## Title :

Japanese Guidelines for Nutrition Support Therapy
in the Adult and Pediatric Critically Ill Patients: General and Disease-Specific Nutrition Support Therapy (Japanese critical care nutrition therapy guidelines)

## Authors:

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## Basic Philosophy and Overview of These Guidelines

### A. Purpose of the guidelines

Numerous nutritional support guidelines have been published worldwide for critically ill patients, but none has been published in Japan. Thus, we have drafted such guidelines with the following objectives:

- To prepare Japanese nutritional support guidelines for critically ill patients. Target patient population for this guideline differs from ones of other preexisting guidelines.
- To outline recommendations for various clinical questions at least partially in accordance with the Japan Council for Quality Health Care EBM Medical Information Division (Minds), "Minds Handbook for Clinical Practice Guideline Development"[1)], and to reevaluate past evidence using a systematic review. The methods for evaluating evidence for these guidelines thus differ from those used in the existing Japanese nutritional support guidelines.
- To assist in determining treatment plans by presenting treatment options and to clarify the theoretical basis for the recommended options; to educate medical professionals about the variety of pathologies encountered in the clinical field during the treatment of critically ill patients.
- To discuss treatments performed in Japan and which are not covered by international guidelines; to discuss treatments covered by international guidelines, but not prevalent Japan, and to present recommendations that are suitable to clinical practice in Japan.

- To tailor the recommendations so that they can be used by all medical professionals involved in nutritional therapy.

B. Limitations of the guidelines

These guidelines are recommendations and not meant to be mandatory. In addition, the use of these guidelines does not guarantee improved outcomes or survival. Medicine is an academic field that seeks possibilities through experience and theory, and thus, it is based on predictions with uncertain outcomes. In addition, in the field of medicine, events/matters that cannot be evaluated or judged from an academic perspective are everyday occurrences. As a result, medical care providers should determine plans for treatment by taking into consideration the clinical condition, background, and circumstances of each individual patient. These guidelines serve as an aid in evaluating previous evidence during the determination of treatment plans. It is important to note that the judgment of medical care providers should always be prioritized over the recommendations in these guidelines.

These guidelines present recommendations supported in light of reviews and analyses of previously published reports, guidelines from domestic and overseas sources, the opinions of experts, and the current circumstances in the clinical field.

The “critically ill patients (intensive care unit (ICU) patients)” in the studies quoted by these guidelines have a variety of disease conditions. The greatest weakness of these guidelines is that target patients have not been explicitly identified. In addition, many of the studies referenced herein were associated with limitations such as a small sample sizes,

non-uniform patient pathologies, unclear evaluations of pathology and severity, no evaluation of the nutritional state of the patients, or deficient statistical power during analyses. The recommendation levels assigned here have been designated to reflect the abovementioned limitations.

C. Future updates

In the future, periodic revisions are planned based on new research results.

D. Users of the guidelines

The users of these guidelines are medical professionals involved in the nutritional therapy of critically ill patients, such as doctors, nurses, dietitians, physiotherapists, and medical technologists.

E. Drafting method

**1. Policy for determining recommendations (1E—1)**

For each item, one member of the Committee on Nutritional Support Guidelines for Critically Ill Patients at the Japanese Society of Intensive Care Medicine was selected to be in charge. Each individual in charge produced clinical questions pertaining to the relevant field. Next, as seen in Table 1, categories were designated for the "policy for determining recommendations," and the policy was determined by classifying clinical questions into the designated categories. The "Guidelines on adult enteral nutrition 2006" (ESPEN—EN 2006)[2—5] published by the European Society for Clinical Nutrition and Metabolism (ESPEN) in 2006, the "Guidelines on adult parenteral nutrition" (ESPEN—

PN 2009)[6—10] published by ESPEN in 2009, the "Guidelines for the Provision and Assessment of Nutrition Support Therapy in the Adult Critically Ill Patient" (ASPEN/SCCM 2009)[11] published jointly by the American Society for Parenteral and Enteral Nutrition (ASPEN) and the Society of Critical Care Medicine (SCCM) in 2009, the "Canadian clinical practice guidelines for nutrition support in mechanically ventilated, critically ill adult patients" (CCPG)[12] published by the Canadian Critical Care Nutrition group in 2003 (still being revised through its web edition), and "Nutrition" in the "Surviving Sepsis Campaign Guidelines 2012"[13] published in 2013, were the primary international guidelines consulted for formulating the "policy for determining recommendations"; in addition, several other international guidelines were also consulted for specific questions, as needed. The international guidelines consulted have been cited at appropriate places within the document.

## 2. Method for selecting documents serving as the basis for recommendations

We performed a systematic and comprehensive search of PubMed, Medline (Ovid), and the Cochran Database of Systematic Reviews online databases using the keywords "(randomized OR randomised) AND [(acute AND (ill OR illness)) OR (critically ill) OR (ICU) OR (sepsis) OR (intensive care)]" to retrieve reports published during the period between January 1980 through December 2014, and also added important reports published in 2015, as appropriate.

Documents pertaining to each individual item were searched by combining keywords related to each clinical question (CQ) and appending the results obtained to the previous

search results. When we made recommendations that matched those of international guidelines, we used the documents cited by the corresponding guidelines. For each item, document titles and abstracts from the search results were evaluated by six committee members for systematic reviews, and by the one individual in charge for other documents, to designate the evidence level ranking.

### 3. Ranking of documents serving as the basis of recommendations (determination of evidence levels) (Table 1E—2)

The evidence level evaluation for each document was performed as described below. The "Minds Handbook for Clinical Practice Guideline Development" as published by the Minds[1)] was used as a reference, and the method described therein was partially emulated:

1) The papers were categorized by study design. RCTs were designated as level A, observational studies as level C, and case series and case studies as level D evidence.

2) Other factors influencing the quality of evidence were evaluated and the evidence level was raised or lowered by +2, +1, 0, -1, or -2, based on these factors. The factors for this evaluation were as described in the Minds handbook, as described below. However, the basic level was not increased in the case of case series and case studies.

3) The evaluations of individual publications as collected in step 2) were combined to derive an overall evaluation parameter, and the overall strength of the evidence level was designated as one of four levels, ranging from A through D. A description of these four evidence levels and the strengths of each of these levels have been described briefly in Table 1E—3 and in Figure 1E—1. When no evidence was available, a level of E was

assigned.

**4. Determination of recommendation levels**

In addition to the evidence levels determined in step 3, we also assigned one of three "recommendation levels" (Table 1E—4), to reflect the "four elements for determining the recommendation level" indicated in Table 1E—5.

**5. Establishing a draft version**

The manuscript was subjected to mutual peer review by two committee members (other than the individual in charge of each clinical question (CQ) (writer of the manuscript)), and was revised by the individual in charge. The revised manuscript was then subjected to four rounds of overall peer review by the entire committee before being established as the final draft version by the committee chairperson.

**6. Completion of the final manuscript**

Public comments were solicited using the website of the Japanese Society of Intensive Care Medicine (April 1-31, 2015), and the opinions obtained were evaluated by the committee. The public opinions thus collected were appropriately incorporated into the manuscript to establish the final manuscript.

**7. Notes**

The phrase "recommended" used in the text describing recommendations has a Japanese-language meaning of "proposed." In other words, the recommendations are opinions for reference when medical professionals are determining a course of action in

the field, and failing to follow the recommendations is not an error. The final determination of actions to be taken rests explicitly with the judgment of the medical professional.

**Nutrition Support Therapy for Adults**

A. Initiating nutrition therapy

**1. Necessity of nutritional support**

CQ1

Is nutritional support necessary for critically ill patients?

A1.

It is recommended that nutritional support be undertaken taking into consideration the pathophysiology and staging of the critically ill patient (1D). (Drafting method A)

Commentary

In critically ill patients, metabolic reactions and hypermetabolic states progress rapidly and cause severe malnutrition. Progression of malnutrition can be a factor that negative effect on prognosis, including an increase in infectious complications and mortality rates; thus, the pathophysiology and degree of organ dysfunction should be ascertained, and the appropriate amount of energy requirements and nutrient substrates should be administered promptly.[14,15)]

A. Initiating nutrition therapy

## 2. Evaluating nutritional status

CQ2

Is there an indicator suitable for nutritional assessment?

A2.

Prior to initiating nutrition therapy, patients should be screened to identify malnutrition and nutritional risk; however, there is no evaluation indicators with high reliability (1D).

(Drafting method A)

Commentary

When implementing nutrition therapy, it is necessary to ascertain nutritional status through an appropriate nutritional assessment. Nutritional screening such as the subjective global assessment (SGA), biochemical testing such as the evaluation of serum protein concentration, nitrogen balance, and physical measurements are being used to identify malnutrition and nutrition risk. However, these assessment methods may not accurately reflect the nutritional status, and so cannot necessarily serve as nutritional indicators.[15),16-17)] Thus, it is necessary to comprehensively evaluate the medical history, food intake, nutritional status prior to hospital admission, body weight fluctuations, comorbidities and complications, physiological findings, disease severity, and digestive tract function for each patient.

A. Initiating nutrition therapy

## 3. Route of nutrient administration

CQ3

Which route of administration should be preferred, enteral nutrition (EN) or parenteral nutrition (PN)?

A3.

We recommend the use of EN (1A). (Drafting method C)

Commentary

In various RCTs and meta-analyses of EN and PN,[12,18-22] there was no difference in mortality rates between patients receiving nutrition through each of these routes, but EN groups were found to have a significantly lower rate of infection. However, in the most recent study by Harvey et al.,[23] there was no significant difference in mortality rate and the mean number of treated infectious complications between the EN and PN groups. Since the overall rate of infection was not reported by Harvey et al.,[23] and this committee was not able to obtain a reply from the authors regarding this information, a meta-analysis of pertinent literature was performed without including this study; the results of the meta-analysis showed that the EN group had a significantly lower rate of infection. Thus, EN may be superior in suppressing infection, and so preferring EN is recommended if possible.

A. Initiating nutrition therapy

## 4. Energy expenditure and energy supply

CQ4—1

Which methods should be used to estimate energy expenditure?

A4—1.

It is recommended that estimates of energy expenditure be made based on the results of indirect calorimeter measurements or calculations using predictive equations (1D).

(Drafting method A)

(For EN, see Chapter 2, B—CQ4)

(For PN, see Chapter 2, C—CQ3)

Commentary

Methods for calculating the target amount of energy requirements include measurements using an indirect calorimeter, the Harris-Benedict equation,[24] and the simplistic weight-based equation of 25-30 kcal/kg/day. However, measurements made using indirect calorimeters are associated with several limitations, and do not account for energy expenditure changes that occur over time. In addition, such measurements are inaccurate when high-concentration oxygen is administered. Furthermore, RCTs comparing groups receiving nutritional support using indirect calorimeters with those receiving nutritional support using other methodologies, have not found a difference in mortality between the study groups.[25,26] In addition, care is needed when applying the Harris—Benedict equation to avoid overfeeding, taking into account the general physique of Japanese people. Thus, any method may be used to estimate energy expenditure at the present time.

A. Initiating nutrition therapy

## 4. Energy expenditure and energy supply

CQ4—2

How much should the target energy intake be?

A4—2.

It is suggested that the amount of energy intake should be set to less than the amount of energy consumption in the first week of the acute phase (EN: 2B) (PN: no recommendation, unknown field). (Drafting method B)

(For EN, see Chapter 2, B—CQ4)

(For PN, see Chapter 2, C—CQ3)

(See the systematic review results under section C. “Parenteral nutrition”)

Commentary

In a RCT of EN, the underfeeding group which received 60-70% of the target amount of energy was found to have a significantly lower in-hospital mortality rate than was ~~a~~ the target-feeding group which received 90-100% of the target amount of energy;[27)] but comparisons between ~~a~~ the trophic feeding group (10-20 kcal/h) for up to six days from the first day and the full feeding group which received the target amount of energy from the first day,[28,29)] showed no difference in outcomes. In addition, a RCT for PN showed that, compared to an early group that was supplemented with the target energy amount within 48 hours of ICU admission, a late group for which supplementation started seven or more days after ICU admission had a reduced rate of infection.[30)] In a study of patients who received less than 60% of the energy requirement from EN, those patients who had early supplemental nutrition to the target energy amount by the third day after ICU admission exhibited a lower infection rate, compared with those patients who had late supplemental nutrition initiated on the seventh day or later[31)]. Furthermore, among subjects incapable of receiving EN, a comparison of a full group that was supplied

100% of the target amount of PN promptly and a group that was supplied a standard amount showed that outcomes were not negatively impacted in the full group.[32] The differences between the results of these studies may have been caused due to differences in patient characteristics, time to start nutrition, and different target energy amounts; thus, although the optimal energy amount has not been established, it is preferable to administer less than the amount of energy consumption during the acute phase.

A. Initiating nutrition therapy

## 5. Amount of protein administration

CQ5

How much should the optimal amount of protein administered be?

A5.

The optimal amount for protein administration is unknown (unknown field).

If the amount of energy intake has reached the target amount, it is suggested that the target for the amount of protein to be administered be set taking into consideration that 1.2-2.0 g/(measured body weight) kg/day of protein is lost (1C). (Drafting method F—1)

Commentary

Protein hypercatabolism is promoted in critically ill patients, and has been correlated with increased mortality, but there are no RCTs indicating the optimal amount of protein to be administered to such patients. However, observational studies have supported the administration of 1.2-2.0 g/ (measured body weight) kg/day of protein for patients with a body mass index (BMI) of less than 30.[33-39)] Furthermore, patients with severe trauma or extensive burns are known to require a higher amount of protein than that mentioned above. The target protein recommendation as mentioned above is based on the idea that, in order to improve nitrogen balance and taking into consideration the amount of protein loss, at least 1.2 g/kg/day is necessary.[35)] However, based on the

standard nutritional supplements available in Japan, the amount of protein to be administered (which corresponds to a target energy amount of 25-30 kcal/kg/day) is about 1.0 g/kg/day. Based on these factors, it is proposed that the target amount of protein to be administered be at least 1-1.2 g/kg/day.

B. Enteral nutrition

## 1. Timing for initiating EN

CQ1

When should EN be initiated?

A1.

We recommend that EN be initiated within 24 hours of starting treatment for the patient's critical condition if possible, and within 48 hours at the latest (1B). (Drafting method A)

Commentary

It has been noted that starting EN early in critically ill patients lowers infectious complications and the mortality.[12,40] In addition, there have been numerous reports about the effect of the timing of initiation of EN on the number of days in the ICU, the duration of hospitalization, and the duration of artificial ventilation (and some reports have shown an improvement in these parameters with early EN administration);[41] however, a meta-analysis published recently has not found a difference in these parameters based on the timing of EN initiation.[12,42]

The decrease in mortality and infections have been explained based on the observation that intestinal permeability is elevated in critically ill patients due to a systemic inflammatory response;[43] the elevation in intestinal permeability is also known to be proportional to the severity of infection.[44] The reducing effect on

infectious complication of early EN is considered to be greater in patients with more severe disease.[41,45] A recent study has shown that a group administered early EN exhibited an improvement in the absorptive ability of the gut (which is usually reduced in critically ill patients); this observation suggests that intestinal function was maintained in the group receiving early EN.

Many articles suggest that starting EN within 24 hours of ICU admission is most effective. In a RCT comparing an EN start timing of within 6 hours of admission and that of 24 hours or more after admission, a reduction in pneumonia was found in the group offered EN within 6 hours of admission. Intestinal permeability was elevated in a group starting EN at 37 hours after admission, but this was not observed in a group starting EN at 4.4 hours. The effects of early EN were not observed when the EN was started at 72 hours after admission.

In addition, several cohort studies have shown that patients administered EN within 48 hours of admission had improved outcomes compared to those administered EN later than 48 hours after admission.[45,46] In particular, outcomes improved in a group with APACHE II scores of at least 25,[45] or in a more severe critically ill group.[46] From these results, it is possible to conclude that starting EN within 24 hours would be highly beneficial, and that starting EN within 48 hours may be characterized as early administration of EN.

B. Enteral nutrition

## 2. Unstable hemodynamics

CQ2—1

Is EN possible for patients with unstable hemodynamics?

A2—1.

For patients with unstable hemodynamics, such as those requiring high-dose vasopressor administration, massive infusion, or massive transfusion, we suggest that EN initiation be delayed until resuscitation is completed (2C). (Drafting method F—1)

Commentary

No RCTs could be consulted for resolving this CQ, since there have been no RCTs of administration of EN in patients with unstable hemodynamics. In a prospective observational study by Khalid et al.,[45] early administration of EN in critically ill patients was reported to correlate with survival, and this correlation was stronger in a group of patients treated with high levels of catecholamine. In addition, even among patients treated with catecholamines, EN administration was possible in 70% of cases;[47] a previous study has reported that although the gastric residual volume (GRV) was greater for EN administration in shock patients compared to that in non-shock patients, there was no difference in the administered EN volume;[48] it has also been reported that the target amount of nutrition administration was achieved through EN in

40% of cases using catecholamines.[49] Furthermore, it is thought that absorption of nutrients through the intestinal tract is a practical possibility in critically ill patients.[50]

Based on the above articles, EN administration may be recommended for patients receiving catecholamines. However, complete resuscitation of the patient is considered necessary, and specifically, EN should likely be initiated when the hemodynamics have stabilized (such as when blood pressure has stabilized, massive infusion/transfusion has ended, and catecholamine dose escalating is no longer necessary). The ASPEN/SCCM guidelines[11] recommend avoiding EN initiation until the hemodynamics have stabilized during high-dose catecholamine administration and during massive infusion; an average blood pressure of 60 mmHg has been recommended as the standard value. According to SEMICYUC—SENPE,[51] EN may be started when 24-48 hours have elapsed since ICU admission in the case of severe imbalances in body hemodynamics such as during intra-aortic balloon pump counterpulsation (IABP). However, the abovementioned recommendations are opinions of experts in the field and have yet to be tested in clinical practice.

