodium, 201mg Potassium, 108mg Calcium, 108mg Phosphorus, 34mg Magnesium, 100mg Chloride (0%E). In this study we will use Nutrison Energy (Numil Ltd, Budapest, Hungary), which is a registered product in Hungary (reg. number: 1217).

**Zero Energy Enteral Tube Feed (100ml):**

**Energy**: 0 kcal (0 KJ), **Protein** 0g, **Carbohydrate**: 0g, Fat: 0g + **Minerals**: 134mg Sodium, 201mg Potassium, 108mg Calcium, 108mg Phosphorus, 34mg Magnesium, 5.562g Chloride (0%E) (in this study the local institutional pharmacy will provide it in accordance with the Hungarian regulations). Whenever 10 or 20 kcal/kg/day calories will be delivered, the mixture of the above-mentioned two solutions will be used.

**Type of enteral tube:** Patients neither vomiting nor having gastric fluid retention >250 ml will receive primarily NG tube. Patients either vomiting or having gastric fluid retention >250 ml will receive NJ tube (placement will be done either endoscopically or radiologically). In case of GCS 14 or lower in a patient who is not intubated, NG tube will be replaced by NJ tube (risk of aspiration). Abdominal X-ray will be used to check the tube's position.

**Start of mixed feeding** (around 2620 kcal): Mixed feeding (1000 ml tap water distributed for 24 h and 300 g (around 1900 kcal) biscuits/toasts/low fat meal (at least 75% CHO containing ones) orally plus enteral tube feed (480ml, 720 kcal/day) will be started on the day when: (1) abdominal pain has been ceased for at least 6 h before the new day started, (2) CRP level has started decreasing and (3) amylase or lipase level has started decreasing

**Start of total feeding** (around 2000kcal): If the patients have no symptoms during the mixed oral/enteral feeding and the CRP, amylase or lipase levels are not rising again. Total feeding (according to local policy) can be started.

**Other issues:** The speed of EN will be different for the patients (depends on the body weight), however, the maximum speed of EN cannot exceed 65ml/h. In case of difficulties reaching the 30 kcal/kg/day calories intake (if the patient's body weight is above 75 kg) additional intravenous calorie will be added using Sterofundin G. Maximum of 2000 ml (= 400 kcal) can be delivered in this way. If NG feeding is not tolerated, NG tube will be replaced to NJ tube as described above. If NJ feeding is not tolerated, EN will be reduced by 50% and increased again gradually until tolerated. If the re-increasing process is still not tolerated total parenteral nutrition (TPN) will be started to reach the required energy target. In case of SAP, TPN has to be delivered via central venous catheter.

## 7. Other treatment of subjects

General treatment indicated by the IAP/APA guideline will be utilized[53].

## 8. Discharge of patients

Uniformization of the length of hospital stay is necessary to avoid bias concerning LOH. Re-admission within one week after discharge has to be considered as the same hospital admission. Patients has to be counted as discharged from hospital/from the study when (1) oral feeding was tolerated for 24h, (2) no amylase/lipase level are elevated after total enteral feeding, (3) CRP level

is less than 50 mg/L, (4) abdominal pain has completely resolved (5) no other pancreatitis-related complication requiring hospitalization is detected.

### 9. Endpoints

The following primary endpoints will be calculated: A combination of MOF more than 48h and Mortality. The following secondary endpoints will be analyzed: (1) pancreatic necrosis, (2) nutrition related complications: diarrhoea, aspiration pneumonia, pneumothorax due to central TPN catheter placement, (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 feeding, (6) use of antibiotics, (7) pain relapse, (8) CRP, (9) WBC, (10) PCT, (11) infection, (12) length of hospital stay, (13) need for ICU admission, (14) length of ICU therapy, (15) organ failure, (16) complications, (17) costs calculation. Notably, only direct costs will be calculated that include all medications, services, salaries of healthcare professionals, equipment and day care costs.

### 10. Monitored parameters during hospitalization

There will be a large variety of parameters monitored during the study (e.g. medical history, physical examination, laboratory tests, diagnostic imaging, therapy, interventions). Form A will contain the parameters collected on admission (Supplementary figure 1). Form B will contain parameters collected every day during hospitalization (Supplementary figure 2). Form C will contain parameters collected 1 month after hospital discharge (Supplementary figure 3). For details see supplementary materials or web page (http://www.pancreas.hu/en/studies/goulash), which will be available from February 2017. Data collection on the case report form (CRF) will be done electronically (see data management).

### 11. Data management and statistical analyses

**Data handling:** Data will be handled by IDMB. Electronic CRF (eCRF) will be used. The Investigator will ensure that the data in the eCRF are accurate, complete and legible. Detailed data

flow will be described in Data Management Plan (DMP). Data from completed eCRFs will be validated under the direction of the Data Manager at IDMB according to Data Cleaning Plan (DCP). Any missing, implausible, or inconsistent recordings in the eCRFs will be referred back to the Investigator using a data query form (DQF), and be documented for each individual subject before clean file status is declared. All changes to eCRF will be recorded. Before Data Base Lock Data Review Meeting will decide and document necessary steps related to any issue in the database and define the analysis sets. Member of the data review meeting are delegated investigator, biostatistician and data manager. Adverse events (AEs) will be coded using MedDRA. AdWare Research Ltd., who will act as IDMB, works according to GCP, GLP, FDA 21CFR PART11 and other relevant regulatory requirements. AdWare Ltd. has GLP and ISO 9001 certificates.

**Study populations:**

Three analysis populations will be defined:

| | |
|---|---|
| Safety Analysis Set (SAS): | all patients enrolled in the study. |
| Per Protocol Set (PPS): | all enrolled patients who finished the study conforming to the requirements of the Study Protocol. |
| Intention to Treat (ITT) | all randomized participants who start on a treatment, excluding consent withdrawals. |

**Withdrawal of a subject from PPS:** Any participants/investigators and IDMB can submit recommendation for dropouts from the PPS group with reasons given to SC. All recommendations will be filed. SC will discuss all the information and if the alteration in the protocol would be expected to have any bearing on the interventions and outcomes of the study, the patient will not be included in the final per-protocol analysis. Automatic dropout from the per-protocol group shall be ordered if: (1) any of the exclusion criteria diagnosed during the course of AP, (2) at least 50% of the energy requirement is not achieved on any days during the study, (3) parameters required for

answering the primary endpoints are missing or (4) serious medical reasons not related to pancreatitis (i.e. accidents, stroke) occur.

**Applied softwares:** Statistical analysis will be performed using SAS 9.2 or SPSS 19 (or later) statistical packages; Microsoft MSWord will be used for reporting.

**Statistical Methods:** Baseline patient and disease characteristics will be analyzed by using descriptive analysis. Demographic and baseline characteristics will be summarized for the overall study population. Continuous variables will be described by mean, median, standard deviation, and ranges and categorical variables will be described by absolute and relative frequencies. A graphical presentation of efficacy variables will be prepared, if applicable. Descriptive statistics for both of the primary and secondary parameters will be analyzed similarly. Mean changes (and their 95% CI) from baseline to end-of-study visit will be presented as well. Chi-squared tests will be applied to compare proportions between the different groups. Mortality/extended MOF will be investigated using the Kaplan-Meier analysis method; while subgroup comparisons will be performed using the Chi-squared or Fisher's exact test, as appropriate. For safety data, descriptive statistics and individual listings of adverse events will be also presented.

**Subgroups:** The following subgroups will be made during statistical analyses: (1) ages (under 40y, 40y-59y, 60y-80y), (2) BMI (below 20, 20-24, 25-29, 30-35, above 35), (3) the start of abdominal pain before admission (≤24h, 24-48h, ≥48h), (4) severity of the disease SAP and MAP. All subgroup analyses, (5) etiologies will be done descriptively. No confirmatory statistical testing will be applied. Hence, statistical tests and the p-values attached to them will be regarded as descriptive and not as tests of hypotheses.

