Research protocol Date: 2002-06-05 Status: draft

Glutamine to intensive care patients - a prospective, double-blind, placebo-controlled multicenter study in the Scandinavian countries

The protocol was approved by the Scandinavian Critical Care Trails Group in Åre, Sweden on March 12, 2002.

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1. Summary

This is a prospective double-blinded placebo-controlled block randomised study in intensive care patients comparing intravenous glutamine supplementation (0.285 g/kg body weight/24 h) to placebo. Inclusion criteria are patients treated for more than 3 days. Primary endpoint is a reduction in SOFA-score on day 7 of treatments. Secondary endpoints are: ICU-mortality, 6-months mortality, length of ICU stay, organ failure free days as well as reduction in SOFA-score on day 10 of treatment. Nutrition will be standardised so that not less than 80% of the target which is basasl energy expenditure according to Harris & Benedict is given daily. Enteral nutrition is preferred, but a combination of enteral and parenteral nutrition is recommended to achieve the nutritional target. Diagnosis and APACHE II score are registered at submission. After that the study drug, nutrition and SOFA-score will be registered on a daily basis. For statistical power calculations, a possible effect upon mortality as well as a limited effect of a short treatment period are considered. For statistical comparison non-parametric rank order statistics will be used. To detect a 0.75-point difference in the reduction of SOFA-score on day 7 of treatment, a total of 1,000 patients will be needed. Patients from 20-25 centre in the Nordic countries will be included in the study over a period of 18 months.

2. Abbreviations

Ala-gln	L-alanyl-L-glutamine
APACHE II	Acute Physiologic and Chronic Health Evaluation
g	gram(s)
h	hour(s)
ICU	Intensive Care Unit

kcal	kilocalory(-ies)
kg	kilogram(s)
L	liter(s)
ml	millilliter(s)
mmol	millimole(s)
NaCl	Sodium chloride
SOFA	Sepsis-related Organ Failure Assessment

3. Background

Glutamine is the most abundant amino acid in the body constituting 60 % of the total amino acid and amino nitrogen pool. Together with alanine it accounts for approximately 2/3 of amino acids released from muscle. The concentration of glutamine in human skeletal muscle is high, approximately 20 mmol/l of intracellular water. Considerable changes in glutamine flux and concentration occur in response to a variety of insults such as trauma, infection, fasting and acidosis. A reduction of free glutamine concentration in plasma and tissues is seen postoperatively (1), and it remains decreased and uninfluenced during a period of several weeks regardless of supply of amino acids (2). When glutamine containing amino acid solutions are given the decrease in plasma concentration is counteracted, while the decrease in tissue concentration is counteracted only if the supplementation is given before the decrease (3,4). Ordinary food is not sufficient to prevent this depletion (5). In postoperative patients glutamine is the last amino acid to be restored back to normal in human muscle (5,6). In critically ill patients in the intensive care unit pronounced and prolonged depletion of muscle free glutamine is seen (7,8). This occurs early in the course and the concentration remains low for a long time. The length of restitution time has so far not been characterised.

Glutamine is a major substrate for the intestinal tract in humans. Both colonocytes and enterocytes utilise glutamine to a greater extent than any other fuel, even glucose (9,10). The glutamine consumption by the intestinal tract is increased by approximately 75% following the stress of a standard elective surgery (11). However, in sepsis and endotoxaemia an impairment in the ability of the intestinal tract to utilise glutamine is sometimes seen (12). Furthermore, glutamine appears to be essential for the normal function and replication of the cells of the immune system shown both in vitro and in vivo (13,14).

Due to its instability and low solubility in aqueous solution there has been problems to provide sufficient amounts of glutamine. The dipeptide L-alanyl-L-glutamine is soluble in water and remains stable after heat sterilisation (15). Peptidase activity in all body compartments shows rapid hydrolyses and release of the appropriate amino acids after intravenous infusion.