In addition, the safety of EN in a hypoxic state has not been established. A published report has suggested that the quantity of EN in acute respiratory distress syndrome (ARDS) patients did not affect survival;[29] a different report has revealed that a group administered approximately 55% of the target amount of nutrition exhibited improved survival compared to a group administered 85% of the target amount. Thus, due to a lack of consensus, a clear recommendation cannot be made in this regard.

B. Enteral nutrition

**2. Unstable hemodynamics**

CQ2—2

What are the precautionary notes for EN administration in unstable hemodynamics?

A2—2.

The occurrence of shock or non-occlusive bowel necrosis should be considered during EN administration and if signs of the above mentioned conditions are observed, it is recommended that EN be suspended (1D). (Drafting method F—1)

Commentary

No RCTs could be consulted for resolving this CQ, since RCTs of nutrition administration in unstable hemodynamics have not been conducted to date. The ASPEN/SCCM guidelines are the only published guidelines which include a discussion of this topic, but due to the high mortality rate (reaching 58-80%) for non-occlusive mesenteric ischemia after nutrient administration,[52,53] we recommend suspending EN for patients with unstable hemodynamics.

Critically ill patients may develop non-occlusive bowel ischemia and non-occlusive mesenteric ischemia (NOMI), and it is possible that the risk for developing these conditions is elevated by EN. Careful attention should be paid when administering EN. In addition, when resuscitation becomes necessary such as the need to increase the

volume of infusions or catecholamines, reduction or suspension of EN should be considered.

Intestinal blood flow is reduced in patients with unstable hemodynamics. If EN is administered in such a state, oxygen consumption in the gastrointestinal tract rises,[54] and intestinal blood flow increases. However, if there is low cardiac output or poor blood flow, it is difficult for the intestinal blood flow to rise to meet the demand, and as a result, blood pressure drops, or bowel ischemia/necrosis. A high mortality rate of 58-80% has been reported for bowel ischemia.[53,55)] However, a previous study has reported that 60% of patients who develop ischemic enteritis were not being administered catecholamines, and had normal blood pressure,[56)] and so it is difficult to predict the occurrence of this condition. It is generally thought that catecholamines reduce intestinal blood flow in a dose-dependent manner,[54,57)] but the threshold dose for elevated risk of bowel ischemia and that for safe EN administration are unknown. For these reasons, it is considered preferable to start EN at a low, continuous dose of 10-20 mL/h in cases of circulatory insufficiency, and then gradually increase the dose while monitoring the patient's condition.

The following risk factors are conceivable. Case series studies have indicated that the incidence of bowel ischemia is 0.29-1.14%[58, 59)] in critically ill patients with post-pyloric feeding who are administered catecholamines; this incidence rate is thought to be higher than that with gastric nutrition. However, in a report in which gastric EN was administered to approximately 95% of subjects, the rate of bowel perforation was reported to be 0.9%;[47)] in this study, all three subjects who experienced bowel

perforation were administered gastric EN, demonstrating that that bowel ischemia may occur even with gastric EN. In addition, postoperative, trauma, and burn patients are considered to have high risk of bowel ischemia.[55,58,59)]

It is believed that high osmotic pressure or nutrients rich in dietary fiber further elevate blood flow in the gastrointestinal tract, and may lead to elevated risk of bowel ischemia. However, there are no RCTs supporting this view. Symptoms of bowel ischemia include a reduction in blood pressure after initiating EN administration, abdominal distension, increase in gastric residue, increased reflux from the gastric tube, decreased stool, decreased intestinal peristalsis, and increased metabolic acidosis. If these symptoms arise, a careful inspection for suspected bowel ischemia is indicated.[60)] However, it has been noted that 20-30% of bowel ischemia patients do not exhibit significant findings in diagnostic imaging,[61)] and so the diagnosis of this bowel condition is considered extremely difficult. Thus, constant caution is necessary during EN in critically ill patients.

B. Enteral nutrition

### 3. Selection of feeding tube position and method of inserting duodenal tubes

CQ3—1

For EN, should administration be performed at postpyloric rather than gastric?

A3—1.

It is suggested that post-pyloric EN be considered for patients at risk of aspiration (2C).

(Drafting method A)

(See Chapter 2, D—CQ4)

Commentary

The clinical data on the advantages of post-pyloric administration have yielded diverse results.[62-65] Meta-analyses conducted by Dhaliwal et al.,[66] Zhang et al.,[67] Jiyong et al.,[68] and Alhazzani et al.[69] have found a reduction in pneumonia and an increase in the volume of nutrition administered as a result of postpyloric feeding. Nevertheless, there was no effect on mortality. We performed a meta-analysis additionally, but found no difference in mortality with postpyloric feeding (odds ratio: 1.04; 95% confidence interval (CI): 0.86-1.26; $I^2$=0%; P=0.67); additionally, the incidence of pneumonia was significantly reduced with post-pyloric nutrition (odds ratio: 0.71; 95% CI: 0.0.58-0.86; $I^2$=0%; P<0.01).

Based on these results, postpyloric feeding is recommended at facilities that have mastered feeding tube placement at postpyloric; however, it has been noted that

insistence on duodenal tube insertion delays the initiation of EN,[62] and so prioritization of early initiation of EN rather than postpyloric administration should be considered.

A previous study has noted a difference in the effects of postpyloric feeding on the severity of the patient's condition,[70] but the results have not been consistent. Based on the above, it is difficult to indicate clear criteria for postpyloric feeding at this time. However, it is suggested to consider postpyloric feeding in patients with an elevated risk of aspiration, such as in critically ill patients who are administered sedatives or muscle relaxants, and in those who are incapable of lifting their heads and are observed to have a high GRV.

B. Enteral nutrition

### 3. Selection of feeding tube placement position and method of inserting duodenal tubes

CQ3—2

Is there the recommendable method for postpyloric feeding tube placement?

A3—2.

Endoscopic and fluoroscopic postpyloric feeding tube insertion are both effective, and so it is suggested that the method routinely used at each facility be implemented. While either method for guiding placement may be selected, placement using a small diameter endoscope has a shorter insertion time. Thus, the use of a small diameter endoscope suggested.

The gastric insufflation insertion technique is suggested for performing blind placements in adults (2D). The use of a prokinetic agent is suggested when there has been a reduction in gastric peristalsis (2D). It is suggested that prokinetics should not be used in children (2D). (Drafting method G)

*There are no reports evaluating clinically important outcomes, so a structured abstract has not been drafted.

Commentary

Postpyloric feeding tubes have been traditionally inserted using a fluoroscopy or using an endoscope. Both methods have been reported to be highly effective. However, there are often limitations on transferring critically ill patients to the radiographic suite

for postpyloric tube insertion, and an endoscopic procedure may not be immediately feasible in some facilities. Thus, blind insertion methods that can be performed at the bedside have been developed. This section investigates the advantages and disadvantages of these methods. The standard insertion method indicated is to attempt insertion blindly without using drugs or the use of the air insufflation method.

Postpyloric feeding tube insertion using a fluoroscopy and an endoscope reportedly have high success rates of at least 90%.[71,72] In studies comparing the two methods, there has been no difference in the rate of successful insertion, and the insertion time has been reported to be equivalent, or to be significantly shorter in the endoscope group.

With an endoscope, it has been reported that the method of placing a guide wire and then inserting a postpyloric tube along this guide wire and the method of placement using a clip have been reported to have superior effectiveness than do methods that do not use a guide wire a clip.

In addition, methods that do not require specialized equipment such as those required for a fluoroscopy or endoscopes, have also been reported. For postpyloric feeding tube insertion, administering prokinetics agent such as erythromycin or metoclopramide, blind insertion while filling the stomach with air, and an insertion method combining both are known, and several studies comparing these methods have been conducted. However, the background characteristics and results of these studies are diverse, and high-quality studies pertaining to this topic are lacking. One systematic review has been published, which includes a pairwise meta—analysis of 14 studies,[73] and reports that gastric prokinetic agents improve the success rate of feeding tube insertion in adults

(odds ratio: 2.263; 95% CI: 1.140-4.490; P=0.02). In addition, the method of injecting air is also reported to increase this success rate (odds ratio: 3.462; 95% CI: 1.63 to 7.346; P=0.001). However, prokinetic agents show low efficacy in patients without a reduction in gastric peristalsis. The effectiveness of prokinetics agents in children is also known to be low.

Diverse studies pertaining to this topic have been published. Among three studies that have compared the efficacy of prokinetic agents with standard insertion methods in critically ill adult patients, [74,75] two showed that the postpyloric insertion success rate was significantly higher in the group administered prokinetics. In addition, one published report has compared air injection to standard insertion methods, and has shown that the air injection method was more effective than were the standard insertion methods. Two other studies have compared prokinetics to air injection, and both these studies have reported a significantly higher success rate using the air injection method. Several studies of non-critical patients have compared patients receiving prokinetics with a placebo group or a non-intervention group; one such study found a significantly higher success rate in the prokinetics group, while two others did not find that the prokinetics were effective in improving the success rates of tube insertion[76,77].

In two studies that have compared the air injection and the standard insertion methods in critically ill pediatric patients, a higher success rate in the air injection group was reported. However, only one of these studies found a statistically significant difference in the success rate. A different study comparing a prokinetics group with a standard

group did not find any difference in success rates of tube insertion. Based on the above, the use of prokinetics is not recommended for pediatric patients.

With regards to complications, it has been reported that insertion into the stomach, the duodenum, and insertion further distally resulted in a 3.2% incidence of endotracheal malpositioning, a 1.2% incidence of pneumothorax, and a 0.5% incidence of mortality.[78] In contrast, another report has indicated that as a countermeasure, a protocol of ruling out endotracheal insertion by using plain chest radiography at the stage of 35 cm insertion reduced the rate of endotracheal malpositioning from 27% to 3% and that of pneumothorax from 0.38% to 0.09%.[79] Thus, caution is recommended during blind insertion.

Based on the above, the use of air injection and prokinetics is suggested for adult patients when performing blind insertion, but it is also suggested that prokinetics should not be used for pediatric patients.

B. Enteral nutrition

## 4. Target of energy for EN

CQ4

What is the optimum target of energy to be supplied by EN early after ICU admission?

A4—1.

In patients without nutritional risks prior to becoming critically ill, it is suggested that the amount of energy equivalent to that expended during the initial week should not be set as the energy supply target.

An energy amount equivalent to approximately 1/4 the energy expenditure or that of about 500 kcal/day have been proposed as optimal energy targets by two studies, but we cannot make recommendation about energy target with these studies (unknown field).

A4—2.

The optimum energy to provide is unknown for patients with a nutritional risk prior to fall in critically ill condition during the initial week.

However, it is necessary to supply an amount that prevents the caloric deficit from becoming too large (unknown field).

Commentary

**Definition of terms**

In this guideline, the following terminology has been used.

Underfeeding: includes 1) and 2) below.

**1) Low-volume EN**

This is also known as trophic feeding. Providing of low level of infusion of EN on the order of 1/4 of the energy expenditure level or about <500 kcal/day (about 20 kcal/h) with the objectives of maintaining the intestinal mucosa and sustaining immune function.[28,29)]

**2) Modestly restricted energy feeding**

This is also known as permissive underfeeding or hypofeeding. In order to avoid exacerbating oxidative stress resulting from overfeeding, the amount supplied is modestly less than the energy expenditure level. The goal is approximately 60-70% of the roughly estimated energy expenditure.

Fullfeeding: includes 3) and 4) below (the recommendation for this type of feeding depends on the study being discussed).

**3) Standard energy feeding**

This method involves starting from low-volume continuous feeding and ultimately targeting the supply of 100% of the energy expended.

**4) Expended energy feeding**

This method specifies starting with the supply of 100% of the energy expended, and then reducing the volume when symptoms of intolerance such as an increase in GRV occur. The goal is to avoid exacerbating the prognosis by minimizing the caloric deficit to the greatest extent possible.

**(1) Studies on underfeeding**

The only studies recommending underfeeding among the relevant RCTs are the Rice (EDEN trial)[28,29] and the Arabi et al., studies.[27,80] In addition, several large-scale observational studies have reported results that contradict the findings from the above mentioned studies. Thus, the available data is insufficient to make a clear recommendation about underfeeding.

**(1-1) Studies on low-volume EN at approximately 1/4 of the energy expenditure level or at 500 kcal/day**

In the EDEN trial,[28] the study of ARDS showed that compared to a group that was administered 1,300 kcal/day aiming for the target amount (standard energy feeding group), a group that was provided low-volume EN of approximately 500 kcal/day (approximately 20 kcal/h) for six days had a reduction in gastrointestinal intolerance and no effect on mortality, duration of hospitalization, days in ICU, duration of artificial ventilation, or in renal failure-free days.

However, for the following reasons, it is not possible to recommend low-volume EN based on this study. 1) While the BMI of the subjects of the above mentioned study was high at approximately 30, a previous observational study has indicated that the amount of energy supplied did not correlate with outcomes in a group of subjects with BMIs in the range of 25-35.[81] 2) There was no improvement in mortality in the EDEN trial. 3) The only benefit was a reduction in gastrointestinal intolerance. 4) Despite lack of differences in physical or psychological function between the two groups,[82] there was a significantly higher rate of admission to rehabilitation facilities within a one-year period

in the low-volume EN group (57/259 patients (23%) vs. 30/228 patients (14%); P=0.01), and so it is possible that the functional prognosis after one year in the standard energy feeding group was favorable.[83)]

**(1-2) Studies on a Modestly restricted energy feeding in the order of 60-70% of the energy expended**

In a study by Arabi et al.[89)] in 2011 on subjects requiring artificial ventilation, the in-hospital mortality rate was lower in the group receiving 60% of the final target amount of energy compared to the group receiving 100% of the final target amount of energy. In this study, the subject BMIs were high at approximately 28-33, while the average age of the patients was low, at approximately 50 - 52 years. In contrast, in a study conducted in 2015 by Arabi et al.,[80)] a group undergoing modest energy restriction for 14 days at multiple facilities (targeting 40-60% of the resting energy expenditure [REE]) was compared to a standard energy feeding group (targeting 70-100% of the REE). The study found no difference in mortality rates between the two groups. However, the probability of requiring renal replacement therapy was 7.1% in the Modestly restricted energy feeding group and was 11.4% in the standard energy feeding group (relative risk of 0.63 and 95% CI of 0.40-0.98); thus, the risk of requiring renal replacement was significantly reduced in the Modestly restricted energy feeding group. In this study as well, the average age was 51 and the average BMI was 29, so the subjects were young and had a high BMI.

**(2) Comparing a standard energy feeding group to a group supplied an amount corresponding to the amount of energy expenditure**

Among head trauma patients,[84] an improvement in functional outcomes and a reduced length of hospital stay were observed in an expended energy feeding group in which the amount of energy supplied was greater, compared to those of a standard energy feeding group. However, a study with critically ill patients[85] showed that in a standard energy feeding group, despite a caloric deficit in the order of 2,000-3,000 kcal during the intervention period, no negative impact was seen in outcomes such as mortality, duration of hospitalization, days in ICU, and duration of artificial ventilation compared to a expended energy feeding group.

**(3) Meta-analysis of studies on the amount of energy supply from EN**

Our committee performed a meta-analysis of mortality, pneumonia incidence and all infections in patients receiving EN. This meta-analysis included the EDEN trial,[28] EDEN phase 2 trial (two-facility),[29] and the studies by Arabi et al. (published in 2011[27] and 2015[80]), Taylor et al.,[84] and Desachy et al.[85] for studying mortality, the EDEN trial, EDEN phase 2 trial (two-facility), and studies by Arabi et al. (2015) and Taylor et al. for studying pneumonia, and the EDEN phase 2 trial (two-facility), and studies by Arabi et al. (2015), and Taylor et al., for studying all infections. In addition, studies by Arabi et al.[27] and Desachy et al. were also used to investigate duration of hospitalization and days in ICU, and the EDEN phase 2 trial (two-facility) and the study by Arabi et al. (2011) to investigate days on artificial ventilation.

Compared to the fullfeeding group, the underfeeding group exhibited no significant difference in mortality (odds ratio: 0.94; 95% CI 0.83-1.07; $I^2$=0%; P=0.36), incidence of pneumonia (odds ratio: 1.04; 95% CI: 0.81-1.33; $I^2$=0%, P=0.92), days in ICU (odds ratio: -1.78; 95% CI: -4.42-0.86; $I^2$=3.9%, P=0.19), or duration of artificial ventilation (odds ratio: -1.04; 95% CI: -3.29-1.20; $I^2$=46.8%, P=0.36). In addition, an analysis of the rate of infection suggested the presence of heterogeneity (odds ratio: 1.08; 95% CI: 0.83-1.41; $I^2$=64%, P=0.57). When the analysis was repeated excluding the study by Taylor et al., the heterogeneity was no longer observed but there was no significant difference between study groups (odds ratio: 0.95; 95% CI: 0.81-1.11; $I^2$=0%, P=0.99). In addition, a meta-analysis was performed on the need for renal replacement therapy using the studies by Arabi et al. from 2011 and 2015. The results of the analysis showed that the probability of requiring renal replacement therapy was lower in the group supplied a modestly restricted amount of energy (odds ratio: 0.64; 95% CI 0.45-0.94; $I^2$=0; P=0.01).