Details of the applied statistical tests will be described in the Statistical Analysis Plan.

## 12. Early quality assessment.

Early quality assessment check will be performed on the first 100 patients. IDMB (AdWare Ltd.) will perform an independent assessment of the trial related documents and activities, with the aim of ensuring the respect of subject's right, safety and well-being and to guarantee the plausibility of clinical data. The similarity of groups at baseline will be also checked. IDMB will report to SC. SC will discuss all the information and if the differences would be expected to have any bearing on the interventions and outcomes of the study or the overall dropout rate from PPS is above 20 percent of all participants who were randomized or allocated into each group or the differential dropout rate is above 15 percent between the arms, the study needs to be reassessed and IDMB will make recommendations regarding either reevaluation of power calculation, extension of recruitment period, extension of number of study centers or termination of trial.

## 13. Interim analyses and premature termination of the study.

IDMB can also recommend to stop the trial early for ethical reasons if one of the groups clearly shows evidence of a significant benefit. An interim analysis will be performed on the primary endpoint when 50% of patients have been randomized and discharged from the hospital. The interim analysis will be performed by the IDMB. IDMB will report to SC.

The Haybittle–Peto boundary approach will be used. If the interim analysis shows a probability of equal to, or less than 0.001 that a difference as extreme between the treatments is found, given that the null hypothesis is true, then the trial will be stopped early.

## 14. Centres

The trial will start in two centres (University of Debrecen and University of Pécs), after which the study is open for other centres. In all cases IDMB will make an audit of the centre and will report to the SC. SC keeps the right to decide whether the centre meets the required quality to join the study. Compulsory requirements for a centres: (1) it needs to treat at least 50 AP patients a year, (2) it needs to have all the equipment required for the study, (3) besides the regular medical team the

centre has to appoint at least one doctor and one nurse/administrator fully available for the trial with no additional commitments which can interfere with her/his duty when her/his availability is required, (4) the blinding described above can be fully utilized, (5) all persons need to attend a preliminary meeting where all the details concerning the studies are discussed fully and have qualified as investigators in a GCP course. Centres wish to join need to send a letter of intent to the corresponding author by e-mail.

## 15. Publication policy

Centres providing more than 25 patients can provide two authors to the authorship list. Every additional 25 patients will give the opportunity to nominate an additional author.

## 16. Feasibility

As a general protocol for the treatment of AP at the Centre for Translational Medicine at the University of Pécs, patients suffering from AP receive early EN (using nasogastric tube). Patients receive 50 ml Nutrison Energy per hour starting immediately when they arrive to the ward from the Emergency Department. Patients data between the period of 1 January – 31 May 2016 were analyzed and the following observations were noted: (1) In 85% of all AP admission early EN could have been started within 24 h. In 15% of the cases it was not achievable due to the delayed transfer of the patients to the ward or vomiting. In these cases patients received NG tube later or they received NJ tube whenever X-ray assistance was available. (2) around 80% of NG-fed patients tolerated NG feeding without any complications. The rest of the patients who had gastric retention or vomiting NG feeding was stopped and they received NJ tube whenever X-ray assistance was available. (3) Comparing the outcome (rate of severity, mortality, necrosis, intervention, etc.) of this treatment protocol with the nil per os protocol utilized in most of the Hungarian hospitals revealed that patients enjoy benefits with no risk of early enteral feeding which data confirm the literature data described in the introduction. Concerning the number of patients at the University of Pécs

around 250 and at the University of Debrecen around 150 patients are admitted annually. Therefore, if no other Institution would join the study it can be completed within 3 years.

### 17. Safety

Since no unknown drugs/therapy are used in the study no adverse and serious adverse events (SAE) are expected/interpretable that would be attributable to the intervention during the trial. In this trial IDMB will examine safety variables after every 16 patients have completed. Moreover, investigators will report AE or SAE via a separate form which has to be sent to IDMB and SC. SC will discuss and if the adverse effect is confirmed it will be reported to the relevant institutional and national ethical committee http://www.ett.hu/tukeb.htm.

### 18. Additional information and future plan.

Blood samples (serum and plasma) will be stored from all patients in order to study laboratory parameters later if required (e.g. the laboratory could not measure it), and in order to build up a biobank for later clinical studies to which all participants will be given informed consent. The samples will be stored on -80$^{o}$C. A follow-up study (called GOULASH PLUS) is under preparation in order to follow the patients for up to 5 years after the study. The study protocol will also be published.

## DISCUSSION

Here we report the protocol of a prospective double-blind RCT to study the effects of early energy restoration in AP. The pre-clinical studies [1, 9] and meta-analyses suggest that early energy supplementation should be beneficial. Our main hypothesis is that elevating the energy level of acinar and ductal cells will prevent these cells from injury, therefore, it will decrease the extent of necrosis during AP. Since both the local and systemic complications (immune response) largely depend on the extent of the necrosis we propose that this intervention will reduce multi-organ

failure and mortality in AP as well. Although nutritional interventions for patients with mild pancreatitis are probably not needed, we must involve all AP patients into the study. It has to be highlighted that the main aim of the study is not to find new treatments in MAP or SAP, but to prevent the development of SAP. This is the reason why severity cannot be a selection criteria but has to be the primary endpoint. Concerning ethical issues, this study has very low risk for patients. The enteral solution (Nutrison Energy) used in this study is widely used in several diseases related malnutrition in patients and has almost no contraindications, therefore no adverse events are expected during the trial.

## ETHICS AND DISSEMINATION

The trial is registered at the ISRCTN registry (ISRCTN63827758) and got the relevant ethical approval with the reference number of 55961-2/2016/EKU issued by The Scientific and Research Ethics Committee of the Medical Research Council. It is almost needless to say that at the end of the project we will disseminate our results in the medical community. We will publish our results in an open access way.

## CONCLUSION

This study provides the first and type A evidence concerning the necessity of energy intake for patients suffering from AP.

This protocol is the first version of the trial completed on 24th May 2017.

## List of abbreviations

AE – adverse event

AP – acute pancreatitis

BMI – body mass index

CRF – case report file

CRP – C-reactive Protein

DCP – data cleaning plan

DMP – data management plan

DQF – data query form

eCRF – electronic clinical report form

EN – enteral nutrition

GOULASH – name of the study: general utilization of early energy administration in acute pancreatitis.

HPSG – Hungarian Pancreatic Study Group

ICU – intensive care unit

IDMB – Independent data management and biostatistics provider company

ITAB – International Translational Advisory Board

ITT – Intention to Treat

LOH – length of hospital stay/hospitalization

MAP – mild and moderate AP

MOF – multi organ failure

NG – nasogastric

NJ – nasojejunal

PCT – procalcitonin

PN – parenteral nutrition

PPS – Per Protocol Set

SAE – severe adverse event

SAS – Safety Analysis Set

SAP – severe AP

SC – Steering Committee

TPN – total parenteral nutrition

WBC – white blood cell count

**Availability of data and materials**

Not applicable, because the trial has not completed patient recruitment.

**Competing interest**

The authors declare that they have no competing interests.

**Funding**

Centre costs (IT, biostatistics, trial organization, etc) are covered by the University of Pécs, Momentum Grant of the Hungarian Academy of Sciences (LP2014-10/2014); and Economic Development and Innovation Operative Programme Grant and Highly Cited Publication Grant of the National Research, Development and Innovation Office (GINOP-2.3.2-15-2016-00015, KH-125678). Since no additional treatment is necessary for the study, the general healthcare costs are covered by the National Healthcare System.