Modern practise includes provision of enteral feeding to the majority of ICU patients, and only implementing parenteral nutrition when enteral feeding failed or is impractical. However, many diseased conditions in which parenteral nutrition is indicated are accompanied by glutamine depletion. Numerous animal studies and emerging human data document a beneficial effect of enteral and parenteral glutamine supplementation during catabolic states such as infection, surgery, burns, chemotherapy and irradiation, intestinal resection and gut mucosal inflammation (16-23). Available studies suggest that beneficial effects associated with glutamine enriched enteral and parenteral diet formulations are probably due to a number a mechanisms. These include improved protein anabolism (24), enhanced number and function of fixed or circulating immune cells (14,17), maintaining of gut mucosal barrier defences (23), and improved tissue antioxidant status (25).

There are potential advantages of parenteral administration of glutamine as compared to enteral administration. These include increased plasma levels of glutamine which may result in better whole body protein anabolism, antioxidant, and immune function effects. In addition the intestine is able to utilise parenterally administered glutamine via the enterocyte basolateral membrane blood supply, which may be of special importance in patients with damaged mucosa and impaired absorptive capacity and/or high need for glutamine. Provision of glutamine by the enteral route also carries the problem of the discrepancy between prescribed and delivered dose. Furthermore, before enteral nutrition is established there is an uncertainty concerning absorption of administered formula. Therefore the parenteral application is preferable in order to be able to provide glutamine independently of the route of nutrient support.

The glutamine containing dipeptide L-ananyl-L-glutamine is available in a 20% infusion concentrate for central venous infusion after addition to a compatible infusion solution. The concentrated dipeptide solution may also be given separately intravenously in a safe manner.

It may be administered by a central or peripheral vein (26). Dipeptiven is endogenously split into amino acids, glutamine and alanine thereby supplying glutamine with infusion solutions parenterally. The released amino acids are distributed as nutrients into their respective body pools, and are metabolised according to the needs of the organisms. A number of studies have demonstrated the hydrolyses of the dipeptide in man following intravenous administration (27,28).

In current literature no cases with adverse reactions have been reported following administration of the dipeptide in clinical investigations. Still, doses up to 60 g L-alanyl-L-glutamine/day have been administered over a period of 5 days (29-31), and doses of 40 g/day have been administrated over periods up to 25 days (32). Moreover, no adverse physiological effects of the intact dipeptide L-alanyl-L-glutamine have been reported. In a large number of studies L-alanyl-L-glutamine has been demonstrated to be suitable for compensating for glutamine deficiency in patients with normal metabolism and which can thus help maintain intestinal mucosal function. No adverse reactions have been reported in the studies.

The dosage recommendations, as a result of extensive experimental and clinical investigations which are reported in the literature, suggest that an increased intestinal and cellular demand for metabolic fuel in postoperative patients can be met by a daily provision of approximately 15 g of glutamine. In intensive care patients this figure is higher, but less well documented. A supply of 25 g of glutamine daily was sufficient to demonstrate a reduction in 6-months mortality (33).

Nutrition of patients in the intensive care unit is a major treatment modality. Over the years recommendations have varied considerable, reflecting mainly insufficient knowledge concerning the pathophysiology of metabolism in severely diseased states. There are numerous reports about the adverse effects of overfeeding as well as there are substantial documentation concerning the hazards of underfeeding (34,35). The state of the art today is to feed enterally on the level of energy expenditure (36). As measurement of energy expenditure is not a clinical routine, recommendations are often given as kg/kcal/body weight or in accord with formulas of Harris & Benedict. Adding calories considering elevated body temperature, sepsis, extensive burns and so on is not used today in general practice without measuring the energy expenditure by indirect calorimetry.

Modern techniques to administer enteral nutrition have developed and consequently enteral nutrition is today a first hand choice. However, among the patients most in need of nutrition, enteral nutrition is sometimes difficult to administer related to a number of reasons. Therefor when enteral nutrition is considered the only option, undernutrition of the patient is very often seen. Therefor it is necessary to have a routine where complementation of enteral nutrition with parenteral administration is ordinated as soon as the enteral nutrition is insufficient.