In addition, a meta-analysis was performed with the results reported by Desachy et al., Taylor et al., and Arabi et al. (2011 and 2015), and a comparison was made between a modestly restricted energy feeding group and an expended energy feeding group. There was no difference in mortality between the two study groups (odds ratio: 0.87; 95% CI: 0.73-1.04; $I^2$=5.11, P=0.12). In order to restrict the meta-analysis to include only data from adults, the study by Taylor et al. (which included subjects aged 10 and older) was excluded. There was no effect of exclusion of the study by Taylor et al., and

the results showed that there was no difference in mortality rates between the study groups (odds ratio: 0.86; 95% CI: 0.71-1.04; $I^2$=13.8, P=0.11).

**The results of observational studies**

In contrast to RCTs, a prospective observational study[86)] showed that outcomes were improved in sepsis patients by supplying protein and energy at amounts close to the target supply amount for each patient as determined at each facility. A study conducted among the subjects of the International Nutrition Survey at ICUs conducted by Heyland et al. included a secondary analysis of subjects with a diagnosis of sepsis, remaining in an ICU for at least three days, and supplied energy solely enterally. Patients (n=2,270) with an average age of 61 years and an average BMI of 27.6 were included. In this study, an increase in energy supply by 1000 kcal/day (for example comparing an average energy supply of 500 kcal/day to 1,500 kcal day) was shown to reduce the 60-day mortality rate with an odds ratio of 0.61 (95% CI: 0.48-0.77; P<0.001). Though this study included a large number of subjects, it was not a prospective, randomized study, and thus, its impact on the present analysis is low; the findings of the study should nevertheless be taken into consideration.

The Conclusion

Based on the above, despite contradictory study results, it is conceivable from the results of RCTs and these meta-analyses, that in the group of patients with a favorable nutritional state prior to becoming critically ill, supplying an amount of energy that did not meet 100% of the energy expenditure for several days from ICU admission did not negatively impact mortality or the risk of infection, and did reduce gastrointestinal

intolerance. Supplying 33-66% of the energy target has possibility to reduce the probability of requiring renal replacement therapy compared to that when supplying 90-100% of the energy target. As a result, supplementing the entirety of energy expenditures cannot be recommended at the present moment for critically ill patients who had a favorable nutritional state prior to (such as a BMI of at least 25).

However, the optimal duration of underfeeding is unknown. This period was six days in the EDEN trial[29] and was 14 days in the 2015 study by Arabi et al.[80].

C. Parenteral nutrition (PN)

When drafting “C. Parenteral nutrition” in these guidelines, the discussion in the guideline drafting committee concluded that the following three articles[30-32] should be consulted when producing the recommendations for sections 1 to 4 under “Parenteral nutrition.”

The summary and characteristics of the three studies are noted below.

**(1) Early PN Trial[32]**

This report was published after the EPaNIC Trial. The intervention method was PN supply to patients relatively contraindicated for tube feeding in the early postoperative period. The patient population included a relatively well-balanced combination of internal medicine and surgical cases, and entry period is also 8 to 9 days, which are similar to the typical situation in most Japanese ICUs. PN included the three main nutrients from the beginning of the intervention. Once EN supply reached at least 475 kcal, PN was discontinued. The intervention was found to result in a significant reduction in artificial ventilator use time, duration of thrombocytopenia, and amount of muscle strength reduction/fat loss. Outcomes did not worsen when PN was initiated promptly. This study was assigned an evidence level of quality A.

**(2) EPaNIC Trial[30)]**

The North American (US and Canada) guidelines differ from the European guidelines in the recommended timing to start PN when EN is insufficient (North America: do not administer for the first week [late PN], Europe: start administration within two days when sufficient energy consumption is not possible [early PN]). The study under discussion was performed to resolve this discrepancy. The EPaNIC trial was a multi-center randomized control study conducted at seven facilities with 4,640 patients admitted to an ICU with a nutrition risk screening (NRS) score of at least 3 (excluding patients with a BMI under 18). When EN was supplied to the extent possible with a target dose set using a prediction formula for the ideal target amount of energy supply per unit of body weight (men aged under 60 years: 36 kcal/kg/day; women aged under 60 years: 30 kcal/kg/day; men aged 60 years and older: 30 kcal/kg/day; women aged 60 years and older: 24 kcal/kg/day), a comparison was made between a group that was started on PN within 48 hours to supplement the shortfall from the target energy dose (early group) and a group that was started on PN on the 8th day or later, with only vitamins and trace elements being provided intravenously during the initial seven day period (late group). Most of the subjects were cardiac surgery patients who stayed in the ICU for three to four days postoperatively. The ICU stay was shorter than that in the other two studies (eight and thirteen days in the other two studies), probably because the study was focused on postoperative ICU patients. The nutrient composition for PN was a 20% glucose solution alone for the initial two-day period in the early group, and

subsequent administration with a total parenteral nutrition (TPN) preparation containing the three major nutrients. In addition, this was the only study to use intensive insulin therapy to manage blood glucose levels, which is not currently recommended. The results of this study showed that there was no difference in mortality rates between the two study groups, but the early PN group was found to have an increased incidence of new infections, a longer duration of artificial ventilation, and a greater number of days spent in the ICU. In addition, similar to that in the early PN group, increased infection frequency and ICU residence duration were also observed in 517 patients who could not wait until the seventh day for PN administration since early EN was contraindicated for surgical reasons. Since this study focused on postoperative ICU patients, its evidence level was designated as ranging from quality A (corresponding to a RCT) to the next lower level of quality B.

**(3) SPN Trial[31)]**

The intervention method used in this study included administration of 100% of the necessary energy on the fourth and following days in combination with PN. Compared to the previous two reports, this study was conducted on a smaller scale. In addition, the study period for the primary outcome of infection rate was set at the 9th-28th day following ICU admission, and the intervention group (full group, who were supplied a full calorie dose using supplementary PN for five days following the fourth day) were found to have a significant decrease in the outcome parameter. However, the study

period for infection rate should conventionally start upon ICU admission, and when this initiation time was used for the analysis, there was no significant difference in the outcome between the two study groups. In addition, the EN-only group (controls) had received approximately 20 kcal/kg/day by the third day. This is nearly identical to the value used as the standard for discontinuing PN in the Early PN Trial and the EPaNIC Trial. The energy supplementation rate from the fourth through eighth day was 103% in the full group and was 77% in the EN-only group. Taking into consideration the number of subjects and the study period used for determining the infection rate, the evidence level of this study was designated as ranging from quality A (corresponding to a RCT) to quality C (two levels lower than that of a RCT).

The subjects of all three studies had a BMI of approximately 28. This differs from the BMI distribution of ICU patients in Japan, and so caution is needed while applying the results as cited above.

C. Parenteral nutrition

## 1. Indications for PN

CQ1

Among critically ill patients, who should receive PN?

A1.

Among patients without malnutrition prior to becoming critically ill, if at least 20 kcal/h can be administered via EN for the first week, then it is suggested that PN with the objective of reaching the target amount not be administered (2B). (Drafting method B)

Commentary

At present, research results pertaining to this issue are contradictory and it is difficult to present a definitive recommendation for this CQ. Thus, for the minimum amount of energy supply via EN, we first consulted the standard values used for discontinuing PN intervention in the Early PN Trial.[32)]In this trial, PN was discontinued when the amount of enteral (oral) nutrition reached at least 475 kcal from the third day onwards in the ICU. In addition to the three studies mentioned above, the EDEN study[29)] (n=1000; age: 52 years; BMI: 30; internal medicine patients: 60%), which investigated the required amount of initial EN energy to be supplied to ARDS patients, was also consulted. The EDEN study was limited to EN, but the primary clinical outcomes (duration of artificial respiration, 60-day mortality rate, incidence of infection) in the energy restriction (trophic) group (at least 400kcal/day, the upper limit is 25% of the required energy

amount) did not differ significantly from those in the full consumption group (sat least 1,300kcal/day, the upper limit is 80% of the required energy amount).

Based on the above, for the first week after an invasive experience, it is suggested that PN not be administered to patients being continuously administered an average of at least 20 kcal/h of EN. In other words, during the first week, patients whose energy supply via EN is less than an average of 20 kcal/h may be administered PN with the objective of reaching the target value. There are no studies on the use of PN when intermittently administering EN.

C. Parenteral nutrition

## 2. Timing for initiating PN

CQ2

When should PN be initiated?

A2.

The appropriate time to initiate PN in patents whose energy supply via continuous EN is less than an average of 20 kcal/h is unclear.

(unknown field). (Drafting method B)

Commentary

Stress hormones (catecholamines, glucagon, growth hormone, cortisol, and cytokines) produced in response to an invasive experience cause hypermetabolism, causing endogenous energy to be consumed. This involves the mobilization and supply of energy from the storage sugar glycogen, the body fat, and body protein stores. However, the amount of glycogen stored in the liver yields approximately 400 kcal, and is depleted within two days (glycogen stored in muscle tissue is only consumed within the muscles)[87]. After depletion, in order to preserve body protein and burn endogenous fat, oxaloacetic acid is required in the tricarboxylic (TCA) cycle,[88] and so supplying a minimum of 400-600 kcal/day (100-150 g/day of glucose) can suppress consumption of glycogenic amino acids (which constitute 30% of body protein).[88] In anticipation of this effect, administration of 100-150 g/day of glucose is required for invasive procedures.

The purpose of intravenous nutrition in the early stage of invasion is to avoid adverse effects due to insufficient energy intake while avoiding harmful overfeeding.[81] The following information from the three studies described above should be consulted for this CQ.

A subgroup analysis of 517 patients participating in the EPaNIC Trial for whom early EN could not be administered for surgical reasons, was performed.[30] The late PN group had a significantly lower incidence of infection than did the early PN group (Late vs. Early: 29.9% vs, 40.2%; P=0.01), while the fraction of early discharge from the ICU was higher in the late PN group (odds ratio: 1.20; P=0.05). In the late PN group, 100 kcal of glucose was administered on the first day and 200 kcal on the second day, followed by continuing administration of a 5% glucose solution at the same volume as in the early PN group. Consequently, during the initial week for postoperative patients spending approximately 3 days in the ICU, the following was suggested: administering approximately 200 kcal intravenously is preferable to administering glucose at 400 kcal on the first day and 800 kcal on the second day, and then combining EN and PN from the third day in order to administer the target amount of energy.

In the Early PN Trial,[32] nutrition therapy administering PN including the three major nutrients from the first day of ICU admission and reaching the target amount on the third day was indicated. This protocol was observed to cause a slight decrease in the duration of artificial ventilation compared to that using the standard nutrition protocol.

The EPaNIC Trial and the Early PN Trial differed in subject characteristics, the day to start administering the three major nutrients, and the target amount of energy, and

these differences may have caused the differences in the observed results. In addition, PN was discontinued when EN exceeded 475 kcal in the Early PN Trial, whereas in the EPaNIC Trial, it was discontinued after EN supply reached 80% of the target amount.

In the SPN Trial,[31] approximately 1000 kcal was already supplied via EN by the third day, and so it is not appropriate to consider this trial for discussing the current CQ.

In patients with a continuous EN energy supply of less than 475 kcal/day (approximately 20 kcal/h by continuous administration), the EPaNIC trial indicated that early PN worsened outcomes, while the Early PN Trial indicated that EN supply with this protocol improved outcomes. Thus, at the present time, it is not possible to make an evidence-based recommendation on the optimum timing to start PN.

The optimal time to start PN should be decided on an individual basis for each patient, based on clinical judgment and a consideration of the studies described above. The details of methods, subject characteristics, day of initiating administration of the three major nutrients, target energy administration amount, and standards for when to discontinue PN should be considered. In addition, there are no studies on the optimum timing for initiating PN in subjects receiving intermittent EN.

C. Parenteral nutrition

### 3. Target amount of energy supply for PN

CQ3

What is the amount of energy to be supplied via PN?

A3.

The optimum amount of energy to be supplied via PN in the acute phase is unclear (unknown field). (Drafting method B)

Commentary

In all three studies discussed above, the initial amount of energy supply was set using the Harris—Benedict calculation formula or using a simple calculation formula (however in the SPN trial, this value was revised based on the results of indirect calorimetry), but there has been no investigation on the efficacy of each of the methods used.

In the Early PN Trial,[32)] PN included the three major nutrients and was administered to attain the set target value by the third day in the intervention group; a clinical effect was obtained in this trial. Thus, these results indicate that initiating PN with all the three major nutrients from the first day of ICU admission, and subsequently attaining the target amount of energy from the third day onwards using EN+PN may be an effective nutrition management strategy. However, additional PN was discontinued when at least

475 kcal of EN was supplied. Therefore, from this intervention method, the favorable amount of PN dose during that period can not be guided.

In the EPaNIC Trial,[30] the intervention group (early PN) was supplemented with PN to attain 100% of the target amount of energy from the third through the seventh days. There was no difference in mortality due to the different PN administration protocols, but various other outcomes were poor in the intervention group. In addition, subgroup analysis of 517 subjects who could not be administered early EN for surgical reasons among the subjects of the EPaNIC Trial indicated that compared to the early PN group, the late PN group that did not receive PN for seven days had a significantly lower frequency of infection, and a higher rate of early ICU discharge (as explained in CQ2). Also, the late PN group was continuously supplemented a 5% glucose infusion from the first day with a quantity of energy at approximately 300+ kcal/day.

In addition, in the SPN Trial,[31] the intervention (Full) group was supplied PN containing the three major nutrients to attain the target value for the five-day period from the third through the seventh day, resulting in a decrease (from the ninth through the 28th day) or no change (from the first through the 28th day) in infection rates; therefore, PN supplementation was not found to be harmful in this trial. However, both groups were administered approximately 1000 kcal/day of EN by the third day, and so according to the recommendation in CQ1, PN was not required in the SPN Trial. Thus, it is difficult to estimate the amount of energy to be supplied as PN based on the results of the SPN Trial.

Based on the above considerations, the amount of energy to be supplied by PN remains as yet unclear.

The results of the three above mentioned studies do not agree on the maximum amount of energy to be supplied as PN. However, taking into consideration the adverse effects in the EPaNIC trial, PN should be restricted to patients who are at high nutritional risk, and it is considered appropriate to avoid administering 100% of the set target value even in cases where PN is supplied with the purpose of supplementing the shortfall in EN.

At present, we recommend that the amount of energy to be supplied in the acute period should be determined based on the pathophysiology and nutritional state of each individual patient, and the benefits and risks of the delivering that target energy level.

C. Parenteral nutrition

**4. Composition of PN**

CQ4

What should the composition of PN be?

A4.

When supplying PN, it is suggested that it should not consist solely of glucose infusions (1C). (Drafting method E—3).

(Concerning amino acids and fat, see Chapter 2, A—4, E—1 to —3, and F—4 to —6.)

Commentary

Based on a comparison of the results of the Early PN Trial, EPaNIC, and the SPN Trial, at the very least, PN using glucose alone cannot be recommended.

C. Parenteral nutrition

## 5. Vitamins, trace elements, selenium, refeeding syndrome

CQ5

Should vitamins and trace elements be administered to intensive care patients who are severely ill?

A5.

It is recommended that the normal quantity of multivitamins and trace element preparations be administered to intensive care patients who are severely ill, but there is not enough data to determine recommended dosage (1B). (Drafting method C)

For patients anticipated to develop refeeding syndrome, it is recommended that serum phosphorus, magnesium, and potassium be monitored (1c). (Drafting method H)

Commentary

In general, when administering PN for more than a certain period, multivitamins and trace elements should necessarily be administered. Intensive care patients in critical conditions are known to require greater quantities of multivitamins and trace elements than are healthy individuals. Numerous clinical studies of supplementation with higher than normal amounts of these nutrients have been conducted, but the data are insufficient to determine a recommended amount to administer.[89)] Caution is needed as commercial trace element preparations for central venous administration in Japan do not contain selenium. A selenium agent for intravenous administration is also not

commercially available, and so parenteral administration requires the production of an agent (sodium selenite) at the facility (IRB approval is also required). For these reasons, selenium is not yet commonly administered parenterally.

When restarting supply of nutrients to patients in a state of starvation or for whom nutrition has been suspended, it is necessary to be alert for symptoms of the refeeding syndrome.[90-92)] Attention is needed for patients with chronic malnutrition, patients with a sudden decrease in body weight of at least 10%, and for patients who have been administered very little nutrition for 7-10 days. Early detection by monitoring serum phosphorus, magnesium, and potassium levels is important in patients requiring intensive care.

C. Parenteral nutrition

## 6. Administration route for PN (central vein, peripheral vein)

CQ6

When should central venous access be used for PN?

A6.

A central venous route is recommended for infusions with an osmotic pressure ratio of 3 or more (1D). (Drafting method H)

(Addendum) The ratio of osmotic pressure of fat emulsions, amino acid preparations, and glucose solutions under 15% is less than 3, and can be administered via a peripheral venous route. In addition, if the ratio of osmotic pressure of a dilute infusion solution for vitamins or trace elements is less than 3, administration is also possible via a peripheral route.

Commentary

When attaining the target quantity of nutrients using PN, the ratio of osmotic pressure becomes higher if the glucose concentration of the nutrition infusion is raised (a 5% glucose solution is isotonic, i.e. the ratio of osmotic pressure is 1, i.e. 280 mOsml/L). If the ratio of osmotic pressure is ≥3, a central venous route should be used. Nutritional administration from the peripheral vein is aimed at reducing the negative energy balance by supplementing a certain proportion of the necessary energy amount, and a low osmotic infusion preparation (<850 mOsml/L; within approximately three times the

plasma osmotic pressure) is used. For example, caution is needed to ensure that the osmotic pressure ratio does not exceed 3 even when various electrolyte solutions are injected at the same time as a 10% glucose solution.

When supplementing vitamins, minerals, and trace elements, there are limitations to the peripheral route administration, depending on the ratio of osmotic pressure of the diluted infusion; however, either route is possible when the ratio of osmotic pressure is <3 (Table 2C—3).