**Authors' contributions**

All authors were involved in the study design, edited the manuscript, read and approved the final manuscript. During the study KM, ANS, DP and PV are going to randomize the patients, obtain the consent form and ensure the blinding. AM, KS, JB, SG, MP, PS, ZV and TT are going to manage the treatment of the patients. ÁV will be responsible for the organization, quality and timing of the endoscopic treatments, ZM and RH for the intensive care, NF and IB for the imaging and interventional radiology, DK and RP for the surgical treatment if needed. PAV and EL will prepare the nutritional solutions. ML, JN, MST and OP are members of ITAB. TM and AS will be members of SC. PH and KM drafted the manuscript.

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**Figure legends**

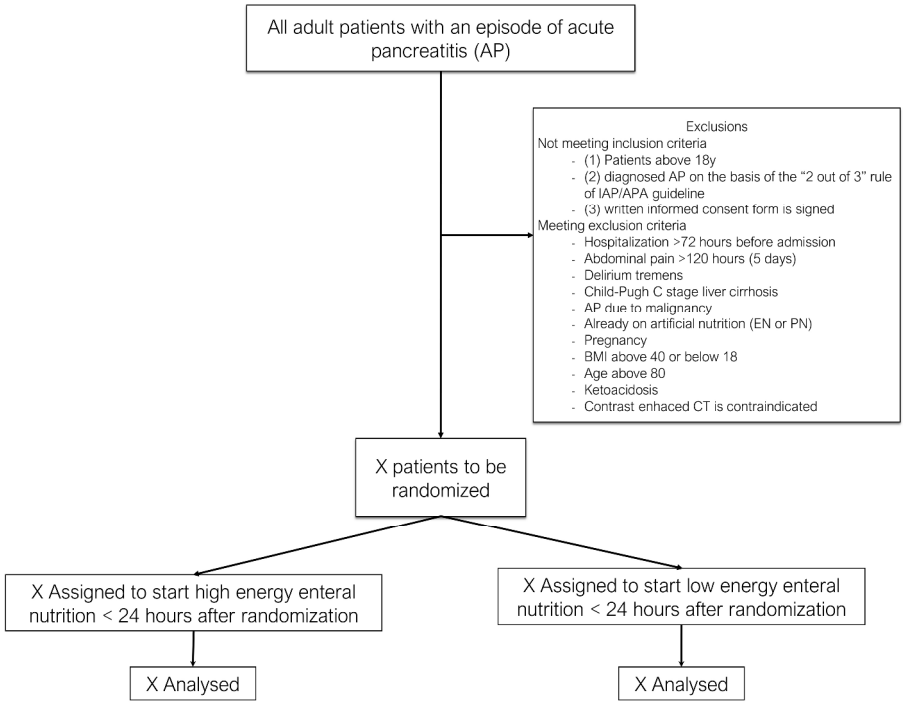
Fig. 1 shows the flow chart of participants according to SPIRIT 2013 statement [52].

Fig. 2 shows the schedule of enrolment, interventions, and assessments according to SPIRIT 2013 statement [52]. Patients will be randomized to group A (high energy) or B (low energy).

Suppl. Fig. 1 Form A contains the parameters collected on admission.

Suppl. Fig. 2 Form B contains parameters collected every day during hospitalization.

Suppl. Fig. 3 Form C contains parameters collected 1 month after hospital discharge.




Flow of participants

361x270mm (300 x 300 DPI)

| | STUDY PERIOD | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | Enrolment | Allocation | Post-allocation | | | | | Close-out |
| TIMEPOINT** | *<24h* | 0 | *day1* | *day2* | *day3* | *dayx* | *discharge* | *1m after discharge* |
| ENROLMENT: | | | | | | | | |
| Eligibility screen | X | | | | | | | |
| Informed consent | X | | | | | | | |
| *Laboratory test* | X | | | | | | | |
| *CT examination* | X | | | | | | | |
| Allocation | | X | | | | | | |
| INTERVENTIONS: | | | | | | | | |
| *High energy administration* | | | ♦— | — | — | —♦ | | |
| *Low energy administration* | | | ♦— | — | — | —♦ | | |
| ASSESSMENTS: | | | | | | | | |
| *Questionnaire A* | | X | | | | | | |
| *Questionnaire B* | | | X | X | X | X | X | |
| *Questionnaire C* | | | | | | | | X |

Intervention. Patients will be randomized to group A (high energy) or B (low energy)

194x169mm (300 x 300 DPI)

# FORM-A Acute Pancreatitis

Early Enteral Nutrition

GOULASH

***The physical examination has to be done ON ADMISSION!***
***The blood for laboratory parameters has to be drawn ON ADMISSION!***
***This form has to be filled ON ADMISSION!***

## *Questionnaire*

| |
|---|
| **Country:** |
| **Town:** |
| **Hospital:** |
| **Doctor:** |
| **Patient No:** |

## 1. Patient personal details

**Insurance number:**.....
**First name:**.....
**Last name:** .....
**Date of birth:**.....
**Gender:** female male
**Ethnicity/Race:** White / Black / Asian-Indian Not known

## 2. Details from the medical history

**Alcohol consumption**: yes / no
if yes: frequency: occasionally/monthly/weekly/dayly
amount (g/day):.....
since when? (years):.....
Alcohol consumption in the last 2 weeks: .....

if not:
Did you drink alcohol earlier? yes/no
if yes: frequency: occasionally/monthly/weekly/daily
amount (g/occasion):.....
For how many years?.....
How long ago did you stop drinking alcohol?.....

*Guide for estimation of the amount:*
*1 dl beer (4.5 vol. %) = ~3.5 g alcohol*
*1 dl wine (12.5 vol. %) = ~10 g alcohol*
*1 dl hard drink (50 vol. %) = ~40 g alcohol*

**Smoking**: yes / no
if yes: amount (cigarettes/day):.....
For how many years? .....
if not:
Did you smoke earlier? yes/no
if yes: amount (pcs/occasion):.....
For how many years?.....
How long ago did you stop smoking? .....

**Drug abuse**: yes / no *Prescribed medication should not be included here.*
if yes: type of drug:..... amount:.....
since when (year):.....
*(if there are more drugs, please describe them in the NOTES section at the end)*

**Diabetes mellitus**: yes / no
if yes: type: Type I. / Type II./Type III. c / MODY
since when (year):.....



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# FORM-A Acute Pancreatitis GOULASH

**Lipid metabolism disorder:** yes / no
if yes: type: ..... since when (year):.....

**Any disease of the pancreas:** yes / no *Not counting the current episode.*
if yes: acute pancreatitis/ chronic pancreatitis/ autoimmune pancreatitis/ tumor/ other
if other: please describe:.....
<u>If the patient had ACUTE PANCREATITIS in the history:</u>
How many times did the patient have acute episodes before this episode:.....
When did the patient have the first acute episode (year):.....

<u>If the patient has CHRONIC/AUTOIMMUNE PANCREATITIS:</u>
When was it diagnosed?.....
How many times did the patient have acute episodes before this episode:.....
When did the patient have the first acute episode (year):.....

<u>If the patient has PANCREATIC CANCER::</u>
When was it diagnosed?.....
Was the patient diagnosed with chronic pancreatitis? yes / no
If yes, when was it diagnosed?.....
How many times did the patient have acute episodes before this episode?:.....
When did the patient have the first acute episode (year):.....

Other information:
.....

**Pancreas disorders in family history:**
acute pancreatitis: yes / no if yes: relationship to patient:.....
chronic pancreatitis yes / no if yes: relationship to patient:.....
autoimmune pancreatitis: yes / no if yes: relationship to patient:.....
pancreas tumor: yes / no if yes: relationship to patient:.....
other (please describe):.....relationship to patient:.....
.....