Concerning the effects of nutritional treatment upon morbidity and mortality there are a number of international multi-center studies presently (34,37). Most of them suffer from problems of not guaranteeing the individual patient a sufficient nutritional intake in terms of calories and nitrogen. The variability on this point is so large that it basically invalidates any conclusions. The most important point when designing future studies is to have a protocol which guarantees every patient provision of nutrients in accord with the hypothesis.

Another problem is how to define morbidity and mortality. The latter is easily defined although the ICU mortality may be influenced by different routines in individual centres. In addition the beneficial effects attributable to nutritional support may be extended also to the convalescence and rehabilitation period and therefore 6-months mortality is considered a more adequate measurer than in unit or in hospital mortality. Concerning morbidity it may be reflected in the SOFA-score, which take failure in several organs into account (38). As there is a close correlation between SOFA-score and mortality, it may be the best integrated measure of morbidity. Morbidity of clinical importance it may also be reflected in the length of ICU-stay. It is obvious that ICU-stay is variable inbetween units as much as it depends upon the pressure on available ICU-beds and the quality of the post-ICU care. Hospitals with step down units may have quite different routines from those hospitals that lack such a facility. Although there will be considerable differences between units, a block-randomisation may at least to some extent take care of these problems. Still definition of morbidity is problematic, and to choose a measure of morbidity as a primary endpoint must always include a number of compromises.

In addition a close record of the nutrition given is also necessary to verify that the intended treatment is actually received by the patients. The record should include the energy given as well as nitrogen content.

4. Trial objectives

This trial is designed to elucidate the effect upon morbidity and mortality in intensive care patients given an extra supply of intravenous glutamine for not less than 3 days. All patients should be guaranteed a minimum nutritional support and daily provision of glutamine will continue as long as the patient stay in the intensive care unit.

4:1 Primary objective

The primary objective is to compare the change in SOFA-score (Appendix 8:2) on day 7 of ICU stay as compared to the day starting nutritional treatment and glutamine supplementation. Only patients who have received glutamine for not less than 3 days will be considered.

4:2 Secondary objectives

The ICU mortality, the 6-months mortality, the length of ICU stay and the change in SOFA-score on day 10 of ICU stay as compared to the day starting nutritional treatment and glutamine supplementation will also be calculated.

5. Trial design

This trial is designed as a prospective block-randomised, double-blinded, placebo-controlled multi-center trial in the Scandinavian countries. A total of 1.000 ICU-patients will receive a daily support of glutamine or placebo-treatment (NaCl) during on at least 3 consecutive days.

5:1 Investigational product

The trial drug will be L-alanyl-L-glutamine 20% (Dipeptiven®) concentrated solution for intravenous infusion, which will be delivered during 12 h intravenously.

5:2 Package and labelling

The trial drug as well as placebo will be manufactured by Fresenius-Kabi and will be provided in 100 ml glass bottles. Labelling will be performed by Apoteksbolaget. As treatment period will be variable among patients, the drug will be delivered to each centre marked A or B. Local Pharmacy will then according to randomisation deliver daily supply to the unit for each patient labelled with the unique 6-digit number given to the patient. Amont of drug administered and time interval of administration will be registered and reported daily.

5:3 Blinding and code breaking

Ala-gln 20% or 0.9% NaCl will have same appearance. The subject number will be noted on the label and on the bottle. Each subject number will consist of 6 digits. The investigator allocates the treatment by assigning subject number in a strict consecutive order. A list of the treatments geiven to the individual patients according to their 6-digit number will be kept at the local Pharmacy until interim analysis and until end of the study.

5:4 Case Report Form as source data

The Case Report Form will be filled in daily and reported electronically to the study coordinator. Paper copies will be signed and filed at each study centre. The information on the Case Study Form will be considered as primary data.