D. Monitoring tolerance of EN

**1. Confirming intestinal motility**

CQ1

Should intestinal motility be confirmed as a condition for initiating EN?

A1.

It is recommended that intestinal motility confirmation should not be used as a condition for initiating EN.

Commentary

It has been reported that early EN can be safely initiated within 48 hours of ICU admission even if bowel sounds or the passage of stool/gas cannot be confirmed. However, the fact that most of such patients are postoperative patients must be taken into consideration. The presence of intestinal motility cannot serve as an evaluation criterion for the initiation of EN, since EN promotes intestinal motility in itself.

Abnormal gastrointestinal function caused by factors such as the disease, patient condition prior to disease onset, the mode of respiratory apparatus used, the drugs administered, and the metabolic state, is observed in 30-70% of patients admitted to the ICU.[93)] There are three causes of gastrointestinal dysfunction in ICU patients and in postoperative patients: 1) disruption of the barrier layer of mucous membrane, 2) decreased motility and atrophy of the mucus membrane, and 3) a reduction in gut-associated lymphoid tissue (GALT) volume. Bowel sounds, which are commonly used

as criteria for initiating EN, are the only signs used for evaluating intestinal motility, but they do not suggest intestinal integrity, function of intestinal barrier, or capability of nutrition absorption.

As long as the patient remains hemodynamically stable, it is safe and valid to administer EN for mild to moderate ileus[94] When initiating EN after stabilization of circulatory conditions and before auscultation of bowel sounds, the rate of achieving the target value within 72 hours is reported to exhibit a variation of 30-85%; however, Kozar et al.[95] have reported that using an EN protocol adapted to the situation at each facility resulted in achieving 70-85% of the target amount to administer.

D. Monitoring tolerance of EN

## 2. Method for monitoring for tolerance of EN

CQ2

How should tolerance (sustainability) of EN be monitored?

A2.

Patient tolerance of EN may be monitored through complaints of pain and/or a sensation of abdominal distension, physiological findings, passing of gas and stool, and abdominal X-ray images.

Inappropriate discontinuation of EN should be avoided.

EN should not be discontinued if the GRV is <500 mL in the absence of other signs of intolerance.

Fasting periods for diagnostic tests and treatment should be minimized to prevent inappropriate nutrition administration and prolonging of paralytic ileus.

The above guidelines are suggested (2C). (Drafting method A)

Commentary

Fasting and interruption of EN can exacerbate ileus. Of the reasons reported for suspending EN, 1/3 were related to patient intolerance of EN (of which only half could be considered to have true intolerance), 1/3 were related to diagnostic tests or treatment procedures, and the remainder were related to increases in GRV and tube replacement.[96)]

GRV is not reported to correlate well to incidence of pneumonia, measures of gastric emptying, or incidence of regurgitation and aspiration. Even if the cutoff value for the GRV is lowered, these complications cannot be prevented, and inappropriate interruption of EN may be caused, leading to a reduction in EN received.[84)] If the GRV is 200-500 mL, sufficient care must be taken to reduce the risk of aspiration (see Chapter 2, H-2 “Managing of GRV”). In the absence of other signs of intolerance, EN should not be discontinued as long as the GRV is less than 500 mL.[97)] In addition, the measurement interval for GRV has been different in each study (the most commonly reported method was confirmation by gastric aspiration every 4-6 hours), and there is no set standard for this parameter. Hence, the recommendation is to check GRV as needed. However, Reignier et al.[98)] have reported that there was no difference in the incidence of mortality and infectious complications in RCT comparing groups that were or were not monitored for GRV (<250 mL).

D. Monitoring tolerance of EN

## 3. Method for titrating EN

CQ3

How should the target amount of EN be titrated?

A3.

Using EN therapy protocol to increase the degree of the target amount is suggested (2C). (Drafting method A)

Commentary

It has been shown that the degree of achievement of the target dose administered increases by using the protocol operated by ICU staff such as nurses, with specific instructions; (1) setting the target rate of infusion, (2) the method for initiating earlier EN, (3) measuring GRV, (4) determining the frequency of tube flushing, (5) reducing/discontinuing nutrition supply, and (6) handling complications.[95,99,100)]

Early initiation of EN is important, but the protocol for titrated administration of a set amount is a matter for investigation. For actively increasing the dose (at least 80% of the target value), it is recommended that past reported protocols[28,29)] be consulted to produce a protocol suited to the situation at the facility. On the other hand, it has been shown that blindly administering the initial dose is harmful [101,102)]

D. Monitoring tolerance of EN

## 4. Aspiration related to EN

CQ4

What can be done to reduce the risk of aspiration during EN?

A4.

Patients administered EN should be assessed for risk of regurgitation and/or aspiration, and taken measures to reduce the risk is recommended if the patients are suspected of having such a risk (the recommendation levels and drafting methods are individually noted for A4-1. to A4-5).

Commentary

Aspiration is one of the most feared complications of EN. Predictive factors for patients with a high risk of aspiration include (1) use of a nasoenteric feeding tube, (2) use of an endotracheal intubation and artificial ventilation, (3) age > 70 years, (4) reduced level of conciousness, (5) insufficient nursing care, (6) hospitalization unit type (ICU vs. other units), (7) patient body positioning, (8) transport out of the ICU, (9) insufficient oral health, and (10) use of intermittent administration of EN[97),103)]. Pneumonia and bacterial colonization of the bronchi are more strongly correlated with aspiration of contaminated oropharyngeal secretions than regurgitation or aspiration of contaminated gastric contents. According to the Ventilator-Associated Pneumonia Prevention Bundle, 2010 Revised Edition,[103)] means of reducing the risk of aspiration

include thorough hand hygiene measures, avoiding frequent changes to the artificial ventilator circuit, appropriate sedation and analgesia (avoiding over-sedation), protocols for ventilator withdrawal, spontaneous breathing trials (SBTs), and avoiding the supine position.

D. Monitoring tolerance of EN

**4. Aspiration related to EN**

CQ4—1

What can be done to reduce the risk of aspiration during EN?

A4-1.

For all intubated patients receiving EN, elevating the head of the bed (upper body) by 30-45° is suggested (1C). (Drafting method A)

Commentary

According to a report by Drakulovic et al.,[104] elevating the head of the bed (upper body) by 30-45° decreased the incidence of aspiration pneumonia compared to positioning the bed in a supine position and a semi-recumbent position, by 23% and 5% respectively (P=0.018). A systematic review of three RCTs including the above mentioned report has been published.[105] Although 24-hour elevation of the head by 45° in patients connected to a ventilator did not exhibit a significant correlation with mortality or to the incidence of ventilator-associated pneumonia or pressure ulcers, the consensus expert opinion was to elevate the head by 20-45° (ideally at least 30°). Regardless of whether the patient is during EN administration, body positioning management based on raising the beds of critically ill patients is the least economically burdensome method of preventing aspiration[103,104] (see Chapter 2, H-3 “Body

positioning during EN administration”). Thorough body position management can be implemented through explicit physician instructions.[106)]

In light of the above, it is proposed that medical staff periodically monitor bed head position with elevation of the head by 30° as a general guideline.

D. Monitoring tolerance of EN

**4. Aspiration related to EN**

CQ4—2

What can be done to reduce the risk of aspiration during EN?

A4-2.

For patients at high risk for aspiration and patients exhibiting intolerance (difficulty in receiving EN), it is suggested that patients receiving intermittent EN is switched to continuous EN (2C). (Drafting method A)

Commentary

Low-quality randomized trials have reported that there was no difference in mortality, infection rate, and duration of hospitalization between continuous and intermittent EN administration, but continuous administration significantly accelerated the achievement of target quantity[107] and decreased frequency of diarrhea[107,108] (see Chapter 2, H-4 “Intermittent and continuous administration of EN”). Although continuous and intermittent EN administration were not compared, a different RCT[102] indicated that when EN aiming for a full dose via intermittent administration was initiated promptly, there was an increase in the risk of aspiration pneumonia compared to when it was initiated late (on the fifth day). During continuous administration, it is possible to minimize fluctuations in flow rate by using an EN pump.

D. Monitoring tolerance of EN

**4. Aspiration related to EN**

CQ4—3

What can be done to reduce the risk of aspiration during EN?

A4-3.

If possible, initiating treatment with prokinetic drugs (metoclopramide and erythromycin), or an antinarcotic agent (naloxone) is suggested for patients exhibiting intolerance to EN and for those who are at a high risk of aspiration (2D). (Drafting method A)

Commentary

Addition of prokinetic agents (metoclopramide and erythromycin) has been shown to improve gastric emptying ability and intolerance to EN, but very little to no effect on ICU patient outcomes has been reported.[109)] In addition, it is important to consider that extrapyramidal symptoms may occur as side effects of metoclopramide administration, and that administration of erythromycin for prokinesis is not covered under the national health insurance system in Japan.

Gastric administration of naloxone (used to antagonize the antispasmodic effect of narcotic analgesics) was found to significantly improve the rate of ventilator-associated pneumonia and decrease regurgitation from the gastric tube compared to a placebo; a tendency towards increased amount of EN administration was also observed in the

treatment group (there was no difference in mortality, duration of artificial ventilation, or ICU stay).[110)]

In Japan, based on the pharmaceutical effects and the experience of use with the objective of improving gastrointestinal motility, drugs like mosapride citrate and rikkunshito are routinely administered to promoted gastric secretion; drugs like prostaglandin (PG) $F_{2\alpha}$, daikenchuto, and sodium picosulfate are administered to promote colon peristalsis and defecation.

D. Monitoring tolerance of EN

## 4. Aspiration related to EN

CQ4—4

What can be done to reduce the risk of aspiration during EN?

A4-4.

Considering a switch to EN administration by a postpyloric route is suggested for patients at a high risk of aspiration and for patients exhibiting intolerance to gastric administration (2C). (Drafting method A).

(See Chapter 2, B—CQ3)

Commentary

It has been shown that altering the route of EN administration from the stomach to the small intestine reduces the incidence of regurgitation and aspiration.[111,112] Randomized trials[64,65,84] have reported a significant decrease in the incidence of pneumonia in patients receiving EN via the small intestine. Several randomized trials[113,114] have reported a significant reduction in ICU stay in a gastric administration group. A meta-analysis was performed by this committee, and no difference in mortality rate and a significant decrease in the incidence of aspiration pneumonia were found to result from using postpyloric administration.

A previous study[70] has reported that compared to gastric administration, intestinal (duodenal) administration improved the amount of EN and delayed gastric emptying

only in patients with more severe conditions; however, a different study[62] did not find an increase in amount of EN or a decrease in the incidence of aspiration pneumonia in patients receiving early intestinal EN, but reported an increase in mild gastric bleeding. Thus, based on relevant literature, routine intestinal administration is not indicated. Intestinal EN should be selected when necessary, as determined based on the degree of severity of disease and patient condition.

In addition, gastric administration is superior in ease of tube insertion and the possibility of early initiation. It has been noted that the initiation of EN may be delayed if insertion of a postpyloric tube is specified,[63] and in such cases, prioritizing prompt EN initiation using gastric administration should be considered. Switching to intestinal administration should be taken into consideration when there is vomiting, regurgitation from the gastric tube, and gastric residue caused by delayed gastric emptying (even if various countermeasures have been implemented for gastric administration); intestinal administration should also be considered for cases when a tube is placed in the small intestine during surgery.

D. Monitoring tolerance of EN

**4. Aspiration related to EN**

CQ4—5

What can be done to reduce the risk of aspiration during EN?

A4-5.

It is recommended that in order to reduce the risk of ventilator-associated pneumonia, mouthwash using chlorhexidine should not be performed at the concentrations used routinely in Japan (1C). (Drafting method F—1)

Commentary

It has been reported that effective mouthwash using chlorhexidine twice a day reduces nosocomial pneumonia and respiratory infections in patients following cardiac surgery.[115,116)] Two studies including oral care using chlorhexidine in a care bundle for ICU patients found a significant decrease in nosocomial respiratory infections.[117,118)]

The chlorhexidine used for oral cleansing is supplied as chlorhexidine gluconate. In western countries, it has been reported that a concentration of 0.12-0.2% of chlorhexidine is effective as a cleansing solution, whereas the concentrations used in Japan are 1/100 of the concentration used in western countries (no greater than 0.002%) (as of April 2015). It is thought that the concentrations used routinely in Japan are not effective against oral bacterial infections. In addition, care must be taken to differentiate between chlorhexidine gluconate used for mouthwash and chlorhexidine available as a

disinfectant (chlorhexidine alcohol). Chlorhexidine alcohol for disinfection is commercially available at a concentration of 2% in western countries and at 1% in Japan, and both these formulations are higher in strength than those of chlorhexidine gluconate solutions used for mouthwash.

Other means of reducing the risk of aspiration are reducing sedatives/analgesics to the extent possible, minimizing the amount of movement from the ICU for performing tests and treatments, and transfer to a unit with a lower patient/nurse ratio [97,119)]

D. Monitoring tolerance of EN

## 5. Response to the onset of diarrhea

CQ5

What should be done if diarrhea occurs?

A5.

It is recommended that a detailed evaluation of the causes be undertaken, and measures be taken based on the evaluation results (1D). (Drafting method F-1)

Commentary

Diarrhea is a common symptom in critically ill patients. Although there are no clear diagnostic criteria for diarrhea, parameters like defecation frequency (≥3-5 times/day) and defecation amount (≥200-300 g/day) are used. Diarrhea has been correlated with a negative energy balance. Strack van Schijndel et al.[120] have reported that a daily defecation mass of ≥250 g may be an indicator of malnutrition; Wierdsma et al.[121] have reported that regardless of the characteristics of the stool itself, the greater the amount of stool excreted, greater the nutrient loss; and that daily defecation of ≥ 350 g causes a high risk of an energy and protein deficit; thus, measuring the amount of defecation has been reported as useful. Malnutrition in critically ill patients is associated with reduced immune function, increased risk of infectious complications, and increased mortality, and so it is important in EN management to reduce the defecation amount to an extent and to alleviate any malnutrition.

Based on pathological characteristics, diarrhea has been classified as secretory, motility-related, exudative, and osmotic. Furthermore, since treatment methods differ based on the presence of infection, these categories have been further sub-divided into infected and non-infected types.

Compared to PN, EN can more favorably maintain the structure and function of the gastrointestinal mucosa, and so if diarrhea occurs during the implementation of EN despite attempts to suppress diarrhea, the following should be immediately evaluated: (1) overconsumption of high osmotic pressure drugs, (2) use of broad-spectrum antibiotics, (3) *C. difficile* infection or related diarrhea, and (4) other infection factors.

For enteral feeding-associated diarrhea, it has been reported that there are no differences in incidence caused by differences in administration route (gastric versus jejunal) [122,123] Among methods for EN administration, continuous administration using a pump has been reported a better prevention of diarrhea more effectively than did intermittent administration, but invalid after diarrhea occurs[108,124]). Composition of enteral formula including carbohydrate content, fat type, high osmolarity, and bacterial contamination is associated with increased incidence of diarrhea.

Caution is also needed for antibiotic-associated diarrhea. The use of antibiotics (including recent or current use), prolonged ICU stay, use of proton pump inhibitors, sex (more frequent in women), the severity of underlying disease, and EN (particularly post-pyloric administration) are risk factors for the highly incident diarrhea caused by *C. difficile*. The incidence of diarrhea differs by type of antibiotic as well, and a higher risk has been associated with use of quinolones or cephalosporins, and a lower risk has

been reported with the use of macrolides.[125)] Other risk factors for diarrhea are fever or hypothermia, the presence of infection foci, malnutrition, hypoalbuminemia, sepsis, multiple organ failure, use of open-type EN container, and total PN.

If diarrhea persists, increased mortality due to the associated malnutrition should be considered. Poor absorption of nutrients increases complications as well, and so supplementation using PN may also be necessary. Diarrhea is associated with hemodynamic instability due to reduced circulating blood volume, metabolic acidosis caused by the loss of electrolytes and bicarbonate ions from the large-scale secretion of digestive juices, and electrolyte imbalances in potassium, magnesium, and zinc. Moreover, contamination of surgical wounds and pressure ulcers have also been linked to diarrhea.

Common treatments for diarrhea include fluid administration, opioids, and anticholinergic drugs. Prevention of enteral feeding-associated diarrhea includes switching to continuous administration and altering the nutriment composition. Enteral formulas of low osmorolity and enriched dietary fibers are preferred. Insoluble dietary fiber is less effective in preventing diarrhea than is water-soluble fiber (see Chapter 2, E-4 “Dietary fiber (soluble and insoluble)”). Water-soluble fiber sources such as pectin and guar gum increase the viscosity of gastrointestinal contents, delay gastrointestinal flow of these contents. It has been reported that when enteral formulas enriched in dietary fiber were administered to critically ill patients with the objective of preventing diarrhea and improving defecation, the diarrhea prevention effect tended to be higher with pectin compared to that with a placebo.[126)] In contrast, in a previously published

meta-analysis[127] has been reported that no effect could be found from administering formula rich in dietary fiber. Similarly, sufficient evidence has not been gathered on the usefulness of pre-/pro-/symbiotics, which are said to maintain gut microflora (see Chapter 2, F-2 “Pre-/pro-/symbiotics”).

E. Specialized nutrients

## 1. Arginine

CQ1

May immunomodulating nutrients enriched with arginine be used for intensive care patients in a highly critical condition?

A1.

We suggest not using immunomodulating nutrients enriched with arginine for intensive care patients in a highly critical condition.