**Congenital Anatomical Malformation of the pancreas:** yes / no / no data
if yes: please describe:.....

**Other illnesses:** yes / no
if yes: please list/describe them:.....

**Medications taken regularly:** yes / no *Please specify the name of the active substance (e.g. "acetylsalicylic acid"). Please specify the amount using the International System of Units –SI (e.g. milligram, gram)*
if yes:
name:.....active substance:.....dose(gram,milligram, etc.).....
if fluid, concentration (e.g. 10%, 1g/2ml, etc.).....how many times per day (e.g. 3)
type of administration:.....other notes: .....

name:.....active substance:.....dose(gram,milligram, etc.).....
if fluid, concentration (e.g. 10%, 1g/2ml, etc.).....how many times per day (e.g. 3)
type of administration:.....other notes: .....


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name:.....active substance:.....dose(gram,milligram, etc.).....
if fluid, concentration (e.g. 10%, 1g/2ml, etc.).....how many times per day (e.g. 3)
type of administration:.....other notes: .....

name:.....active substance:.....dose(gram,milligram, etc.).....
if fluid, concentration (e.g. 10%, 1g/2ml, etc.).....how many times per day (e.g. 3)
type of administration:.....other notes: .....

**Diet:** yes / no
if yes: please describe:.....

## 3. Etiology

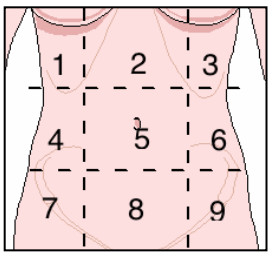
*The answer is "yes" if the etiological factor is proved, the answer is "no" if the etiological factor can be ruled out, the answer is "no data" if the etiological factor was not examined. Please answer "yes" to " Idiopathic" if etiological factor was not identified.*

| | | | |
|---|---|---|---|
| Biliary | yes | no | no data |
| Alcohol | yes | no | no data |
| Virus infection | yes | no | no data |
| Trauma | yes | no | no data |
| Drug-induced | yes | no | no data |
| Congenital anatomical malformation | yes | no | no data |
| Cystic fibrosis | yes | no | no data |
| Gluten-sensitive enteropathy | yes | no | no data |
| Hypertrigliceridaemia | yes | no | no data |
| Genetic | yes | no | has not been tested yet |
| Idiopathic | yes | no | |
| Other | yes | no | |

if yes: please describe:.....

## 4. Complains, symptoms

**Abdominal pain:** yes / no
if yes: since when (hours):.....
type: cramping / dull / sharp
intensity (1-10):.....
location: diffuse / localized
Please mark the location!
radiation:.....




**Nausea:** yes / no

**Vomiting:** yes / no
if yes: how many times:.....
contents of cast:.....

# FORM-A Acute Pancreatitis GOULASH

**Subfebrility/fever:** yes / no
if yes: since when:.....
degree (°C):.....

**Appetite:** good / retained / bad

**Weight loss:** yes / no
if yes: how much (kg):.....
How long did it take? (weeks):.....

**Jaundice:** yes / no
if yes: for how long:.....

**Stool:** normal / diarrhea / constipation / fatty / putrid / undigested food/bloody/mucus
*Please refer to the period just before your symptoms has started.*

## 5. Admission details and state

**Blood pressure (Hgmm):**..... **Heart rate (/minute):**.....
**Body weight (kg):**..... **Body height (cm):**.....
**Respiratory rate (/minute):**..... **Body temperature (°C):** .....
axillary/rectal

**Oxygen saturation (%):** ..... Previous O2 therapy: yes/no

**Abdominal tenderness :** yes / no **Abdominal guarding:** yes / no

**Jaundice:** yes / no

**Glasgow Coma Scale (GCS):**.....

**Glasgow Coma Scale:**
**Eye response**
4 points: Spontaneous eye opening
3 points: Eye opening in response any speech
2 points: Opening to response to pain
1 point: No eye opening

**Verbal Response**
5 points: Orientated
4 points: Confused conversation
3 points: Inappropriate speech
2 points: Incomprehensible speech
1 point: No verbal response.

**Motor Response**
6 points: Obeying command
5 points: Localizing response to pain
4 points: Withdraws to pain
3 points: Decorticate posture
2 points: Decerebrate posture
1 point: No response to pain

## 6. Laboratory parameters on admission

**OBLIGATORY PARAMETERS:**

| | |
|---|---|
| Amylase (U/l) | |
| Lipase (U/l) | |
| White blood cell (WBC) count (G/l) | |
| Red blood cell (RBC) count (T/l) | |
| Hemoglobin (g/l) | |
| Hematocrit (%) | |
| Thrombocyte (G/l) | |
| Serum glucose (mmol/l) | |
| Hemoglobin A1C (%) | |
| Blood urea nitrogen (mmol/l) | |
| Creatinine (umol/l) | |
| eGFR | |
| C-reactive protein (mg/l) | |
| ASAT/GOT (U/l) | |
| Lactate dehydrogenase LDH (U/l) | |
| Calcium (mmol/l) | |
| Sodium (mmol/l) | |
| Potassium (mmol/l) | |
| Total protein (g/l) | |
| Albumin (g/l) | |
| Cholesterol (mmol/l) | |
| Triglyceride (mmol/l) | |
| ALAT/GPT (U/l) | |
| Gamma GT (U/l) | |
| Total bilirubin (umol/l) | |
| Direct/Conjugated bilirubin (umol/l) | |
| Alkaline phosphatase (U/l) | |
| Procalcitonin (ng/ml) | |

**OTHER PARAMETERS (if measured):**

| | |
|---|---|
| IgA (g/l) | |
| IgM (g/l) | |
| IgG (g/l) | |
| IgG4 (g/l) | |
| CA 19-9 (U/ml) | |
| $PaO_2$ (Hgmm) | |
| $HCO_3$ (mmol/l) | |
| $sO_2$ (%) | |
| sweat chloride (mmol/l) | |
| urine amylase | |
| uirne lipase | |
| urine creatinine | |
| (other) | |

Virus serology: yes / no Which viruses?..... results:.....

## 7. Imaging examinations on admission

Does the patient have pleural fluid? yes no N/A
Does the patient have lung infiltrate? yes no N/A
Does the patient have abnormal pancreatic structure? yes no N/A
If yes: hypoechoic/hyperechoic/peripancreatic fluid/irregular and blurred contours/Wirsung dilatation (above 1mm)/ascites/calcification/cyst

**Abdominal X-ray:** yes no
Description:
.....
.....

**Chest X-ray:** yes no
Description:
.....
.....

**Chest Computed Tomography:** yes no
Description:
.....
.....

**Abdominal Computed Tomography:**
Modified CTSI Score: .....0-10.....
*Please NOTE! Abdominal CT is compulsory on admission*

**CTSI Score: (I)** Normal pancreas 0 point, intrinsic pancreatic abnormalities with or without inflammatory changes in peripancreatic fat 2 points, Pancreatic or peripancreatic fluid collection or peripancreatic fat necrosis 4 points **(II)** Necrosis absent 0 Points, < 30% necrosis 2 Points, > 30% necrosis 4 points **(III)** presence of extrapancreatic findings 2 points.
MAXIMUM OF: 10 points

- **CTSI:**

**I. Pancreas**

- Normal pancreas
- Intrinsic pancreatic abnormalities with or without inflammatory changes in peripancreatic fat
- pancreatic or peripancreatic fluid collection or peripancreatic fat necrosis

**II. Size of Necrosis**

- Necrosis absent
- < 30% necrosis
- > 30% necrosis
- > 60% necrosis

**III. Extrapancreatic findings**

- presence of extrapancreatic findings

**DETAILED REPORT**

- **Pancreas Size:**
  - Normal
  - Partially enlarged (body AP diameter is over 2 cm and/or head AP diameter is over 2,5 cm, none exceeds 3 cm)
  - Definitely enlarged (any part over 3 cm AP diameter)
- Largest diameter of peripancreatic **fat infiltration**: …… cm