6. Selection and withdrawal of subjects

All patients that receive nutrition in the ICU are eligible for inclusion into the study and may be included until discharge form the unit.

6:1 Screening

Screening will be performed when it is decided to prescribe full nutrition to the patient, usually during the initial 2 days of ICU-stay before the trial starts. During the screening following tasks will be performed.

a) Detailed patient/relative information by the investigator and handout of the written patient/relative information
b) List of inclusion/exclusion criteria will be checked
c) Subject's demographic data will be controlled

Recording of APACHE II score at admission (during first 24 h of stay)

6:2 Inclusion criteria

Subjects will be enrolled in the trial when they meet the following criteria:

a) admission to the ICU

b) decision to give the patient full nutrition

c) APACHE II score >10 at admission

d) age 18-85 years

6:3 Exclusion criteria

Subjects will be excluded for anyone for the following reasons:

a) readmission to the ICU after a previous ICU-stay in which the patient has been included into the study. Dismissal and readmission may be regarded as one treatment period if the absence of treatment is not more than 24 hours.

b) subjects with any condition which in the opinion of the attending physician makes the subject unsuitable for inclusion.

6:4 Withdrawal of subjects

Patient's participation may be terminated at any time at the discretion of the investigator or at the patint's/relativve's request. Should this happen the following information will be recorded:

a) subject's/relative's comments or complains

b) reason for termination

6:5 Randomisation

Subjects will be randomised to treatment only if they satisfy all inclusion criteria. The trial will include 500 subjects in each treatment group. Block randomisation means that the subjects will be assigned randomly to active or placebo treatment with equal size of the two treatment groups at each investigational centre. A computer program using the method of random allocation within fixed blocks will generate a randomisation list. It will provided for a defined number of subjects and a defined number of reserve subjects at each investigational centre. The randomisation list will be securely locked away during the trial by the responsible statistician until clean file has been declared.

7. Treatment

Patients will receive a daily support of undiluted L-alanyl-L-glutamine (Dipeptiven®) containing glutamine 0.13 g/ml or placebo-treatment (NaCl) as a 12 h intravenous infusion during at least 3 consecutive days. In the trial the patients will receive intravenous administration of glutamine 0.285 g/kg/body weight or placebo treatment during 12 h intravenous infusion each day. The dosage of glutamine in relation to body weight will not continue above 90 kg, which is the upper limit.. The volume to be infused will depend upon the subject's body weight and calculating from the formula 0.285 g/kg body weight/12 h corresponding to a infusion rate of 0.024 g/kg body weight/h. The infusion may be done in a

central venous line or in a peripheral line. As Dipeptiven contains 20 g alanyl-glutamine per 100 mL, corresponding to 13 g of glutamine per 100 mL, the infusion rate will be 0.183 mL/kg body weight/h (Appendix 8.4). The treatment will continue as long as the patient stays in the ICU.

In parallel nutritional support of the patient will be standardised. The recommended routine is that the energy content should comprise no less than 80% of basal energy expenditure according to Harris & Benedict (Appendix 8.3). Preferably the enteral route should be used. If enteral nutrition is not sufficient to correspond to 80% of the energy expenditure, parenteral nutrition should be given complementary. It is recommended that a combination of enteral and parenteral nutrition is planned initially and that follow-ups during each 24-hour period are done to guaranty that every patient is given not less than 80% of the targeted nutrition. As routines will differ somewhat in between units this recommendation is given and nutrition will be recorded on a daily basis in terms of the energy content and nitrogen administered. Dipeptiven®/Glavamin® may not be used as concomitant medication during the trial.

8. Efficacy assessment

Each day of the study following things will be performed:

a) study drug (glutamine or placebo) will be given intravenously during 12 h.

b) volume of infused solution and time interval of infusion will be registered.

c) total amount of nutrition during 24 h will be recorded.

d) SOFA score will be calculated.