Commentary

Arginine plays a role in improving immune function, promoting protein synthesis, and accelerating wound healing, and is a substrate for nitric oxide (NO) production, which is important in microcirculatory regulation. However, excessive NO production risks excessive peripheral vasodilation and negatively impacts circulatory dynamics. In a meta-analysis of the literature, the use of an arginine-enriched nutriment in intensive care patients did not affect mortality or the rate of infection. The evaluation of the effect of arginine-enriched nutriment for sepsis in critically ill patients has not yielded conclusive results,[128-129)] and since there are multiple reports that such nutriment negatively impacts pathophysiological conditions, [130-131)] it is suggested that arginine-enriched nutriment not be used in critically ill patients.

E. Specialized nutrients

## 2. Glutamine

CQ2

What are the indications for administering glutamine-enriched EN?

A2—1.

It is suggested that administering glutamine-enriched EN is considered for burn and trauma patients (2B). (Drafting method A)

A2—2.

Avoiding the administration of glutamine-enriched EN is recommended for patients exhibiting shock and multiple organ failure (1A). (Drafting method F—1)

Commentary

In the gastrointestinal tract, glutamine is a nutrient used by intestinal epithelial cells, and maintains intestinal integrity. Glutamine enrichment of EN administered to burn patients in ICUs has been reported to significantly lower mortality,[132] though such an enrichment has been reported to not affect mortality of other intensive care patients.[133] It has also been reported that administration of glutamine-enriched nutrition significantly reduced the occurrence of pneumonia, bacteremia, and sepsis in trauma patients, and significantly reduced the incidence of wound infection in burn patients [134,135]

A large-scale clinical study (the REDOXS Study) has been performed using glutamine administration of approximately 50 g (parenteral administration of 0.35 g/ideal body weight in kg/day and enteral administration of 30 g/day) and administration of selenium and antioxidants.[136] The subjects included 1223 patients with multiple organ failure; when the groups administered and not administered glutamine were compared, the mortality was significantly elevated in the glutamine-administered group. However, the mortalities occurred in subjects with elevated serum glutamine levels prior to glutamine administration, and so avoiding the administration of glutamine is recommended for critically ill patients exhibiting shock and organ failure, and for trauma and burn patients.

E. Specialized nutrients

### 3. n—3 polyunsaturated fatty acids

CQ3—1

For ARDS patients, should the use of EN enriched with n-3 polyunsaturated fatty acids (EPA), gamma-linolenic acid, and antioxidants be considered?

A3—1.

Using EN enriched with n-3 polyunsaturated fatty acids (EPA), gamma-linolenic acid, and antioxidants for ARDS patients is suggested (2B). (Drafting method A)

Commentary

Seven overseas RCTs[29,137-142)] have reported the effectiveness of preparations containing n-3 polyunsaturated fatty acids on ARDS and acute lung injury (ALI) patients.

Four studies have compared nutriment enriched in n-3 polyunsaturated fatty acids (by including a 55% admixture of fat rich in n-3 polyunsaturated fatty acids [EPA]), and nutriment containing approximately 55% fat but composed primarily of n-6 fatty acids. It is to be noted that a fat content of 55% is relatively high compared to the fat content of nutriments routinely used in the ICU. According to a report by Gadek et al.,[137)] there was a significant reduction in days on ventilation management and days in the ICU in a group administered nutriment enriched in n-3 polyunsaturated fatty acids. In addition, a significant improvement in oxygenation ability was found on the fourth and seventh days, and the incidence of additional organ failure decreased significantly. According to

a report by Singer et al.,[138] although there was no significant difference between the two groups in terms of number of days in the ICU and the number of days under artificial ventilation management, the group supplied nutriment enriched in n-3 polyunsaturated fatty acids was found to have a significant improvement in oxygenation ability on the fourth and seventh days. Although there was a significant difference in survival on the 28th day, there was no difference in survival at a follow-up on the 90th day. According to a study by Pointes—Arruda et al.,[139] a group provided nutriment enriched in n-3 polyunsaturated fatty acids showed a significant reduction in days on artificial ventilation and days in the ICU. Oxygenation ability improved significantly on the 4th and 7th days, and there was a significant decrease in the incidence of new organ failure. There was a significant difference in survival rate at 28 days of follow-up. According to a study of ARDS patients in mixed surgical/internal medicine ICUs at two facilities in the US conducted by Elamin et al.,[140] a group supplied nutriment enriched with n-3 polyunsaturated fatty acids was found to have a significantly improved lung injury score on the first through the fourth days of ICU admission, a significant reduction in days in the ICU, and a significant decrease in the multiple organ dysfunction (MOD) score at the 28th day in the ICU.

Grau et al.[141] evaluated severe sepsis patients complicated by ALI or ARDS, and compared the frequency of organ failure and the incidence of nosocomial pneumonia in a group administered nutriment enriched with n-3 polyunsaturated fatty acids with that in a group that received a control nutriment (different from the control group nutriment in documents 170-173). No significant difference was found in the sequential organ

failure assessment score (SOFA score) (an organ failure indicator), the $PaO_2/F_IO_2$ ratio, and the duration of artificial ventilation, but the number of days in the ICU was significantly greater in the control group. Furthermore, the ARDS network in the US conducted a RCT using a nutriment enriched with n-3 polyunsaturated fatty acids and other similar nutriments, and surveyed the necessity for prompt EN and the need for various other nutriments. However, an interim analysis revealed that the mortality rate was significantly higher in the group receiving n-3- polyunsaturated fatty acids, and so the experiment was suspended (272 subjects remained in the intervention group, in contrast to the planned number of 1000 subjects).[29] Nevertheless, several issues were noted in the study: the enriched nutrients were administered as a bolus every 12 hours; the administration start timing for the 2×2 design followed a mixture of both early and late administration protocols; and the target caloric value for the initial six days for late EN was restricted to approximately 240-360 kcal/day and was subsequently raised to the target amount (25-35 kcal/kg). In 2014, a study[142] of patients requiring artificial ventilation management was conducted to compare a group (152 subjects) using a nutriment enriched in n-3 polyunsaturated fatty acids (with a different composition from what was used in prior articles [137-141]) with a control group (149 subjects) using a calorie and protein-matched nutriment without any enrichment. There was no significant difference in the incidence of new infection between groups. In addition, a sub-group analysis comparing internal medicine subgroups categorized based on nutriment supplied, the six-month mortality rate was significantly higher in the enriched nutriment subgroup. Also, not all the subjects of this study were ARDS patients.

There is no consensus about the effectiveness of nutriment enriched with n-3 polyunsaturated fatty acids, since there is evidence to support as well as to refute the usefulness of such enrichment. In addition, the nutriment used for the control group has not been a standard preparation across various studies. Thus, the overall recommendation level has been reduced by one level, and this committee suggests (2B) the use of an enteral nutriment enriched with n-3 polyunsaturated fatty acids (EPA), gamma-linolenic acid, and antioxidants (beta carotene, vitamin C, vitamin E, zinc, selenium) for ARDS patients.

[Note: Documents 1-7 are listed under CQ3－2 on page 81]

E. Specialized nutrients

### 3. n—3 polyunsaturated fatty acids

CQ3—2

Should the use of an enteral nutriment enriched in n-3 polyunsaturated fatty acids (EPA), gamma-linolenic acid, and antioxidants be considered for patients with sepsis/severe sepsis/septic shock?

A3—2.

For patients with sepsis/severe sepsis/septic shock, considering the use of an enteral nutriment enriched in n-3 polyunsaturated fatty acids (EPA), gamma-linolenic acid, and antioxidants is suggested (2B). (Drafting method A)

Commentary

Four RCTs have been reported on the use of enteral nutriment enriched in n-3 polyunsaturated fatty acids for sepsis/severe sepsis/septic shock patients. The first report[139)] found that a group using a nutriment enriched with n-3 polyunsaturated fatty acids showed a significant reduction in days of ventilator management and days in ICU compared to the control group (using a nutriment with a high fat content of 55%). Pulmonary oxygenation ability on the fourth and the seventh day, the incidence of organ failure, and the 28-day survival rate improved significantly in the group supplied with enriched nutriment. The second study[143)] was conducted with patients in early-phase sepsis without organ failure; in this study, a group using nutriment enriched with n-3 polyunsaturated fatty acids showed a significant decrease in the frequency of respiratory

and circulatory failure compared to the control group (using a nutriment that differs from that used in the first report; a nutriment formulation that is conventionally used in the ICU was used, with carbohydrates as the main component). A significant decrease in exacerbation to severe sepsis/septic shock was seen in the enriched-nutriment group. In addition, there was also a significant reduction in duration of hospitalization and length of ICU stay in the enriched-nutriment group; the reduction in duration of hospitalization and days in ICU contributed to a reduction in cost. The third study by Grau et al.[135] studied severe sepsis patients complicated with ALI or ARDS, and found no difference in SOFA score, $PaO_2/F_IO_2$ ratio, or duration of artificial ventilation between a group supplied with n-3 polyunsaturated fatty acid-enriched nutriment and a control group; number of days in ICU was also significantly higher in the control group. The nutriment enriched in n-3 polyvalent fatty acids used in documents 170-174 and in document 177 (Oxepa®) has been commercially available since 1997 in the US and since 2007 in Japan. In a multicenter collaborative study in Japan with severe sepsis and septic shock patients as subjects, a group using the n-3 polyvalent fatty acid-enriched nutriment was compared with a control group; no significant difference in the primary evaluation variable of oxygenation ability on days 4, 7, or 14 was found between the groups. In addition, the 28-day cumulative survival rate was also not significantly different between the groups (91.9% and 90.5% in the enriched-nutriment and the control groups, respectively).[144]

It should be noted that although there are studies suggesting the usefulness of an enteral nutriment enriched in n-3 polyunsaturated fatty acids, the nutriment used by the

control groups in the studies was not a standard preparation. Thus, the overall recommendation level was reduced, and this committee suggests (2B) considering the use of an enteral nutriment enriched in n-3 polyunsaturated fatty acids for patients with sepsis/severe sepsis/septic shock.

E. Specialized nutrients

## 4. Dietary fiber (soluble and insoluble)

CQ4

Should dietary fiber be administered?

A4.

It is suggested to consider using soluble fiber in patients suffering from diarrhea (2C).

It is suggested to avoid using insoluble fiber for critically ill patients in general (2C).

(Drafting method A)

Commentary

Dietary fiber is the general term used for components of food that cannot be digested by human digestive enzymes, and is broadly categorized into soluble dietary fiber (SDF) and insoluble dietary fiber (IDF) subtypes. The expected effects of dietary fiber are similar to those of other prebiotic preparations. Examples of SDF include pectin, hydrolyzed guar gum, polydextrose, and glucomannan. Examples of IDF include cellulose, hemicellulose, lignin, chitin, and glucan.

Five RCTs,[126,145-148)] three observational studies,[149-151)] and one meta-analysis[127)))] have compared the effect of nutriment with added dietary fiber to that of a nutriment without such addition. According to three reports that discuss mortality, added dietary fiber was associated with decreased mortality (one study used SDF,[146)] and two used SDF and IDF[149,151)]). Two studies have reported on the rate of infection,[146,148)] and did

not find a significant difference between fiber-supplemented and unsupplemented groups. Four reports have evaluated the duration of admission in fiber-supplemented and unsupplemented groups,[126,146,148,151] and two of the studies showed a decrease in the number of duration of hospitalization in the fiber-supplemented group, although none found a significant difference between groups in the number of days in ICU. The number of days until ventilator withdrawal was not reported by any study. Regarding diarrhea, although one study reported that SDF significantly reduced the number of individuals and number of days affected, [146] and that dietary fiber including SDF and IDF decreased the diarrhea score of sepsis patients,[151] other reports did not find a significant difference in these parameters based on fiber supplementation. In addition, a meta-analysis reported a significant decrease in the number of duration of hospitalization and no difference in diarrhea or infection between groups, although the subjects included postoperative patients as well.

There may be value in adding SDF to EN for preventing diarrhea in patients with stable hemodynamics. However, it has been reported that administering a nutriment containing IDF caused bowel obstruction in postoperative patients and in burn patients [152,153] and so IDF cannot be recommended for critically ill patients in general. Thus, use of both soluble and insoluble fiber should be avoided for high-risk patients such as those with bowel ischemia and extremely low bowel motility.

Among other reports, a review by Hayes et al.[154] has stated that dietary fiber is beneficial only for reducing diarrhea. In addition, according to a report by the Metabolism and Nutrition Working Group of the Spanish Society of Intensive Care

Medicine in 2011,[155] addition of fiber to EN is not recommended for burn patients. The 2013 Canadian Practice Guidelines have also concluded that although dietary fiber has no effect on diarrhea, it may be linked to a reduction in mortality and duration of hospitalization.

In light of the above evidence, and considering reports that do not distinguish between soluble and insoluble dietary fiber for reference, the use of soluble fiber should be considered for patients suffering from diarrhea, while insoluble fiber should be avoided for critically ill patients in general.

E. Specialized nutrients

## 5. Polymeric formulas and oligomeric formulas (peptide-based formulas)

CQ5

Which type of EN should be preferred: peptide-based formulas or polymeric formulas?

A5.

Either may be used (2C). (Drafting method F—1)

Commentary

Oligomeric formulas have not been reported to be useful by any study in terms of a clinical effect on length of hospital stay, rate of infection, and mortality. In addition, compared to polymeric formulas, oligomeric formulas have been shown to increase,[156] to decrease,[157] or to result in no effect[158] on diarrhea, and to improve stool hardness.[159] Thus, certain results have not been obtained for evaluating the effectiveness of oligomeric formulas.

In addition, the use of oligomeric formulas containing whey peptides has not been reported to lead to a difference in terms of length of ICU stay or mortality in patients with cerebral infarction ~~patients~~ compared to that by polymeric formula use.[160] Thus, there is no basis to recommend oligomeric formulations (peptide-based formulations) over polymeric formulations in critically ill patients.

F. Supplemental therapy

## 1. Selective digestive decontamination (SDD) and selective oral decontamination (SOD) disinfection

CQ1

Should SDD and SOD be performed?

A1.

It is suggested that SDD and SOD should not be performed (2A). Drafting method F—2)

Commentary

SDD is a method for preventing nosocomial infections such as ventilation-associated pneumonia and bloodstream infection caused by bacterial translocation. This method involves selectively suppressing the proliferation of fungi and aerobic gram-negative bacilli, which are the primary causes of nosocomial infections, by administering non-absorbable antibiotics. SDD, performed in conjunction with SOD (a subtype of SDD), has been reported to be effective by numerous RCTs and meta-analyses.[161-166)] However, considering that SDD and SOD may increase the incidence of resistant bacteria and that the efficacy in carriers of resistant bacteria is undetermined,[167)] it is suggestsed that SDD and SOD not be actively carried out. Also, the concentration of chlorhexidine for oral cleansing that can be used in Japan is low and cannot be expected

to have an antibacterial effect. Thus, it is recommended that SOD not be performed for critically ill patients. (See Chapter 2, D, A4—5)

F Supplemental therapy

## 2. Pre-/pro-/symbiotics

CQ2

Should pre-/pro-/symbiotics be administered?

A2.

The use of pre-/pro-/symbiotic preparations is suggested (2B).

However, it is suggested to not administer these preparations for severe acute pancreatitis (2B).

(Drafting method C) (see Chapter 2, J “Nutrition therapy by pathophysiology”)

Commentary

**An overview of pre-/pro-/symbiotics is given below:**

The effects expected from pre-/pro-/symbiotic agents are those resulting from useful microbes that can improve the bacterial flora in the gastrointestinal tract and bring about a beneficial effect on the host. Such effects may result from the consumption or administration of substances promoting the proliferation and health of bacterial flora in the gastrointestinal tract, while concurrently ameliorating disease. Among such agents, prebiotics are indigestible dietary components that selectively stimulate the growth or activity of a single or limited number of bacteria in the colon, thereby imparting a beneficial effect on the host. Representative examples are indigestible oligosaccharides such as fructooligosaccharides, xylooligosaccharides, galactooligosaccharides, and

lactosucrose. The effects of these agents are similar to those of dietary fiber. Probiotics are microorganisms that are beneficial to the body (such as *Bifidobacterium* and *Lactobacillus*). Symbiotics is the term coined for a combination of prebiotics and probiotics. A number of meta-analyses have reported on the effectiveness of probiotic preparations on diarrhea symptoms caused by antibiotics in hospitalized patients not limited to critically ill patients.

It has been hypothesized that[168-170)] using pre-/pro-/symbiotic preparations regulates the bacterial environment in the colon subjected to an invasive experience. Bacteria in the colon supply short-chain fatty acids to the damaged intestinal mucosa, and thus help in maintaining an appropriate host immune response, in improving infectious complications and in reducing mortality. The above evidence favors the use of these agents in critically ill patients with bowel ischemia and in those being administered broad-spectrum antibiotics.

However, although a number of studies have been performed at the present time, there are differences between studies regarding the type of prebiotic preparation used, the bacteria used as probiotics, and the composition of the combination of the each agents. Additionally, the majority of studies have involved preparations that cannot be used in Japan, and none of the preparations have yet been established for routine use in Japan. In a limited way, a RCT has reported a decrease in infectious complications in patients receiving these agents after transplantation, major abdominal surgery, and severe trauma, suggesting improved outcomes. In addition, based on subgroup analysis

in a meta-analysis study, the 2013 Canadian Clinical Practice Guidelines[171] have indicated that pre-/pro-/symbiotics may have a more effect in critically ill patients.

Besselink et al.,[172] in a study of severe acute pancreatitis patients, have reported adverse effects such as a significant (P=0.01) increase in in-hospital mortality, increase in surgical treatment, organ failure, and bowel ischemia in a group using probiotics. However, the design, methods, and analysis of this study have been criticized.[173-175] A meta-analysis[176] investigating six RCTs including the study by Besselink et al. could not find a beneficial or harmful effect associated with the use of probiotics, on mortality, overall infections, infections of pancreas necrosis, or duration of hospitalization.