- **Peripancreatic fluid:**
  - none
  - present
  - Large pseudocyst(s)
- Size of peripancreatic fluid or pseudocyst: …… cm

- **Necrotizing area** (nonenchancement):
  - Largest diameter of necrosis area: …… cm
  - Location of necrosis: ……
  - Type: patchy / full width
  - Estimated necrosis: 0% , < 30% , 30% - 60%, above 60%

- **Wirsung** dilatation: YES / NO (yes, diameter: …… mm)

- Distant **abdominal fluid**:
  - Small amount (hard to see, less than 2 cm in lesser pelvis, less than 1 cm around liver/spleen)
  - Moderate amount (easy to see, but without pelvic or abdominal distension)
  - Large amount with abdominal/pelvic distension

- **Pleural effusion:**
  - none
  - one sided:……. (AP diameter: …… cm)
  - Both sides, L - …… cm, R - …… cm

- **Extrapancreatic findings**:
  - Inflammation (Cholecystitis, Duodenitis, etc.) location: ……
  - Cholecystolithiasis
  - Choledocholithiais
  - Signs of bowel ischaemia
  - Bowel distension, ileus
  - Venous thrombosis
  - Pseudoaneurysm
  - Parenchymal organ involvement, define: ……

Other Description:
……
……

## 8. Genetic testing

Has it been performed earlier? yes no
if yes: please describe:

……
……
……

## 9.a Intravenious fluid in the early period

**Intravenious fluid in the early period……ml**

*To be counted from the first moment (including ambulance car) until the start of the early enteral nutrition. 5–10 ml/kg/h should be given in the first 2h. It has to be continued until: heart rate <120/min, mean arterial pressure between 65 and 85 mmHg (8.7–11.3 kPa), and urinary output >0.5–1 ml/kg/h*

## 9.b Immediate therapy on admission

**Intravenous fluid** **yes** **no**
if yes: type of fluid……
amount (ml)……

*If not contraindicated the type of fluid has to be Ringer Lactate. No glucose should be given if it is not compulsory due to hypoglycaemia*

**Pain management:** **yes** **no**
if yes:
name:……active substance:……dose(gram,milligram, etc.)……
if fluid, concentration (e.g. 10%, 1g/2ml, etc.)……how many times per day (e.g. 3)
type of administration:……other notes: ……

# FORM-A Acute Pancreatitis

Early Enteral Nutrition

GOULASH

name:.....active substance:.....dose(gram,milligram, etc.).....
if fluid, concentration (e.g. 10%, 1g/2ml, etc.).....how many times per day (e.g. 3)
type of administration:.....other notes: .....

name:.....active substance:.....dose(gram,milligram, etc.).....
if fluid, concentration (e.g. 10%, 1g/2ml, etc.).....how many times per day (e.g. 3)
type of administration:.....other notes: .....

**Insulin:** **yes** **no**
if yes: name of the medication:.....
total dose of medication:.....

**Intensive care:** **yes** **no**
if yes: namely (ventilation, vasopressor therapy):.....

**Other:**
if yes: please describe:.....
.....

## 10. Interventions, endoscopic treatment: yes no

if yes: ERCP-EST/endobiliary stent/Wirsung stent/cysta drainage
Stent: 1 plastic stent/more plastic stents/uncovered metal stent/covered metal stent
Early complications: none/bleeding/perforation
**ERCP:** yes no
if yes:

| | | | |
|---|---|---|---|
| Successful biliary cannulation: | yes | no | if yes: notes: ..... |
| Precut: | yes | no | if yes: needleknife/precut papillotomia |
| EST: | yes | no | if yes: biliary/pancreatic |
| Stone extraction: | yes | no | |
| Stent: | yes | no | if yes: metal/plastic<br>How many pcs? diameter(Fr)? length(cm)? |
| Pancreatic duct filling: | yes | no | if yes: notes: ..... |

## 11. Complications

*Please register pancreatic complication of fluid collection/pseudocyst/necrosis only if you had imaging proof on the day of admission, otherwise, please mark "no data".*

**Pancreatic:** yes no no data
if yes: fluid collections /pseudocyst / necrosis / diabetes

**Organ failure:** yes no
if yes:, lung /heart / kidney /other

**Death:** yes no
If yes: the exact time of death: ..... *e.g. 10.25 or 22.45*



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FORM-A Acute Pancreatitis GOULASH

## 12. Epicrisis *A short summary of the hospitalization (how the patient got to medical care, diagnosis, most important facts and events of the hospitalization, what happened with the patient after the hospitalization, any recommended control examinations, surgery).*

……

……

**NOTES**

……

……

**DATE:**

YEAR: …… MONTH: …… DAY: …… HOUR …… MIN: ……

THE TOTAL TIME SPENT THE PATIENT ON ADMISSION: HOUR …… MIN: ……

**NAME OF THE DOCTOR MADE THE RANDOMIZATION:** ……**SIGNATURE:** ……

*Please NOTE! The doctor made the randomization MUST NOT involved in the treatment of patients any longer. She/He has to keep the information secretly from the patients and medical team involved in the treatment.*

**NAME OF THE DOCTOR EXAMINED/TREATED THE PATIENT:** ……**SIGNATURE:** ……

# FORM-B Acute Pancreatitis

Early Enteral Nutrition

GOULASH

*PLEASE FILL IN EVERY DAY DURING THE HOSPITAL STAY*

**Day No:**
**Date** (+hour, min)

**GOULASH No:**

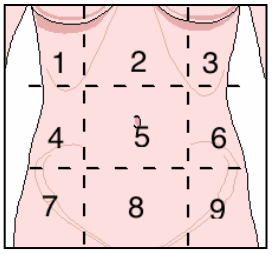
**(Automatically generated)**

## 1. Patient personal details

**First name:**.....

**Last name:** .....

## 2. Complains, symptoms




**Abdominal pain:** yes / no
if yes: since when (hours):.....
type: cramping / dull / sharp
intensity (1-10):.....
location: diffuse / localized
Please mark the location!
radiation:.....

**Nausea:** yes / no
*If YES, retention measurement has to be performed.*
**Vomiting:** yes / no
*If YES, NG tube has to be replaced by NJ tube.*

**Subfebrility/fever:** yes / no
if yes: since when:.....
degree (°C):.....

**Appetite:** good / retained / bad

**Stool:** yes / no

if yes: normal / diarrhea / constipation / fatty / putrid / undigested food/bloody/mucus





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FORM-B Acute Pancreatitis GOULASH

## 3. Patient's state

**Blood pressure (Hgmm):**..... **Heart rate (/minute):**.....
**Body weight (kg):**.....
**Respiratory rate (/minute):**..... **Body temperature (°C):** .....
axillary/rectal

**Oxygen saturation (%):** ..... O2 therapy: yes/no

**Abdominal tenderness :** yes / no **Abdominal guarding:** yes / no

**Jaundice:** yes / no

**Glasgow Coma Scale (GCS):**.....

**Glasgow Coma Scale:**

**Eye response**
4 points: Spontaneous eye opening
3 points: Eye opening in response any speech
2 points: Opening to response to pain
1 point: No eye opening

**Verbal Response**
5 points: Orientated
4 points: Confused conversation
3 points: Inappropriate speech
2 points: Incomprehensible speech
1 point: No verbal response.