End of ICU-stay will be recorded and as well as the route of discharge. If the patient is moved to another intensive care unit, the patient leaves the study. Still if the patient is treated more than 3 days, he is included and evaluated in the study although the ICU-stay is prolonged in another unit and patient during that time does not receive any controlled treatment. Provision of nutrition after ICU-stay (or after readmission to ICU) will not be recorded. If patient is readmitted to ICU within 24 h study protocol is continued. If patient is readmitted to ICU after more than 24 h the patient will not be included. Patient will not be included again in the study and the second (or consecutive) stay will not be recorded as ICU-stay in the protocol.

8:1 Primary objective

The difference in SOFA-score will be calculated from the day starting nutritional treatment as well as glutamine supplementation until day 7 of ICU stay. For patients discharged or dead before day 7, the SOFA score on the day of discharge/death will substitute the latter score. In case of restrictions in treatment, SOFA score will be recorded as long as the nutrition of the patient is maintained.

8:2 Secondary objectives

Mortality in the ICU and after discharge up to 6 months will be recorded and the cause of death will be registered. The difference in SOFA-score will also be calculated until day 10 of ICU stay according to the same procedure as for the primary objective under section 8:1. Length of ICU stay will also be recorded. If the patient is readmitted within 24 h after discharge the study continues. Readmission later than 24 h after discharge will not be recorded.

9. Safety assessment

As administration of the drug is in accord with clinical practice, documentation of safety will not be a primary or secondary objective of the study. Nevertheless as mortality and morbidity are the objective of the study, events characterised as adverse events or serious adverse events will be recorded and reported.

9:1 Adverse event

In the study any event, regardless if there is any suspected connection to the study drug or not, that requires treatment and that is not reflected in the SOFA score, will be recorded as an adverse event. The investigator's concerning possible relation to the study drug will be noted.

9:2 Serious adverse event

All deaths occurring in patients randomised in the study will be reported as serious adverse events, using the specific form. The study monitor should be contacted within 24 h and a signed copy of the form should be faxed to the monitor within 5 working days.

10. Statistics

The study is designed with one primary endpoint as the primary objective and several secondary endpoints as secondary objective. The statistical power calculation to determine the sample size is performed for the primary endpoint. Parametric and non-parametric statistics will be used depending on whether the parameters are normally distributed or not. As 3 days of treatment is an inclusion criteria all calculation will be made on included as well as randomised patients (intention to treat)

10:1 Primary objective

The change in SOFA score between day of start of treatment and day 7 of ICU stay will according to historical data be normally distributed, and therefor the groups will be compared using parametric statistics (Student's t-test). As the primary endpoint will be used in the planned interim analysis after inclusion of 500 patients, an adjustment for the level of significance will be performed accordingly.

10:2 Secondary objectives

The 6-months mortality will be recorded from the public register. Mortality rates will be compared using a Kaplan-Meyer plot and $?^2$-analysis. The change in SOFA score will be compared between groups using Student's t-test, as for the primary end-point.

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10:3 Sample size

The sample size is calculated to enable detection of a 0.75-point difference in change in SOFA-score after 7 days of treatment with 80% statistical power is based upon parametric statistics. In particular a limited effect during a short treatment period was taken into considerations. The choice of change in SOFA score was partly done on account that it can be assumed to be neutral to a non-identical The sample size of approximately 500 patients in each group are needed under these assumptions.

10:4 Multi-centre

The major centres in the Scandinavian countries do not have more than approximately 100 patients that stay for more than 5 days in the ICU, therefor a multi-centre design of the study is necessary. It is also desirable that the study can be concluded within 18 months. It is also desirable that each centre participating contribute with not less than 25 patients. It is therefor

natural that this protocol is a multi-centre study in the Scandinavian countries. The plan is to recruit 500 patients in 10 centres in Sweden and 500 patients in 10 centres in Denmark, Finland and Norway.