It has also been reported that seven ICU patients who were administered *Saccharomyces boulardii* (a type of yeast) developed fungemia from this microbe.[177] However, preparations containing this fungus are not commercially available in Japan.

F. Supplemental therapy

## 3. Stress-ulcer prophylaxis

CQ3—1

In which patients should gastrointestinal bleeding prophylaxis be indicated?

A3-1.

We suggested preventing gastrointestinal bleeding in patients at high risk of bleeding (2C). (Drafting method H)

Commentary

Table 2F-1 lists risks for bleeding of the upper gastrointestinal tract.[178-180] These risks are frequently applicable to critically ill patients. However, the risk of bleeding is low in low-risk patients (incidence of 0.2%, 95% CI of 0.02-0.5).[178] In a recent large-scale cohort study with 78,394 non-ICU hospitalized patients, antacids were prescribed to 59% of all the subjects, and the incidence of gastrointestinal tract bleeding was 0.29%.[181] When this value was adjusted using propensity-matching, the effect of preventing gastrointestinal bleeding by the use of antacids was significant at 0.63 (95% confidence interval (CI) of 0.42-0.93), but the number needed to treat was high, at 770. So, prophylactic administration of antacids for non-critically ill patients cannot be recommended. It is reasonable to evaluate the risk of gastrointestinal bleeding in hospitalized patients, and consider prophylaxis based on such evaluation. However,

there are no reports evaluating the clinical outcomes from performing the intervention based on risk stratification.

F. Supplemental therapy

### 3. Anti-ulcer drugs

CQ3—2

Should anti-ulcer drugs be used to prevent gastrointestinal bleeding?

A3—2.

We suggested administering anti-ulcer drugs for preventing gastrointestinal bleeding (2A). (Drafting method E-1)

Commentary

Drugs for preventing gastrointestinal bleeding include gastric acid secretion inhibitors, gastric acid neutralizers, and drugs for enhancing gastric mucosal protection factors. Gastric acid secretion inhibitors have a superior anti-ulcer effect, and among gastric acid secretion inhibitors, proton pump inhibitors (PPIs) have the characteristic of suppressing acid secretion. In 1996, Cook et al.[182] conducted a meta-analysis of 63 RCTs, showing that prophylactic administration of histamine $H_2$-receptor antagonists (H2RAs) to critically ill patients resulted in a significant decrease in apparent gastrointestinal bleeding (odds ratio: 0.58; 95% CI: 0.42-0.79) and clinically significant gastrointestinal bleeding (odds ratio: 0.44; 95% CI: 0.22-0.88). However, a more recent meta-analysis conducted in the year 2000 has found that the incidence of gastrointestinal bleeding was similar in ranitidine (a H2RA)-treated, and placebo-treated patient groups.[183]

However, in these reports, administering drugs for gastrointestinal bleeding prophylaxis has not been shown to improve mortality. It has been hypothesized that adverse effects associated with the prophylactic agent may have exceeded the benefit of preventing bleeding in certain cases. When using drugs for gastrointestinal bleeding prophylaxis, it is thus necessary to evaluate the risk of pneumonia and *C. difficile* infections. Recent meta-analyses have also found that mortality is not affected by the administration of PPIs or H2RAs.[184)]

F. Supplemental therapy

## 3. Anti-ulcer drugs

CQ3-3

How should anti-ulcer drugs be selected?

A3-3.

1) We suggested the use of H2RAs and PPIs in patients for whom the beneficial effect of bleeding prophylaxis is considered greater than the risk due to its side effects (1A). (Drafting method E-1)

2) We suggested the use of gastric mucosal protective agents for patients in whom the risk of bleeding is unlikely to be high (1A). (Drafting method E-1)

3) We suggested not administering anti-ulcer drugs prophylactically for patients with no risk of bleeding and who are receiving EN (2A). (Drafting method E-1)

Commentary

H2RAs have superior efficacy in preventing gastrointestinal bleeding than do sucralfate and acid neutralizers.[182)] In a large-scale RCT, the relative risk (RR) of clinically significant gastrointestinal bleeding was 0.44 (CI: 0.21-0.92).[185)]

In an RCT comparing omeprazole and cimetidine,[186)] the occurrance of clinically significant gastrointestinal bleeding was lower with omeprazole. In a meta-analysis of seven RCTs, PPIs and H2RAs were equivalent in bleeding prevention, incidence of pneumonia, and length of ICU stay.[187)] In eight RCTs and a meta-analysis of five

abstracts, prophylactic administration of PPIs resulted in a significantly lower risk of gastrointestinal bleeding than when H2RAs were administered (odds ratio=0.30; 95% CI: 0.17-0.54), but there was no difference in the rate of nosocomial pneumonia or mortality.[188] In a large-scale cohort study, when PPIs were used compared to H2RAs, after adjusting for confounding factors, the odds ratios for gastrointestinal bleeding, pneumonia, and *Clostridium difficile* infection (CDI) were 2.24 (95% CI: 1.81-2.76), 1.2 (95% CI:1.03-1.41), and 1.29 (95% CI: 1.04-1.64), respectively.[189] Although H2RAs reduced gastrointestinal bleeding compared to a placebo, they did not improve mortality.[190]

In an observational study, the odds of CDI were significantly higher with PPI use.[190-192] In a meta-analysis of 10 RCTs, the incidence of pneumonia in a sucralfate group compared to that in a H2RA group was significantly lower (odds ratio=1.32; CI: 1.07-1.64).[193] A hospitalized patient database-based analysis found that the odds of nosocomial pneumonia were significantly higher in patients using antacids (particularly PPIs), after adjusting for severity.[194] A meta-analysis of 31 studies including 23 RCTs found that the odds of pneumonia were significantly higher when using PPIs (adjusted odds ratio=1.27; 95% CI: 1.11-1.46) and H2RAs (1.22; 95% CI: 1.09-1.36).[195]

It has been noted that the benefits of administering prophylaxis for bleeding are potentially outweighed by the risk of harm in patients receiving EN. Marik et al. [196] performed a meta-analysis evaluating the association between an effect of H2RAs and provision of EN. The analysis included 1,836 patients from 17 studies (in three studies, over half of the patients were receiving EN). Although H2RAs significantly decreased

gastrointestinal bleeding (odds ratio: 0.47; 95% CI: 0.29-0.76), this therapeutic effect was only obtained in the group that did not receive EN. Conversely, in the group of patients receiving EN, the decrease in risk of gastrointestinal bleeding from using H2RAs remained unchanged (odds ratio: 1.26; 95% CI: 0.43-3.7), the rate of nosocomial pneumonia increased (odds ratio: 2.81; 95% CI: 1.20-6.56), and mortality also increased (odds ratio: 1.89; 95% CI: 1.04-3.44).[196)]

In summary, when the risk of gastrointestinal bleeding is high, a PPI or H2RA with a superior prophylactic effect should be used, while when the risk is not particularly high, in light of the risk of complications, the use of sucralfate is recommended. When the risk of gastrointestinal bleeding is low or enteral feeding is being provided, there is an option of not administering a gastrointestinal bleeding prophylaxis. However, as stated above, prevention of gastrointestinal ulcers has not been associated with improving mortality. The efficacy in selecting drugs based on a risk-stratification of gastrointestinal bleeding has not also been validated in a prospective controlled study. It is essential to carefully evaluate risk for gastrointestinal bleeding in each patient, and to make a decision for the use of prophylaxis under careful observation and evaluation for the balance between the benefits and risks associated with prophylaxis.

F. Supplemental therapy

## 4. Branched chain amino acids (BCAA)

CQ4

Should BCAA-rich PN be supplied?

A4.

In general, it is suggested that BCAA-rich PN should not be administered to critically ill patients (2B). (Drafting method F—1)

(For patients with consciousness disorders due to hepatic failure, see Chapter 2, J "Nutrition therapy by pathophysiology")

Commentary

There are currently only five RCTs [197-201] (quality B) of the usefulness of BCAA for critically ill patients. Of these, four RCTs [197,199-201] have discussed mortality, while only one[201] has reported that BCAA-rich PN significantly reduced mortality. A meta-analysis[66] of the four studies that have discussed mortality have found that although the BCAA-rich nutrition was superior (risk ratio=0.58 [0.26, 1.28]), the difference was not statistically significant (P=0.09). BCAA has not been listed in the most recent edition of nutritional guidelines from the US[11] and Europe,[10] and was only mentioned in the 2009 Canadian guidelines. Furthermore, there have been no RCTs or meta-analyses about BCAA supplementation from 2009 until the present, and there has been no change

about the BCAA supplementation in the revised edition of the Canadian guidelines published in 2013.[66)]

F. Supplemental therapy

## 5. High fat & low carbohydrate (CHO) formulation

CQ5

Should high fat & low CHO formulation be provided to critically ill patients?

A5.

It is suggested that high fat & low CHO formulation should not be routinely used for critically ill patients (2D).

(Drafting method F—1)

Commentary

There is no consensus on the materials and compositions to be used for lipids contained in EN and PN for patients with respiratory failure. It is known that specialized high fat & low CHO formulation with a regulated respiratory quotient reduces $CO_2$ production. However, increasing the composite ratio of fat to CHO significantly decreased $CO_2$ production only in the ICU patients supplied excessive nutrition, and this effect was not pronounced when the necessary amount of nutrition was supplied appropriately.[202)]

High fat & low CHO formulation for ICU patients has been reported to not affect mortality, the incidence of infectious complications, or the duration of hospitalization, compared to a standard formulation. Compared to a standard formulation, a high fat & low CHO EN has been shown to significantly reduce the duration of artificial

ventilation in patients with acute exacerbation of chronic obstructive pulmonary disease (COPD).[202] In patients prone to $CO_2$ accumulation, administration of more than the required quantity of nutrition should be avoided [202,203]

In addition, it has been reported that high fat & low CHO formulation significantly decreased blood glucose levels in hyperglycemia patients compared to a standard formulation, and decreased the amount of insulin use.[204] However, only two documents[203,204] have reported the efficacy of high fat & low CHO formulation, and thus there is insufficient data to recommend its use.

A review[205] of burn patients has reported that compared to low fat & high CHO formulation, high fat & low CHO formulation increased the incidence of pneumonia; it is therefore possible that high fat & low CHO formulation is harmful, depending on the patient characteristics.

It is important to note that the fat described in this section differs from the fish oil and borage oil sources of fat as recommended for ARDS/ALI, and so care must be taken to discriminate between these fat sources.

F. Supplemental therapy

## 6. Fat emulsions

CQ6—1

Is it safe to administer lipid emulsions and at which rate?

A6—1.

When administering fat emulsions, it is suggested that the rate of administration be up to 0.1-0.2 g triglycerides/kg/h, with a dose that does not exceed 0.7-1.5 g/kg/day (2C).

(Drafting method F—1)

Commentary

Carpentier et al.[206)] have reported that up to 0.1-0.2 g triglycerides/kg/h is a safe rate of administration for fat emulsions. A rate of 0.1 g/kg/h implies that 200 mL of a 10% soybean oil emulsion can be administered to a 50 kg patient in four hours. According to the ESPEN PN guidelines,[10)] fat emulsions should be administered without exceeding 0.7-1.5 g/kg/day.

F. Supplemental therapy

**6. Fat emulsions**

CQ6—2

What type of fat emulsions should be administered and when should they be administered?

A6—2.

1) If EN can be administered, it is suggested to avoid administering soybean oil fat emulsions (2C). (Drafting method A)

2) If EN cannot be administered and the duration of PN is within a 10-day period, it is suggested to avoid administering soybean oil fat emulsions (2C). (Drafting method A)

3) If EN cannot be administered and the duration of PN has been at least 10 days, there is no sufficient basis for determining, but soybean oil fat emulsions should be administered; the optimum dosage is also unclear (unknown field). (Drafting method A)

4) For critically ill patients with malnutrition, there is no sufficient basis for determining, but soybean oil fat emulsions should be administered; the optimum dosage is also unclear (unknown field). (Drafting method A)

Commentary

Currently in Japan, the sedative 2,6-diisopropylphenol (Diprivan®, Propofol®) (used frequently in the ICU) is formulated as a fat emulsion, and is available either with just the soybean oil (LCT) (Diprivan®) or with soybean oil (LCT) + medium-chain fatty

acids (MCT) (Propofol®). Nutrition management should take into consideration that such fat emulsions contain 1.1 kcal/mL of energy.

For critically ill patients who can receive EN and have only been receiving PN for less than 10 days, the administration of soybean oil fat emulsions should be avoided according to two RCTs.[207,208] Battistella et al. have reported that,[207] a group of trauma patients who received soybean oil fat emulsions had a significantly higher rate of pneumonia and sepsis than did the group who did not receive such emulsions. McCowen et al.[208] have compared low calorie administration (1000 kcal/day of carbohydrates, 70 g/day of protein) and normal calorie administration (25 kcal/kg/day of carbohydrates, 1.5 g/kg/day of protein, with a soybean oil fat emulsion used), and have reported that the normal calorie group using a soybean oil fat emulsion exhibited a tendency toward a higher rate of infection. According to these two reports, there was no difference in mortality between the group using and that not using fat emulsions.

For critically ill patients with malnutrition who have been receiving PN for at least 10 days, it is difficult to make a definitive recommendation for fat administration since there is no RCT-based evidence for this aspect. However, it is necessary to start administration of fats in accordance with the individual needs and characteristics of the patient to avoid an essential fatty acid deficiency.

F. Supplemental therapy

## 7. Oriental medicine approach

CQ7—1

Should Japanese (Kampo) herbal medicine be administered to improve gastrointestinal motility?

A7—1.

The evidence is insufficient to formulate a conclusive recommendation for the use of Kampo medicine with the objective of improving gastrointestinal motility (unknown field). (Drafting method G)

*Most of the evidence documents have been assigned a quality of D, so a structured abstract has not been prepared.

Commentary

No randomized trials applicable to critically ill patients could be found. In the field of intensive care, two types of Kampo medicine with potential to have benefit are described below. Basic research studies have reported an improvement in gastrointestinal motility with the use of both these Kampo medicine treatments. The first Kampo treatment is Rikkunshito, which has been reported to promote gastric emptying,[209] secretion and inhibition of the breakdown of ghrelin (stimulating appetite),[210] and to participate in the activation of ghrelin signaling.[211] However, there is a need for studies evaluating the use of this treatment in intensive care patients with large GRVs. The second Kampo treatment is Daikenchuto, which has been reported to

promote gastrointestinal motility (by stimulating the release of acetylcholine, which mediates activities through the 5—HT3 and 5—HT4 receptors),[212-214] stimulate motilin secretion,[215] and to stimulate receptors in the intestinal mucosa.[216] Clinical studies of these treatments include a RCT[217] which showed that the emptying time of the ascending colon was significantly decreased in a group of healthy Americans administered 15 g/day of Daikenchuto for five days compared to a placebo group, a RCT[218] which showed that the rate of recurrence and rate of reoperation were reduced in patients with post-laparotomy ileus, and a RCT[219] which showed an alleviation of symptoms during administration of nutrition to jejunostomy patients following total gastrectomy.

The mechanisms of action of these treatments are expected to be similar and equally efficacious in critically ill patients, but there are no studies investigating the effect these treatments on critically ill patients. Thus, this is an unknown field, and future reports in the field of intensive care are desired.

F. Supplemental therapy

## 7. Oriental medicine approach

CQ7—2

Should acupuncture be performed to improve gastrointestinal motility?

A7—2.

There is insufficient evidence for the efficacy of acupuncture in improving gastrointestinal motility (unknown field). (Drafting method G)

*There is only one report available, so a structured abstract has not been prepared.

Commentary

Pfab et al., [220)] have published a report based on data from a RCT studying patients who were sedated after aneurysm surgery for grade III/IV subarachnoid hemorrhage, intracerebral hemorrhage, or traumatic brain injury, with at least 500 mL per day of GRV for two consecutive days. The subjects were divided into an electroacupuncture treatment group (EAG) (15 subjects) and a drug treatment group(DTG) (15 subjects). In the EAG, electric needle stimulation was performed on the bilateral PC-6 point (called Neiguan, located at the center of the palmar side 2 cun (1 cun = patient's thumb width) proximal of the distal hand crease), while the DTG received the standard treatment of intravenous administration of 10-20 mg of metoclopramide every 8 hours. In case of persistence of delayed gastric emptying, cisapride in a dosage of 3 × 10 mg IV every 8 hours was added. After cisapride was withdrawn from the market because of serious

side effects, erythromycin 500 mg IV every 24 hours was added instead. Successful treatment (feeding tolerance) was defined as GRV <200 mL per 24 hours. Demographic and hemodynamic data were similar in both groups. After 5 days of treatment, 80% of patients in the EAG successfully developed feeding tolerance versus 60% in the DTG. Within 48 hours, 7 of 15 (47%) patients in the electroacupuncture group compared with 3 of 15 (20%) patients in the drug treatment group were below the threshold level of 200 mL GRV per 24 hours ($P < 0.05$). In addition, GRV decreased and feeding balance (defined as enteral feeding volume minus GRV) increased in more patients in the EAG (14 of 15) than in the DTG group (7 of 15; $P = 0.014$). Overall, the feeding balance improved significantly on all days of treatment in comparison with the DTG. There were no side effects.

At present, this is the only RCT available for reference, and since the number of patients and illnesses were limited, the evidence level was set to “unknown field”. In the future, reporting of more studies relevant to this topic is desired.

G. Blood glucose management

## 1. Target blood glucose level

CQ1

What should the target blood glucose level be?