**Motor Response**
6 points: Obeying command
5 points: Localizing response to pain
4 points: Withdraws to pain
3 points: Decorticate posture
2 points: Decerebrate posture
1 point: No response to pain

## 4. Laboratory parameters

**OBLIGATORY PARAMETERS**

| | |
|---|---|
| Amylase (U/l) | |
| Lipase (U/l) | |
| White blood cell (WBC) count (G/l) | |
| Red blood cell (RBC) count (T/l) | |
| Hemoglobin (g/l) | |
| Hematocrit (%) | |
| Thrombocyte (G/l) | |
| C-reactive protein (mg/l) | |





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# FORM-B Acute Pancreatitis

Early Enteral Nutrition GOULASH

**OTHER PARAMETERS (if measured):**

| | |
|---|---|
| Serum glucose (mmol/l) | |
| Blood urea nitrogen (mmol/l) | |
| Creatinine (umol/l) | |
| eGFR | |
| ASAT/GOT (U/l) | |
| Lactate dehydrogenase LDH (U/l) | |
| Calcium (mmol/l) | |
| Sodium (mmol/l) | |
| Potassium (mmol/l) | |
| Total protein (g/l) | |
| Albumin (g/l) | |
| Cholesterol (mmol/l) | |
| Triglyceride (mmol/l) | |
| ALAT/GPT (U/l) | |
| Gamma GT (U/l) | |
| Total bilirubin (umol/l) | |
| Direct/Conjugated bilirubin (umol/l) | |
| Alkaline phosphatase (U/l) | |
| Procalcitonin (ng/ml) | |
| IgA (g/l) | |
| IgM (g/l) | |
| IgG (g/l) | |
| IgG4 (g/l) | |
| CA 19-9 (U/ml) | |
| $PaO_2$ (Hgmm) | |
| $HCO_3$ (mmol/l) | |
| $sO_2$ (%) | |
| sweat chloride (mmol/l) | |
| urine amylase | |
| uirne lipase | |
| urine creatinine | |
| (other) | |

**Blood glucose (by finger stick test)** *Compulsory on the first day*:

| | | |
|---|---|---|
| 4h | mmol/l | amount of insulin if administered : …… IU |
| 8h | mmol/l | |
| 12h | mmol/l | |
| 16h | mmol/l | |
| 20h | mmol/l | |
| 24h | mmol/l | |





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# FORM-B Acute Pancreatitis GOULASH

## 5. Imaging (if performed) yes no

**Abdominal ultrasonography:** yes no

*2 hours before the examination the enteral feeding has to be stopped. The amount of enteral feeding which was not given have to be administered additionally to the normal feeding in the next 10h. (for example: If the patient receive 45 ml/h and 90ml was not given due to the examination, the patient has to receive 54ml (45ml + 9ml) for the forthcoming 10h.*

- ***Visualization:***
  - Good, complete (head at least partially visualized, body and neck well visualized, tail: partially visualized)
  - Partially, incomplete (only body or only head visualized)
  - Poor, non-diagnostic
- **Size:**
  - Normal
  - Partially enlarged (body AP diameter is over 2 cm and/or head AP diameter is over 2,5 cm, none exceeds 3 cm)
  - Definitely enlarged (any part over 3 cm AP diameter)

- **Peripancreatic fluid:**
  - none
  - present
  - Large pseudocyst(s)
- Size of peripancreatic fluid or pseudocyst: …… cm

- **Pancreas homogeneity:**
  - Homogenous
  - Inhomogeneous, includes area(s) of low echogenicity
  - Inhomogeneous, includes calcifications

- In case of circumscribed low echogenicity area, it's size: …… cm

- **Wirsung** dilatation: YES / NO (yes, diameter: …… mm)

Other Description:

……

……

**Abdominal X-ray:** yes no

Description:

……

……

**Chest X-ray:** yes no

Description:

……

……

**Chest Computed Tomography:** yes no

Description:

……

……





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Principal Investigator:
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# FORM-B Acute Pancreatitis

Early Enteral Nutrition

GOULASH

**Abdominal Computed Tomography:** yes/no
Modified CTSI Score: ……0-10……
*Please NOTE! Abdominal CT is compulsory when the patient is discharged*

**CTSI Score: (I)** Normal pancreas 0 point, intrinsic pancreatic abnormalities with or without inflammatory changes in peripancreatic fat 2 points, Pancreatic or peripancreatic fluid collection or peripancreatic fat necrosis 4 points **(II)** Necrosis absent 0 Points, < 30% necrosis 2 Points, > 30% necrosis 4 points **(III)** presence of extrapancreatic findings 2 points.
MAXIMUM OF: 10 points

- **CTSI:**
  - **I. Pancreas**
  - Normal pancreas
  - Intrinsic pancreatic abnormalities with or without inflammatory changes in peripancreatic fat
  - pancreatic or peripancreatic fluid collection or peripancreatic fat necrosis
  - **II. Size of Necrosis**
  - Necrosis absent
  - < 30% necrosis
  - > 30% necrosis
  - > 60% necrosis
  - **III. Extrapancreatic findings**
  - presence of extrapancreatic findings
  -

**DETAILED REPORT**

- **Pancreas Size:**
  - Normal
  - Partially enlarged (body AP diameter is over 2 cm and/or head AP diameter is over 2,5 cm, none exceeds 3 cm)
  - Definitely enlarged (any part over 3 cm AP diameter)
- Largest diameter of peripancreatic **fat infiltration**: …… cm

- **Peripancreatic fluid:**
  - none
  - present
  - Large pseudocyst(s)
- Size of peripancreatic fluid or pseudocyst: …… cm

- **Necrotizing area** (nonenchancement):
  - Largest diameter of necrosis area: …… cm
  - Location of necrosis: ……
  - Type: patchy / full width
  - Estimated necrosis: 0% , < 30% , 30% - 60%, above 60%

- **Wirsung** dilatation: YES / NO (yes, diameter: …… mm)



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- Distant **abdominal fluid**:
  - Small amount (hard to see, less than 2 cm in lesser pelvis, less than 1 cm around liver/spleen)
  - Moderate amount (easy to see, but without pelvic or abdominal distension)
  - Large amount with abdominal/pelvic distension

- **Pleural effusion:**
  - none
  - one sided:……. (AP diameter: …… cm)
  - Both sides, L - …… cm, R - …… cm

- **Extrapancreatic findings**:
  - Inflammation (Cholecystitis, Duodenitis, etc.) location: ……
  - Cholecystolithiasis
  - Choledocholithiais
  - Signs of bowel ischaemia
  - Bowel distension, ileus
  - Venous thrombosis
  - Pseudoaneurysm
  - Parenchymal organ involvement, define: ……

Other Description:
……
……

## 6. Microbiology examination

Biological sample collection yes no
If yes: place: /blood, urine, airway, pancreas, other/
result: ……




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## 7. Therapy

**Total oral feeding** yes no

**CHO reach oral feeding** yes no

**Intravenous fluid** yes no

if yes, type of fluid……
amount (ml)……

type of fluid……
amount (ml)……

**Enteral feeding** yes no

if yes, naso-gastric / naso-jejunal
formula: ……
amount:…… (ml)
speed of the pump:…… ml/h

**Gastric retention measurement** *Compulsory on the first day*

amount:…… (ml)

**Did the patient need change in EN from NG to NJ feeding?** yes no

if yes, type of fluid……
amount (ml)……
speed of the pump:…… ml/h

**TPN** yes no

if yes, type of TPN……
amount (ml)……

type of TPN……
amount (ml)……

**NOTES FOR ENTERAL FEEDING**

……
……

**Total delivered calorie on the day?** …… kcal, ……kcal/kg

Calorie delivery by NGF: …… kcal
Calorie delivery by NJF: …… kcal
Calorie delivery by iv glucose: …… kcal
Calorie delivery by TPN: …… kcal
Calorie delivery by mixed oral feeding: …… kcal
Calorie delivery by total oral feeding: …… kcal





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# FORM-B Acute Pancreatitis GOULASH

**Pain management:** yes no

if yes:

name:.....active substance:.....dose(gram,milligram, etc.).....

if fluid, concentration (e.g. 10%, 1g/2ml, etc.).....how many times per day (e.g. 3)

type of administration:.....other notes: .....

name:.....active substance:.....dose(gram,milligram, etc.).....

if fluid, concentration (e.g. 10%, 1g/2ml, etc.).....how many times per day (e.g. 3)

type of administration:.....other notes: .....

name:.....active substance:.....dose(gram,milligram, etc.).....

if fluid, concentration (e.g. 10%, 1g/2ml, etc.).....how many times per day (e.g. 3)

type of administration:.....other notes: .....