10:5 Statistical methods

Student's t-test will be used to compare the 2 groups when variables are normally distributed, this is expected to be the case for the change in SOFA score. For length of stay a rank-test will be used where survival is ranked higher than death and death after a long period of time is ranked higher than death after a short period of time. For mortality a Kaplan-Meyer plot and $?^2$-analysis will be used.

10:6 Subject classification

All patients who are eligible for the study are registered and if they are not randomised the reason is noted. All patients that are randomised are registered as randomised and as included if treatment is started. For patients who are randomised but not included the reason is noted. Patients who are randomised and have received treatment will be classified as withdrawals. Patients may withdraw from the trial at their own request or at the discretion of the investigator. Patients treated for less than 3 days (3 treatment periods) will also be classified as withdrawals. Patients with failure of treatment on two consecutive days will also be withdrawn from the study. A minimum of 3 treatment periods on consecutive days will be necessary for evaluation. Analyses of the results will be made on the basis of included patients as well as on the basis of "intention to treat" and "screened patients". "Intention to treat" meaning all patients randomised, including those not given 3 days of treatment depending upon death, discharge or discontinuation of other reasons. "Screened patients" meaning all patients possible to include.

10:7 Drop-outs and Missing Data

Drop-outs before day 7 of ICU stay will be considered as withdrawals. Drop-outs after that day will be evaluated in the primary outcome variable, and the same goes for day 10. For evaluation in length of stay and mortality, drop-out will be considered as withdrawals. Missing data will be considered as non-existent.

11. Study co-ordinator

A study co-ordinator will support the study and register all the electronic reports. Investigators not reporting daily will be contacted to inquire whether they need any type of support. Whenever daily reports are not complete or any other question arises, study co-ordinator will also contact the investigator. Study co-ordinator will also help to see that study drug is available in sufficient amounts at the local Pharmacies at the participating centres.

12. Quality control

The principal investigator or country responsible investigator will together with the study co-ordinator visit participating centres to help local investigators to have uniform routines, uniform data collection and to assure storage of the signed paper copies of case report files.

13. Stopping rules

After recruitment of 200 patients a check up will be done in order to see that the protocol is functional and that the recruitment is sufficient to complete the study within the expected time. After 500 patients a interimistic calculation a difference in the primary endpoint between the two treatment groups will be made. A decision will then be taken whether to continue or not.

14 Ethics

As glutamine supplementation of nutrition is not evaluagted in a prospective double-blinded placebo-controlled multi-centre trail in ICU patients this needs to be done. The protocol is in accord with the Declaration of Helsinki.

14:1 Ethics approval

Ethical permission will be applied for separately in the participating countries. In Sweden Ethics Committees of all universities should be approached simultaneously, while in Denmark, Finland and Norway the procedure starts at one university.

14:2 Regulatory approval

Permission from national regulatory authorities will be applied for in each participating country.

15. Documentation and record keeping

15:1 Case Report Form

Data will be reported electronically and a special case report form will be designed for the report (Appendix 8.5). The study co-ordinator will check the input from the different centres on a daily basis and immediately make contact when reporting fails.

15:2 Data management

Signed paper copies of the case report forms will be kept at the participating centres. All electronically submitted case report forms will be stored electronically, and patients will only be identified by their 6-digit trail number.

15:3 Record retention

The case report forms will be stored safely at the local centres for 3 years. The electronic data-filfes will be stored safely by principal investigator for 5 years.

16. Reporting and publication

As the study is a part of the activities of the Scandinavian Critical Care Trails Group, it will be reported and published in the name of the Network. Accompanying studies using the protocol of the multi-centre study and adding other investigational parameters are encouraged. Such extensions may then give reference to the multi-center study and Scandinavian Critical Care Trails Group when publishing. As the study is an investigators trail, without any industrial sponsor, publication of the results is at the discretion of the principal investigator and the steering group of the study within the framework of the Scandinavian Critical Care Trails Group.