A1.

If a patient exhibits hyperglycemia as a glucose level ≥180 mg/dL, insulin administration should be started to reduce blood glucose levels. When controlling blood glucose levels, the target value should be less than 180 mg/dL, and it is recommended not to use “intensive insulin therapy” to maintain blood glucose levels at 80-110 mg/dL (1A). (Drafting method A)

Commentary

A single-center randomized controlled trial in a cardiac surgery ICU reported that intensive insulin therapy with a target blood glucose level of 80-110 mg/dL reduced mortality.[221] This was followed-up with a RCT conducted on internal medicine ICU patients expected to require intensive care for ≥ three days; the use of intensive insulin therapy did not reduce mortality in the group composed of all patients.[222]

Since the publication of the Surviving Sepsis Campaign 2008 (SSCG2008) guidelines, [223] a number of RCTs[224-226] and meta-analyses[227,228] on intensive insulin therapy have been reported. In these studies, intensive insulin therapy significantly increased the incidence of severe hypoglycemia (blood glucose ≤ 40 mg/dL),[216,225-228]

but did not decrease mortality. [225,228)] In addition, in the NICE—SUGAR trial, intensive insulin therapy increased the 90-day mortality rate.[216)] In a meta-analysis by Friedrich, intensive insulin therapy was reported to not be beneficial even when only surgical or only internal medicine ICU patients were analyzed.[227)]

These recommendation for initiating an insulin at a blood glucose level ≥180 mg/dL, and a target blood glucose lease <180 mg/dL, was based on results of the NICE—SUGAR trial. The NICE—SUGAR trial is the largest RCT verifying the target values for blood glucose management in ICU patients. According to subgroup analysis of the NICE—SUGAR trial, the effects of intensive insulin therapy on the mortality rate did not differ significantly between non-diabetic patients and diabetic patients (odds ratio, non-diabetic patients vs. diabetic patients: 1.12 vs. 1.21; P=0.60).[216)] Consequently, the use of intensive insulin therapy cannot be recommended and the target blood glucose level is recommended to be <180 mg/dL even for diabetic patients.

The DIGAMI study is a multi-center RCT conducted in post-myocardial infarction patients with a HbA1c of about 8%, and compared a target blood glucose value of <198 mg/dL with glycemic management without using insulin.[229)] According to the DIGAMI study, the one-year mortality rate was significantly lower with a target blood glucose value of <198 mg/dL than that without insulin use. Prior study reported that diabetic patients had significantly higher incidence of hypoglycemia, [230,231)] thus, if physicians considered that patients with chronic poor blood glucose control is under the higher risk of hypoglycemia, the slightly higher target as like <198 mg/dL can be used, instead of a target of 144-180 mg/dL.

Some countries currently use mmol/L as the unit for blood glucose levels. Applying the conversion formula 1 mmol/L = 18 mg/dL, 180 and 198 mg/dL are equivalent to 10 and 11 mmol/L, respectively. Since the error in blood glucose measurement values is large (as described below), when implementing blood glucose control, a threshold that is easy to use such as 200 mg/dL instead of 198 mg/dL may also be used.

Depending on the patient condition and severity of illness, and the decision of physicians, critically ill patients may be administered parenteral nutrition or continuous enteral nutrition. In such cases, it is thought that continuous intravenous administration of insulin reduces hypoglycemia and blood glucose variability more effectively than does intermittent administration. Therefore, continuous intravenous insulin administration is uniformly recommended by all guidelines. When administering intermittent enteral nutrition, the use of intermittent insulin administration may also be considered.

In studies conducted in postoperative patients, continuous blood glucose management using an artificial pancreas has been reported to reduce the incidence of hypoglycemia, lower the amount of insulin used, and decrease the number of duration of hospitalization and the incidence of infection, in compared to ordinary blood glucose management,.[232,233)] In hospitals that artificial pancreases would be available, some may consider the use of artificial pancreas. In this case, physicians should consider that their own nutrition therapy and patient case-mix is similar with those in studies that the effect of artificial pancreas was assessed.

G. Blood glucose management

**2. Blood glucose control**

CQ2

How should blood glucose level be measured?

A2.

1) It is recommended that all patients receiving intravenous insulin therapy were measured blood glucose level every 1-2 hours until the insulin dose would be stabilized, and every four hours thereafter (1C). (Drafting method C)

2) Blood glucose measurements using glucose meters with capillary blood have a greater measurement error and lack accuracy compared to measurements using a blood gas analysis device, and so it is recommended to measure blood glucose level using blood gas analyzer. (1B). (Drafting method C)

3) Because of a presence of measurement error even with blood gas analyzers, it is recommended to check the accuracy of its measurements using a central laboratory test, as appropriate (1B). (Drafting method C)

Commentary

In order to avoid dangerous hypoglycemia occurring during insulin use, it is necessary to perform frequent blood glucose measurements. In past studies of blood glucose management in acute patients, measurements have been taken at least every four hours. Blood glucose were also measured at least every four hours in the normal

blood glucose management group in the NICE—SUGAR study. In that study, 15.8% of patients experienced moderate hypoglycemia (41-70 mg/dL), and 0.5% of patients experienced severe hypoglycemia (40 mg/dL or below). These occurrences of hypoglycemia correlated significantly with an increase in mortality.[234)] In critically ill patients using insulin, it is recommended that blood glucose level were measured at least every four hours because hypoglycemia is highly risky in this patient population.

Blood glucose levels were often measured using glucose meters in critically ill patients, however such measured values are inaccurate, and may lead to under-diagnosis of hypoglycemia. Blood glucose measurements using glucose meters with capillary blood have a significantly higher rate of measurement error than do measurements using a blood gas analysers[235)]. In addition, glucose measurements using glucose meters with whole blood have a tendency, though insignificant, towards a higher rate of measurement error compared with blood glucose measurements using a blood gas analysis device.[235)] Thus, it is recommended that blood glucose management in critically ill patients be performed using blood gas analyzers. In the hypoglycemic range (blood glucose level of 80 mg/dL or lower), the rate of measurement error using a blood gas analyzers increased significantly in compared with normal or higher range. So it is necessary to check the accuracy of its measurements using a central laboratory test, as appropriate (using serum instead of whole blood).

H. Patient management during EN therapy

## 1. Confirmation of gastric tube positioning

CQ1

How should the positioning of a gastric tube be confirmed?

A1.

When placing or replacing a gastric tube, confirmation by X -ray imaging is recommended (1D). (Drafting method G)

*Since there are no documents evaluating outcomes, a structured abstract has not been prepared.

Commentary

An observational study about the insertion of over 2000 gastric tubes reported that misplacement of gastric tube was found in 1.3-2.4% of cases and about half of these cases were of patients undergoing artificial ventilation management. [236)] The most common complication of gastric tube misplacement is pneumothorax,[237)] and deaths due to this cause have been reported in Japan and overseas. [236, 238)]

Methods to confirm the position of the gastric tube tip include X-ray imaging, pH measurement of aspirated fluid, auscultation of bubble sounds, and detecting exhaled carbon dioxide. The methods other than those using X-ray imaging are blind confirmation methods. Patients receiving intensive care are in an environment where X-

ray imaging is easy to perform, so confirmation by X-ray imaging is recommended during gastric tube placement and replacement.

H Patient management during EN therapy

## 2. Management of GRV

CQ2

To what extent can GRV continue EN?

A2.

If the GRV is no greater than 500 mL, then it is suggested that EN not be discontinued.

Commentary

According to the SCCM and ASPEN joint guidelines,[239] as long as the GRV is within 250-500 mL, EN should not be discontinued; the Canadian Clinical Practice Guidelines[66] use a GRV of 500 mL as a threshold, and continuation of EN is permitted as long as the GRV is within 250-500 mL.

For the aspirated fluid after checking the GRV, amounts of up to 250 mL may be returned to the stomach, or discarded without affecting complications such as hyperglycemia, diarrhea, and delayed gastric emptying.[240] Therefore, the method for dealing with gastric residue is at the discretion of the concerned facility personnel.

H. Patient management during EN therapy

### 3. Body position during EN administration

CQ3

What should the body position be during EN administration to a tracheally intubated patient?

A3—1.

During EN administration, it is recommended that the patient maintain the semi-Fowler's position at 30-45° (1C). (Drafting method A)

A3—2.

It is recommended that the physician clearly instruct the body position for the patient during enteral feeding (1C). (Drafting method A)

Commentary

Regardless of whether the patient is undergoing EN management, body position management with an elevated head is the least economically burdensome aspiration prevention measure for critically ill patients[104,241,242)] (see Chapter 2, D—CQ4—1). More thorough body position management can be achieved with providing explicit instructions by the relevant physician.[106])

H. Patient management during EN therapy

## 4. Intermittent and continuous administration of EN

CQ4

Among intermittent and continuous infusion of EN administration, which is preferable?

A4.

It is recommended that EN for critically ill patients be administered continuously whenever possible.

Commentary

Although there is no significant difference in terms of aspiration, it has been reported that complications tend to be lower in patients administered continuous EN. [108,243] Especially, it has been reported that continuous infusion results in a significantly lower incidence of diarrhea[107] (see Chapter 2, D—CQ4—2). The incidence of aspiration and diarrhea in critically ill patients may prevent EN lasting, so continuous EN administration is preferable when possible.

H. Patient management during EN therapy

## 5. Open system and closed system for administering EN

CQ5

Which system is preferable for administering EN: an open system or a closed system?

A5.

There is insufficient evidence to recommend an open system or a closed system as more effective for preventing diarrhea from infected nutrition formulas (unknown field, D). (Drafting method G)

*This topic has not been covered in the previous guidelines and has been newly created here; there is only one available document pertinent to this topic with a quality level of D, and so a structured abstract has not been prepared.

Commentary

EN administration systems include closed systems, in which the bottle and route are directly connected for administration, and open systems, in which enteral formulas are transferred to another bottle/pack. In clinically, the incidence of diarrhea due to contaminated nutriment is a concern.

According to two reports compared between the open and the closed systems of EN administration for ICU patients, there was no significant difference in the incidence of diarrhea, the amount of energy administered and protein. [244,245)] As a result, there is no sufficient evidence to recommend one system over the other system.

H. Patient management during EN therapy

## 6. Fecal incontinence management systems

CQ6

Should a fecal incontinence management system be used for severe diarrhea during EN administration?

A6.

It is suggested that a fecal incontinence management system be used for severe diarrhea during EN administration (2D). (Drafting method G)

*This topic has not been covered in the previous guidelines and has been newly created here; there are only two available documents pertinent to this topic with a quality level of D, and so a structured abstract has not been prepared.

Commentary

The use of a fecal incontinence management system reduces the rate of urinary tract infections and soft tissue infection in burn patients.[246)] It has been reported that this prevents or ameliorates fecal incontinence-associated dermatitis in critically ill patients.[247)]

There is significant value in using fecal incontinence management systems for diarrhea that is difficult to control, but such systems should be used under sufficient monitoring and supervision to avoid health issues while adhering closely to the descriptions in the appended documentation.

H. Patient management during EN therapy

## 7. Relationship between feeding tube diameter and aspiration

CQ7

To prevent aspiration, should as small a diameter as possible be selected for the feeding tube?

A7.

To prevent aspiration, it is suggested to select as small a diameter as possible for the feeding tube (2D). However, when measuring GRV, a large-diameter tube becomes necessary. (Drafting method G)

* This topic has not been covered in the previous guidelines and has been newly created here; there is only one available document pertinent to this topic with a quality level of D, and so a structured abstract has not been prepared.

Commentary

Smaller-diameter feeding tubes have less effect on swallowing,[248)] and so could reduce the risk of aspiration. Thus, it is preferable to select a feeding tube that is no greater than 8 Fr. However, when measuring the GRV, a wide-diameter tube is necessary.[249)]

H. Patient management during EN therapy

## 8. Indications for gastrostomy

CQ8

Should a gastrostomy be created in patients requiring long-term nasogastric nutrition?

A8.

It is suggested that a gastrostomy should not be created in patients requiring long-term nasogastric nutrition (2D). (Drafting method G)

* This topic has not been covered in the previous guidelines and has been newly created here; the only available documents pertinent to this topic have been assigned a quality level of D, and so a structured abstract has not been prepared.

Commentary

In a cohort study of non-critically ill patients,[250] 78% of patients survived 30 days after the creation of a gastrostomy (percutaneous endoscopic gastrostomy: PEG), and there were fewer issues regarding self (accidental) removal of the feeding tube compared to those in patients with nasogastric tubes. In addition, in a small-scale RCT,[251] patients in whom a gastrostomy was constructed early had a lower incidence of pneumonia than in those with nasogastric feeding. In contrast, in the FOOD Trial[252] comparing PEG and nasogastric feeding for patients following a brain stroke, the functional prognosis after six months and the mortality rates were worsened in the PEG group than those in the tube feeding group; thus, early PEG construction cannot be

recommended. In these reports, patients have different disease and medical conditions, and results are not oriented in a certain direction; therefore, these reports do not serve as a sufficient basis for making a definitive recommendation for this CQ.

I. Patient management during PN therapy

## 1. Preventing infection during central venous catheter insertion

CQ1

What are effective methods for preventing infection during central venous catheter insertion?

A1.

At the time of central venous catheter insertion, it is recommended that maximum barrier precautions be used (1A). (Drafting method A)

Commentary

When inserting a central venous catheter, thorough hand washing prior to insertion and thoroughly implementing maximal barrier precautions using caps, masks, sterile gowns, sterile gloves, and large sterile drapes have been shown to reduce catheter-related bloodstream infections.[253-256)] Furthermore, the rate of infection may be reduced by disinfecting the catheter insertion site with chlorhexidine, avoiding femoral vein placement, and removing unneeded central venous catheters.[255)] In agreement with the summary provided in the CDC guidelines[257)] on infection management for central venous catheters (published in the US), there is a high likelihood of reducing the rate of infection via proper insertion procedure and management; thus, enforcement of infection countermeasures including maximum barrier precautions is recommended.

I. Patient management during PN therapy

## 2. Selecting the placement site for a central venous catheter

CQ2

Does the insertion site for a central venous catheter affect the incidence of catheter infections?

A2.

The rate of central venous catheter-related bloodstream infections does not change based on the site selected on the internal jugular vein, the subclavian vein, or the femoral vein, as long as maximum barrier precautions are used (2B). (Drafting method A)

Commentary

Compared to central venous catheter placement in the subclavian vein or the internal jugular vein, placement in the femoral vein has been shown to be associated with a higher rate of bloodstream infections;[258,259] placement in the internal jugular vein was reported to be associated with a tendency towards a higher rate of bloodstream infections than placement in the subclavian vein.[260] However, it has also been reported that there was no difference in bacterial colonization or infection rate in central venous catheters, [261] and that bacterial colonization was lower in the subclavian vein, though there was no difference in infection rates. [262] In addition, in a recent meta-analysis,[263] no difference in catheter-related bloodstream infections between each of the access

routes has been reported. At central venous catheter insertion, maximum barrier precautions should be implemented, and an access route with a low risk of complications such as pneumothorax, and one that the operator is accustomed to, should be selected.

I. Patient management during PN therapy

## 3. Parenteral catheter replacement

CQ3

When should parenteral catheter replace?

A3.

Central venous catheters are only replaced when there is suspicion of catheter-related bloodstream infection. Peripheral venous catheters are not replaced every 72-86 hours as long as there are no clinical issues such as extravasation or infection (2C). (Drafting method A)

Commentary

Concerning about the frequency of central venous catheter replacement, there is no difference in the rate of catheter-related bloodstream infections, even if replacement periods are designated and replacements are performed periodically.

For peripheral venous catheters, no difference has been reported in the incidence of phlebitis even for catheters which are not replaced for more than 96 hours.[264-266] The replacement frequency of central and peripheral venous catheters as mentioned above is in accordance with the recommendations of the CDC guidelines[257] from the US.

J. Disease-Specific Nutrition Support Therapy

## 1. Respiratory failure

CQ1

Should the routine use of an enteral nutriment with specialty high fat & low CHO formulation designed to manipulate the respiratory quotient and reduce $CO_2$ production be recommended for ICU patients with acute respiratory failure?

A1.

We suggested that the routine use of an enteral nutriment with specialty high fat & low CHO formulation designed to manipulate the respiratory quotient and reduce $CO_2$ production should not be used for ICU patients with acute respiratory failure. (Drafting method F1)

*For ARDS, see Chapter 2, E—3 “n-3 polyunsaturated fatty acids.” The present section pertains to ICU patients with respiratory failure, and should not be applied for ARDS patients.

Commentary

Compared to existing enteral nutriments, high-fat formulation have a higher fat content and a lower carbohydrate content. Since the respiratory quotient during fat metabolism is lower than that during carbohydrate metabolism, this composition is expected to prevent an increase in the partial pressure of carbon dioxide in the arterial blood. A small-scale study evaluating the effect of a high-fat formulation on 20 acute respiratory failure

patients requiring artificial ventilation reported that the duration of ventilation was reduced by approximately 2.5 days.[203] However, this study was carried out in the 1980s, and the clinical effects of the preparation have not been sufficiently studied, so its use has not been recommended by guidelines published in the US.[11,267] A trial conducted using a preparation of a high fat & low CHO formulation containing a high proportion of inflammation-inducing n-6 fatty acids as the control nutriment, has revealed that such a composition was potentially harmful to patients.[268] However, at present, n-6 fatty acids are adjusted to less than 20% of the total fatty acid content in high-fat formulation available commercially in Japan (n-9 fatty acids: 43%; n-3 polyunsaturated fatty acids: 5%). Therefore, the above-cited evidence may not be useful as a reference. With the additional consideration that there are no high-quality RCTs on this topic, it was decided to suggests against the routine use of high-fat formulation with low CHO in patients with acute respiratory failure.