**Antibiotic therapy:** yes no

if yes:

name:.....active substance:.....dose(gram,milligram, etc.).....

if fluid, concentration (e.g. 10%, 1g/2ml, etc.).....how many times per day (e.g. 3)

type of administration:.....other notes: .....

name:.....active substance:.....dose(gram,milligram, etc.).....

if fluid, concentration (e.g. 10%, 1g/2ml, etc.).....how many times per day (e.g. 3)

type of administration:.....other notes: .....

name:.....active substance:.....dose(gram,milligram, etc.).....

if fluid, concentration (e.g. 10%, 1g/2ml, etc.).....how many times per day (e.g. 3)

type of administration:.....other notes: .....

**Insulin:** yes no

if yes, name of the medication:.....

dosage:.....

**Intensive care:** yes no

if yes, namely (ventilation, vasopressor therapy):.....

**Other:**

if yes, please describe:.....

.....

.....





THE RCT IS ORGANIZED BY THE HUNGARIAN PANCREATIC STUDY

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## 8. Interventions, endoscopic treatment: yes no

if yes: ERCP-EST/endobiliary stent/Wirsung stent/cysta drainage
Stent: 1 plastic stent/more plastic stents/uncovered metal stent/covered metal stent
Early complications: none/bleeding/perforation

**ERCP:** yes no
if yes:

Successful biliary cannulation: yes no if yes: notes: .....
Precut: yes no if yes: needleknife/precut papillotomia
EST: yes no if yes: biliary/pancreatic
Stone extraction: yes no
Stent: yes no if yes: metal/plastic
How many pcs? diameter(Fr)? length(cm)?
Pancreatic duct filling: yes no if yes: notes: .....

## 9. Complications

Pancreatic: yes no no data
if yes, fluid collections / pseudocyst / necrosis / diabetes
Organ failure: yes no
if yes, lung / heart / kidney /other
Duration of organ failure: <48 hours >48 hours
Death: yes no
if yes: the exact time of death: ..... *e.g. 10.25 or 22.45*

**NOTES**

.....
.....
.....

**DATE:**
YEAR: ..... MONTH: ..... DAY: .....

**NAME OF THE DOCTOR:** .....**SIGNATURE:** .....

**NAME OF THE NURSE:** .....**SIGNATURE:** .....

**NAME OF THE SCIENCE ADMINISTRATOR:** .....**SIGNATURE:** .....







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# FORM-C Acute Pancreatitis GOULASH

## *Questionnaire*

**GOULASH No:**

**(Automatically generated)**

## 1. Patient personal details

**First name:**.....

**Last name:** .....

## 2. Details from the medical history (in the last month)

**Alcohol consumption**: yes / no
if yes: frequency: occasionally/monthly/weekly/daily
amount (g/day):.....

*Guide for estimation of the amount:*
*1 dl beer (4.5 vol. %) = ~3.5 g alcohol*
*1 dl wine (12.5 vol. %) = ~10 g alcohol*
*1 dl hard drink (50 vol. %) = ~40 g alcohol*

**Smoking**: yes / no
if yes: amount (cigarettes/day):.....

**Drug abuse**: yes / no *Prescribed medication should not be included here.*
if yes: type of drug:..... amount:.....
*(if there are more drugs, please describe them in the NOTES section at the end)*

**Any re-hospitalization?:** yes / no

if yes: cholecystectomy: yes no
recurrent AP: yes no
other: .....

**Medications taken regularly in the last month:** yes / no
*Please specify the name of the active substance (e.g. "acetylsalicylic acid"). Please specify the amount using the International System of Units –SI (e.g. milligram, gram)*
if yes:
name:.....active substance:.....dose(gram,milligram, etc.).....
if fluid, concentration (e.g. 10%, 1g/2ml, etc.).....how many times per day (e.g. 3)
type of administration:.....other notes: .....

name:.....active substance:.....dose(gram,milligram, etc.).....
if fluid, concentration (e.g. 10%, 1g/2ml, etc.).....how many times per day (e.g. 3)
type of administration:.....other notes: .....

name:.....active substance:.....dose(gram,milligram, etc.).....
if fluid, concentration (e.g. 10%, 1g/2ml, etc.).....how many times per day (e.g. 3)
type of administration:.....other notes: .....

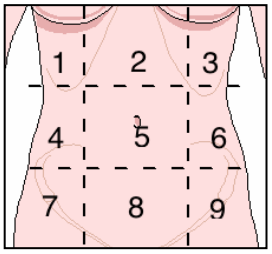
# FORM-C Acute Pancreatitis

Early Enteral Nutrition

GOULASH

**Diet:** yes / no
if yes: please describe:.....

## 3. Complains, symptoms




**Abdominal pain:** yes / no
if yes: since when (hours):.....
type: cramping / dull / sharp
intensity (1-10):.....
location: diffuse / localized
Please mark the location!
radiation:.....

**Nausea:** yes / no

**Vomiting:** yes / no
if yes: how many times:.....
contents of cast:.....

**Subfebrility/fever:** yes / no
if yes: since when:.....
degree (°C):.....

**Appetite:** good / retained / bad

**Weight loss:** yes / no
if yes: how much (kg):.....
How long did it take? (weeks):.....

**Jaundice:** yes / no
if yes: for how long:.....

**Stool:** normal / diarrhea / constipation / fatty / putrid / undigested food/bloody/mucus

## 4. Laboratory parameters

**OBLIGATORY PARAMETERS**

| | |
|---|---|
| Amylase (U/l) | |
| Lipase (U/l) | |
| White blood cell (WBC) count (G/l) | |
| Red blood cell (RBC) count (T/l) | |
| Hemoglobin (g/l) | |
| Hematocrit (%) | |
| Thrombocyte (G/l) | |
| C-reactive protein (mg/l) | |

**OTHER PARAMETERS (if measured):**

| | |
|---|---|
| Serum glucose (mmol/l) | |
| Blood urea nitrogen (mmol/l) | |
| Creatinine (umol/l) | |
| eGFR | |
| ASAT/GOT (U/l) | |
| Lactate dehydrogenase LDH (U/l) | |
| Calcium (mmol/l) | |
| Sodium (mmol/l) | |
| Potassium (mmol/l) | |
| Total protein (g/l) | |
| Albumin (g/l) | |
| Cholesterol (mmol/l) | |
| Triglyceride (mmol/l) | |
| ALAT/GPT (U/l) | |
| Gamma GT (U/l) | |
| Total bilirubin (umol/l) | |
| Direct/Conjugated bilirubin (umol/l) | |
| Alkaline phosphatase (U/l) | |

**5. Imaging examination**

**Abdominal ultrasonography:** yes no
Description:

**Ultrasound:**

- *Visualization:*
  - Good, complete (head at least partially visualized, body and neck well visualized, tail: partially visualized)
  - Partially, incomplete (only body or only head visualized)
  - Poor, non-diagnostic
- **Size:**
  - Normal
  - Partially enlarged (body AP diameter is over 2 cm and/or head AP diameter is over 2,5 cm, none exceeds 3 cm)
  - Definitely enlarged (any part over 3 cm AP diameter)
- **Peripancreatic fluid:**
  - none
  - present
  - Large pseudocyst(s)

- Size of peripancreatic fluid or pseudocyst: …… cm

- **Pancreas homogeneity:**
  - Homogenous
  - Inhomogeneous, includes area(s) of low echogenicity
  - Inhomogeneous, includes calcifications

- In case of circumscribed low echogenicity area, it's size: …… cm

- **Wirsung** dilatation: YES / NO (yes, diameter: …….. mm)