17. Amendments

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19. Appendages

19:1 SOFA-score table

19:2 Harris-Benedict table

19:3 Dosage table

19:4 Electronic report form

19:1 SOFA-score

SOFA -score	1	2	3	4
Respiration				
PaO_2/FiO_2, mmHg (kPa)	300-399 (40.1-53.3)	200-299 (26.8-40.0)	100-199 (13.3-26.7)	<100 (<13.3)
Coagulation				
Platlets $x10^3/mm^3$	100-140	50-99	20-49	<20
Liver				
Bilirubin, mg/dl (µmol/l)	1.2-1.9 (20-32)	2.0-5.9 (33-101)	6.0-11.9 (102-204)	>12.0 (>204)
Cardiovascular				
Hypotension	MAP <70 mmHg	Dopamine ≤5[a] or dobutamine (any dose)	Dopamine >5 or epinephrine ≤0.1 or norepinephrine ≤0.1	Dopamine>15 or epinrphrine >0.1 or norepinephrine >0.1
Central nervous system				
Glasgow Coma Scale	13-14	10-12	6-9	<6
Renal				
Creatinine, mg/dl (µmol/l) or urinary output	1.2-1.9 (110-170)	2.0-3.4 (171-299)	3.5-4.9 (300-499) or <500ml/day	>5.0 (>440) or<200ml/day

[a] Adrenergic agents administered for at least 1h (doses given are in µg/kg · min)

19:2 Harris-Benedict’s Formula

Basal energy expenditure (kcal/24h)

Men	66,5 + 13,7xW + 5,0xH – 6,8xA
Women	655,1 + 9,6xW + 1,8xH - 4,7xA

A = age (years)
H = height (cm)
W = body weight (kg)

19:3 Dosage of Dipeptiven or placebo

Body weight (kg)	Total dose (g/day)	Infusion rate (ml/h)
40	16.9	7.0
50	21.2	8.8
60	25.4	10.6
70	29.6	12.3
80	33.9	14.1
90 or more	38.1	15.9

19:4 Patient report form

Inclusion:

Serial number: xxxxxx
Sex: f/m
Age: yyyy-mm

Day of ICU admittance: yyyy-mm-dd
APACHE II at ICU admittance: xx
Diagnosis: xxxxxxx

Start of treatment: yyyy-mm-dd

Daily report:

Serial number: xxxxxx
Day of treatment: xx
Period of time: yyyy-mm-dd hh:mm – yyyy-mm-dd hh-mm

Volume (ml) of treatment drug administered: xxx

Volume (ml) of nutrienets administered:

Iv glucose 50mg/ml	xxxx
Iv glucose 100mg/ml	xxxx
Iv glucose xxx mg/ml	xxxx
Iv fat emulsion 10mg/ml	xxxx
Iv fat emulsion 20 mg/ml	xxxx
Iv amino acid xx mg/ml	xxxx
Iv Kabiven	xxxx
Iv propofol	xxxx
Po formula 1 kcal/ml	xxxx
Po formula 1.4 kcal/ml	xxxx
Po probiotic xx kcal/ml	xxxx

Organ failure score:

Max FiO_2 (%)	xxxx
Min oxygen pressussre (Pa)	xxxx
Min platlets ($x10^3/mm^3$)	xxxx
Max bilirubin(μmol/l)	xxxx
Min BP (mmHg)	xxxx
Max dose dopamine (μg/kg · min)	xxxx
Max dose dobutamine (μg/kg · min)	xxxx
Max dose epinephrine (μg/kg · min)	xxxx
Max dose norepinephrine (μg/kg · min)	xxxx
Min GCS	xxxx
Max creatinine (μmol/l)	xxxx
Urinary output (ml)	xxxx

Discharge:

Serial number xxxxxx
Day of discharge yyyy-mm-dd

Route of discharge:
- Step-down unit
- Ordinary ward
- Another hospital/ICU
- Dead
- Other way

Drop out: Y/N
- Withdrawn consent
- Failure of drug administration
- Other reason