Other Description:

……
……

**Abdominal Computed Tomography:** yes no
Modified CTSI Score: ……0-10……

*Please NOTE! Abdominal CT is compulsory if*
*- Abdominal ultrasonography is not fully completed **OR***
*- There is any alteration on abdominal ultrasonography*

**CTSI Score: (I)** Normal pancreas 0 point, intrinsic pancreatic abnormalities with or without inflammatory changes in peripancreatic fat 2 points, Pancreatic or peripancreatic fluid collection or peripancreatic fat necrosis 4 points **(II)** Necrosis absent 0 Points, < 30% necrosis 2 Points, > 30% necrosis 4 points **(III)** presence of extrapancreatic findings 2 points.
MAXIMUM OF: 10 points

- **CTSI:**

**I. Pancreas**
  - Normal pancreas
  - Intrinsic pancreatic abnormalities with or without inflammatory changes in peripancreatic fat
  - pancreatic or peripancreatic fluid collection or peripancreatic fat necrosis

**II. Size of Necrosis**
  - Necrosis absent
  - < 30% necrosis
  - > 30% necrosis
  - > 60% necrosis

**III. Extrapancreatic findings**
  - presence of extrapancreatic findings

**DETAILED REPORT**

- **Pancreas Size:**
  - Normal
  - Partially enlarged (body AP diameter is over 2 cm and/or head AP diameter is over 2,5 cm, none exceeds 3 cm)

- Definitely enlarged (any part over 3 cm AP diameter)

- Largest diameter of peripancreatic **fat infiltration**: …… cm

- **Peripancreatic fluid:**
  - none
  - present
  - Large pseudocyst(s)
- Size of peripancreatic fluid or pseudocyst: …… cm

- **Necrotizing area** (nonenchancement):
  - Largest diameter of necrosis area: …… cm
  - Location of necrosis: ……
  - Type: patchy / full width
  - Estimated necrosis: 0% , < 30% , 30% - 60%, above 60%

- **Wirsung** dilatation: YES / NO (yes, diameter: …… mm)

- Distant **abdominal fluid**:
  - Small amount (hard to see, less than 2 cm in lesser pelvis, less than 1 cm around liver/spleen)
  - Moderate amount (easy to see, but without pelvic or abdominal distension)
  - Large amount with abdominal/pelvic distension

- **Pleural effusion:**
  - none
  - one sided:…… (AP diameter: …… cm)
  - Both sides, L - …… cm, R - …… cm

- **Extrapancreatic findings**:
  - Inflammation (Cholecystitis, Duodenitis, etc.) location: ……
  - Cholecystolithiasis
  - Choledocholithiais
  - Signs of bowel ischaemia
  - Bowel distension, ileus
  - Venous thrombosis
  - Pseudoaneurysm
  - Parenchymal organ involvement, define: ……

Other Description:
……
……

# FORM-C Acute Pancreatitis

Early Enteral Nutrition

GOULASH

## 6. Complications

*Please register pancreatic complication of fluid collection/pseudocyst/necrosis only if you had imaging proof on the day of admission, otherwise, please mark "no data".*

**Pancreatic:** yes no no data
if yes: fluid collections /pseudocyst / necrosis / diabetes

**Organ failure:** yes no
if yes:, lung /heart / kidney /other

**Death:** yes no
If yes: the exact date of death: ..... *e.g. 10.25 or 22.45*

## 7. Epicrisis

*A short summary (what happened with the patient after the hospitalization, any recommended control examinations, surgery).*

.....
.....

**DATE:**
YEAR: ..... MONTH: ..... DAY: ..... HOUR ..... MIN: .....

**NAME OF THE DOCTOR : .....SIGNATURE:** .....


SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

| Section/item | Item No | Description | Addressed on page number |
|---|---|---|---|
| **Administrative information** | | | |
| Title | 1 | Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym | 1 |
| Trial registration | 2a | Trial identifier and registry name. If not yet registered, name of intended registry | 2,17 |
| | 2b | All items from the World Health Organization Trial Registration Data Set | 17 |
| Protocol version | 3 | Date and version identifier | 17 |
| Funding | 4 | Sources and types of financial, material, and other support | 17 |
| Roles and responsibilities | 5a | Names, affiliations, and roles of protocol contributors | 1,18 |
| | 5b | Name and contact information for the trial sponsor | 5 |
| | 5c | Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities | 5, 17 |
| | 5d | Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee) | 5, 12 13 |

| | | | |
|---|---|---|---|
| **Introduction** | | | |
| Background and rationale | 6a | Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention | 3, 4 15, 16 |
| | 6b | Explanation for choice of comparators | 4 |
| Objectives | 7 | Specific objectives or hypotheses | 4 |
| Trial design | 8 | Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory) | 4, 6 |
| **Methods: Participants, interventions, and outcomes** | | | |
| Study setting | 9 | Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained | 13, 10 |
| Eligibility criteria | 10 | Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists) | 6, 13 |
| Interventions | 11a | Interventions for each group with sufficient detail to allow replication, including how and when they will be administered | 7, 8, 9 |
| | 11b | Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease) | 9 |
| | 11c | Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests) | 14 |
| | 11d | Relevant concomitant care and interventions that are permitted or prohibited during the trial | 9 |
| Outcomes | 12 | Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended | 9, 10, 11, 14 |
| Participant timeline | 13 | Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure) | 7, 10 |

| | | | |
|---|---|---|---|
| Sample size | 14 | Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations | 6_____ |
| Recruitment | 15 | Strategies for achieving adequate participant enrolment to reach target sample size | 6_____ |
| **Methods: Assignment of interventions (for controlled trials)** | | | |
| Allocation: | | | |
| Sequence generation | 16a | Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions | 6, 7_____ |
| Allocation concealment mechanism | 16b | Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned | 7_____ |
| Implementation | 16c | Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions | 6, 18_____ |
| Blinding (masking) | 17a | Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how | 7_____ |
| | 17b | If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial | _____ |
| **Methods: Data collection, management, and analysis** | | | |
| Data collection methods | 18a | Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol | 10, 11, 12, 13, 14, 15__ |
| | 18b | Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols | 6, 10_____ |

| | | | |
|---|---|---|---|
| Data management | 19 | Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol | 10 |
| Statistical methods | 20a | Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol | 11, 12, 13 |
| | 20b | Methods for any additional analyses (eg, subgroup and adjusted analyses) | 12, 13 |
| | 20c | Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation) | 10, 11, 12 |
| **Methods: Monitoring** | | | |
| Data monitoring | 21a | Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed | 6, 10, 12 |
| | 21b | Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial | 13, 14 |
| Harms | 22 | Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct | 14 |
| Auditing | 23 | Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor | 14, 6, 10, 12 |
| **Ethics and dissemination** | | | |
| Research ethics approval | 24 | Plans for seeking research ethics committee/institutional review board (REC/IRB) approval | 2, 17 |
| Protocol amendments | 25 | Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators) | 14 |

| | | | |
|---|---|---|---|
| Consent or assent | 26a | Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32) | 6, _____ |
| | 26b | Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable | 15_____ |
| Confidentiality | 27 | How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial | 10_____ |
| Declaration of interests | 28 | Financial and other competing interests for principal investigators for the overall trial and each study site | 17_____ |
| Access to data | 29 | Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators | 2_____ |
| Ancillary and post-trial care | 30 | Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation | 14_____ |
| Dissemination policy | 31a | Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions | 2_____ |
| | 31b | Authorship eligibility guidelines and any intended use of professional writers | 13_____ |
| | 31c | Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code | 2_____ |
| **Appendices** | | | |
| Informed consent materials | 32 | Model consent form and other related documentation given to participants and authorised surrogates | _____ |
| Biological specimens | 33 | Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable | 15_____ |

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.