J. Disease-Specific Nutrition Support Therapy

## 2. Acute kidney injury

CQ2—1

Which type of nutrition should be administered for acute kidney injury (AKI)?

A2—1.

It is suggested that standard EN be administered, and that the administration of protein and energy follow the standard ICU recommendations. In cases of severe electrolyte imbalance, it is suggested to consider using specialized formulations for kidney failure (2D). (Drafting method F—1)

For patients with renal insufficiency, the amount of protein intake should not be restricted as a means of avoiding or delaying the initiation of dialysis (2C). (Drafting method F—1)

Commentary

AKI in critically ill patients has been recognized as one component of multiple organ failure, and so the metabolic dynamics are known to change greatly depending on other organs involved, whether renal replacement therapy was performed, and on the severity of the underlying disease and nutritional disorder. Thus, the amount of protein needed and the target amount of energy to be administered needs to be appropriate for patients with various pathophysiologies. Nevertheless, the amount of protein to administer must be restricted to delay initiation of renal replacement therapy.[4)] However, certain cases

may benefit from receiving special nutriments with a reduced amount of specific electrolytes (phosphates, potassium, etc.).[4,269,240)]

## 2. Acute kidney injury

CQ2—2

How should protein requirements be set for patients undergoing renal replacement therapy?

A2—2.

It is suggested to administer an amount of protein during renal replacement therapy that takes into consideration the amount that is lost through the membrane. For carbohydrates administration, the amount of glucose in the dialysate solution should be considered. For fat, the normal amount should be administered (2C). (Drafting method F—1)

Commentary

During continuous renal replacement therapy, approximately 10-15 g/day of amino acids are lost, and an amount of protein administration of less than 1 g/kg/day may exacerbate nitrogen deficiency; therefore, taking into consideration protein loss, administering 1.5-2.0 g/kg/day is necessary.[271)] In addition, in order to achieve positive nitrogen balance during continuous renal replacement therapy, it has been reported that protein intake of 2.5 g/kg/day is necessary.[272-274)] However, since the dose continuous renal replacement therapy in western countries is greater than the amount approved by the national healthcare insurance system in Japan, the amount of amino acids to administer should take into consideration the amount lost through the membrane in the actual conditions used.

J. Disease-Specific Nutrition Support Therapy

### 3. Liver failure

In these guidelines, chronic liver disease is defined as “severe, chronic liver pathology such as cirrhosis of the liver”, while acute liver failure is defined as “severe pathology such as fulminant hepatitis or awaiting a liver transplantation.”

CQ3—1

In patients with chronic liver disease or acute liver failure, can traditional nutrition assessments such as the subjective global assessment (SGA) or the objective data assessment (ODA) be trusted?

A3—1.

Traditional nutrition assessments are inaccurate and have lower reliability, so it is suggested that they be used with caution in patients with chronic liver disease or acute liver failure (2C). (Drafting method F—1)

Commentary

SGA is a nutrition assessment method that subjectively evaluates the state of nutrition using data that can be obtained during a routine medical examination, and the variables used are age, sex, body weight change, gastrointestinal symptoms, changes in food consumption status, functionality (level of independence), hypermetabolic state, emaciation/edema (triceps skin fold, arm muscle circumference, etc.), and ascites. In addition to nutrition disorders, SGA can accurately predict patients at risk for infection

and delayed healing of wounds. ODA is performed when SGA results show that there is a nutrition disorder, and this assessment evaluates the nutrition state based on various test data including blood and urine biochemistry test data.

Malnutrition is often observed in patients with chronic liver disease and awaiting a liver transplantation. During the clinical consequences of chronic liver disease and acute liver failure, traditional nutrition assessments become inaccurate because of complications such as ascites, hypovolemia, edema, portal hypertension, and hypoalbuminemia, and so the reliability of such assessments is low. Malnutrition is caused by poor oral intake due to multiple factors. In patients with liver cirrhosis, malnutrition may increase morbidity and mortality rates. Furthermore, severe malnutrition prior to transplantation surgery leads to reduced postoperative survival and increased rate of complications. The amount of necessary energy varies in critically ill patients with liver disease, and is difficult to predict using a simple formula; thus, the use of an indirect calorimetry is recommended to determine energy needs. [275-280)]

J. Disease-Specific Nutrition Support Therapy

**3. Liver failure**

CQ3—2

Which route of administration should be used for nutrition therapy in patients with chronic liver disease? Should protein restrictions be implemented?

A3—2.

It is suggested that EN should be prioritized as the preferred route of nutrition therapy in patients with chronic liver disease (2C).

It is suggested that protein restrictions should not be implemented during nutrition therapy in patients with chronic liver disease (2C). (Drafting method F—1)

(For acute hepatic insufficiency, see CQ3—4)

Commentary

In patients with end-stage liver disease and during all phases of liver transplantation, nutrition therapy is indispensable. In liver disease and after liver transplantation, EN reduces infections and metabolic complications more effectively than does PN. Long-term PN is associated with exacerbation of hepatic complications, sepsis, blood coagulation disorders, and increased mortality. Cholestasis, which is correlated with nutrition, ordinarily occurs alongside long-term PN, and is a significant problem. EN improves the nutrition status, reduces complications, and prolongs survival in liver disease patients, and so is recommended as the optimal route of nutrition administration.

Protein should not be restricted with as a management strategy to reduce the risk of developing hepatic encephalopathy. [275,281)] The protein requirements for the patients with chronic liver disease should be determined to approximately the same level as that for critically ill patients in general.

### 3. Liver failure

CQ3—3

Which EN compositions should be selected for patients with chronic liver disease?

A3—3.

The use of EN with standard formulations is suggested for chronic liver disease patients (2C).

It is suggested that EN enriched with branched-chain amino acids (BCAA) be administered only to patients with refractory hepatic encephalopathy (2C). (Drafting method F—1)

Commentary

There is no evidence suggesting that EN enriched with BCAA improves outcomes in critically ill patients with liver disease compared to standard whole protein formulations.[275,282-284)] Based on RCT results, it has been suggested that long-term oral supplementation with BCAA granules for 12 months [282)] or 24 months[283)] may delay the progress of liver damage, and prolong the event-free survival. In patients with hepatic encephalopathy refractory to useful treatment, EN enriched with BCAA may potentially reduce coma grade compared to standard formulations.[282)]

J. Disease-Specific Nutrition Support Therapy

## 3. Liver failure

CQ3—4

What is the nutrition therapy for patients with acute liver failure?

A3—4.

There is no nutrition therapy shown to be effective for patients with acute liver failure. Treatment by administering glucose as necessary with attention to the onset of hypoglycemia is suggested (1D).

There is no nutriment for acute liver failure that can be recommended. Therefore, it is suggested to avoid administering a nutriment specialized for chronic liver failure. (1D).

It is suggested to avoid administering amino acid preparations, including special amino acid preparations (1D). (Drafting method F—1)

Commentary

In acute liver failure, energy metabolism is accelerated.[285)] However, damage to hepatocytes decreases efficiency of energy use. Consequently, excessive administration of energy may cause a deterioration in disease condition, and so administration of nutrients using energy substrates that are easily metabolized is required. Rather than administering nutrition to satisfy the necessary daily dose, stabilization of metabolism should be undertaken. [275)]

In acute liver failure, the plasma insulin concentration and the C-peptide concentration rise, but insulin sensitivity decreases; thus, the pace of glucose metabolism decreases and glucagon concentration rises, resulting in hyperglycemia.[286] In fulminant hepatitis, hepatocytes rapidly and dramatically break down, and hypoglycemia caused by the depletion of hepatic glucagon and the failure of gluconeogenesis occurs at a high frequency. Therefore, treatment should be performed by administering glucose enterally or parenterally as appropriate, with attention to the onset of hypoglycemia. [275]

EN should also be administered to patients with acute liver failure.[275] However, among the nutriments adjusted for each disease, none can be recommended. In acute liver failure, the capacity to process ammonia decreases, and for this reason amino acids should not be administered liberally. Hyperammonemia predisposes patients to hepatic encephalopathy, and is a cause of cerebral edema. In addition, glutamine accumulation in the brain may also lead to edema.

However, in recent years, it has been reported that among recipients of living donor liver transplants, the preoperative nutritional condition and the administration of BCAA-enriched nutrition affected the onset of postoperative sepsis, [287] and that preoperative BCAA administration could potentially inhibit the onset of postoperative bacteremia. [288]

J. Disease-Specific Nutrition Support Therapy

## 4. Acute pancreatitis

CQ4—1

Is evaluation of nutritional status and severity necessary before and during nutrition therapy?

A4—1.

It is recommended that severity and nutritional status be evaluated before and during nutrition therapy (1C). (Drafting method A)

Commentary

In acute pancreatitis, mild cases have a favorable prognosis, but severe cases are complicated by organ failure and severe infection, resulting in a high mortality rate. In addition, the mortality rate increases if a positive nitrogen balance cannot be achieved in response to the excessive hypermetabolism and protein catabolism. Therefore, severity assessments standards are useful. In Japan, the 2008 severity assessment standards from the Japanese severity score are being used (If prognostic factors are scored as 3 points or more, or if CT grade is judged as grade 2 or more, the severity grading is evaluated to be as severe), but scoring systems such as the Ranson score, APACHE II score, and the revised Atlanta classification are also being used.[289-291)] In addition, since patients with mild symptoms at initial onset can undergo a rapid deterioration in symptoms, severity should be re-evaluated on a daily, in particularly 48 hours after admission.[289)]
Therefore, it is important to evaluate nutritional status chronologically.

J. Disease-Specific Nutrition Support Therapy

## 4. Acute pancreatitis

CQ4—2

Is aggressive nutrition therapy needed for mild acute pancreatitis?

A4—2.

For mild cases, forcible administration of nutrition is not recommended, except when unexpected complications arise or when oral intake cannot be started within 5-7 days (1B). (Drafting method A)

Commentary

The studies of total PN compared to peripheral PN administration(292) and PN compared to EN administration in patients with mild acute pancreatitis(293) showed no difference in duration of hospitalization or the incidence of complications in the period until oral intake was started. Consequently, in *mild* acute pancreatitis, *oral* intake can be started immediately and so aggressive nutrition therapy and type of administration routes do not affect prognoses.

## 4. Acute pancreatitis

CQ4—3

Which route of administration should be preferred in severe acute pancreatitis, EN or PN?

A4—3.

After resuscitation is complete and hemodynamics have stabilized, it is recommended that EN is preferred route of feeding (1A). (Drafting method C)

Commentary

In a study of severe cases comparing EN and PN initiated within 48-72 hours from onset or diagnosis, the EN group exhibited a significant shortening of hospitalization period, reduction of infection rate and organ failure rate, decrease in rate of surgical treatment and mortality, shortening of the period until oral intake, and greater cost-benefit economy. Furthermore, seven meta-analyses [294-300)] have found a reduction in hospitalization period, [294-296)] reduction in infection rate, [295-299)] decrease in rate of surgical treatment,[295,298,299)] decrease in rate of complication by organ failure, [297-299)] and reduction in mortality in an EN group. [297,299)] Thus, EN initiated within 48-72 hours of onset or diagnosis in severe acute pancreatitis patients is considered to be useful for improving the prognosis. However, according to an epidemiological study, the current reality is that the rate of implementing EN in Japan is low, and only 10.7% of severe cases are being administered EN.[300)]

## 4. Acute pancreatitis

CQ4—4

When should EN be initiated for severe acute pancreatitis?

A4—4.

Initiating EN within 48 hours of hospitalization is recommended whenever possible (1A). (Drafting method C)

Commentary

According to comparison studies of groups receiving EN and PN initiated within 24-28 hours, [301-303)] the EN group exhibited improved outcomes. In addition, a meta-analysis of EN initiated within 48 hours of hospitalization found that the total infection rate, pancreatic infection rate, hyperglycemia rate, and organ failure complication rate decreased, length of hospitalization shortened, and mortality declined[304]). Thus, for severe cases, EN is recommended within 48 hours of hospital admission while being attentive for bowel ischemia and abdominal compartment syndrome. However, the current reality in Japan is that there are many cases of EN initiation on the ninth day after onset or later (average: 10.8±6.4 days).[305])

## 4. Acute pancreatitis

CQ4—5

What is the preferred route for EN?

A4—5.

EN administration through a feeding tube placed in the jejunum is suggested. However, if jejunal tube cannot be placed, gastric feeding or duodenal feeding may also be performed (2B). (Drafting method C)

Commentary

In a comparison study of gastric and jejunal feeding and in a comparison study of gastric and parenteral nutrition, there was no difference in complications, length of hospitalization, or mortality; further, several meta-analyses studies of these routes for EN[306,307)] have reported no difference in the incidence of aspiration and diarrhea, the rate of pain exacerbation, and the energy balance achieved between the study groups. However, among the studies published so far, a number of studies of EN via the duodenal and jejunal routes have been reported. One such study showed that early gastric feeding increased pulmonary complications. Furthermore, in pancreatitis, stomach motility has been reported to decrease to a greater extent than is small intestine motility. As a result, administration of nutrition via the jejunal route is preferable, but

administration via the stomach or duodenum may also be performed if jejunal placement is not possible.

## 4. Acute pancreatitis

CQ4—6

Of the types of formulations used for EN, which type is superior: oligomeric (peptide-based nutrition) or polymeric?

A4—6.

Either formulation type may be used (2C). (Drafting method A)

Commentary

Oligomeric formulations are considered less stimulating of pancreatic enzymes compared to polymeric formulations, but a comparison study [308)] of oligomeric and polymeric formulations has indicated that the former reduced length of hospitalization and a prevention of declining body weight. A meta-analysis investigating studies on EN [309)] did not find any difference in rate of complications, infection, or mortality between groups administered these formula types. However, only one study[308)] has been conducted with the objective of evaluating formulation type, and so caution is needed while interpreting the results. Thus, either nutrition formulation may be used.

J. Disease-Specific Nutrition Support Therapy

## 4. Acute pancreatitis

CQ4—7

Should an immunomodulating enteral diet be administered?

A4—7.

There is no basis for indicating the efficacy of immunomodulating nutrition such as glutamine, arginine, and n-3 polyunsaturated fatty acids preparations, and so it is suggested that such nutriments should not be administered (2B). (Drafting method E1)

Commentary

In a comparison study of standard nutrition and immunomodulating nutrition enriched with glutamine, arginine, n-3 Polyunsaturated Fatty Acids, and antioxidants, no improvement in prognosis was found; in addition, a meta-analysis [310)] also did not demonstrate a clinical effect of such enrichment. However, a different meta-analysis [311)] including studies on intravenous glutamine administration has reported that mortality and infection rate decreased significantly as a result of supplemental intravenous administration of glutamine. Thus, while there is no reason to recommend against administering immunomodulatory nutrition, glutamine preparations for intravenous administration are not commercially available in Japan.

## 4. Acute pancreatitis

CQ4—8

Should pre- or probiotics be administered for severe acute pancreatitis?

A4—8.

There is no basis for indicating their efficacy, so it is suggested that pre- and probiotics not be administered.

Commentary

A study evaluating pre-/probiotics (symbiotics) and probiotics has reported a reduction in infectious pancreatic necrosis and complications, and a reduction in length of hospitalization. However, a multicenter large-scale study[172)] has reported that the intervention group exhibited an increase in surgical treatment rate and organ failure, an increase in bowel ischemia, and a higher rate of mortality. Furthermore, a meta-analysis[176)] of these studies did not find any benefit or harm due to pre- and probiotic use with regards to infection and mortality.

J. Disease-Specific Nutrition Support Therapy

**4. Acute pancreatitis**

CQ4—9

What are the indications for PN and when should PN be initiated?

A4—9.

In severe cases, it is suggested that PN be administered when EN is not possible (2D).

(Drafting method A)

Commentary

Early PN for mild pancreatitis increased intravascular catheter-associated infections.[292] In addition, there is no clinical investigation on the timing to initiate PN for severe acute pancreatitis. As a result, it is recommended that when EN is not possible, such as due to progressive ileus, pancreatic fistula, abdominal compartment syndrome, and non-occlusive mesenteric ischemia, PN should be considered.

J. Disease-Specific Nutrition Support Therapy

**5. Central nervous system disorders**

(1) Nutrition therapy for severe head trauma patients

CQ5—1—1

When should nutrition administration be initiated?

A5—1—1.

It is recommended that tube feeding be initiated within one week (1C). (Drafting method E—1)

CQ5—1—2

Which administration route should be prioritized: EN or PN?

A5—1—2.

Although PN has a tendency towards reducing mortality and improving outcomes more effectively as compared to EN, recent evidence is scarce, and so a priority level has not been determined (no recommendation level, D). (Drafting method E—1)

CQ5—1—3

Which EN administration route should be prioritized: the gastric or the postpyloric route?

A5—1—3.

Although there is no evidence regarding survival, in order to reduce the incidence of pneumonia, postpyloric administration rather than gastric administration is suggested (2A). (Drafting method E—1)

Commentary

Several studies have reported a correlation between early initiation of nutrition therapy and a decrease in mortality in severe head trauma patients. [113, 312-317)] Since these research reports differ in study design, there are many issues that need to be considered. However, it is preferable to initiate PN or EN administration by the seventh day after injury.

Small-scale studies [313,314)] comparing administration routes (parenteral versus enteral) of early nutrition have indicated a tendency towards a lower mortality and improved outcomes when using the parenteral route compared that when using the enteral route. Early initiation of EN has been shown to improve outcomes, [315,317)] and it has also been reported [315)] that EN initiation within 48 hours of injury resulted in a significant improvement in survival and in the Glasgow coma scale.

It has been shown that early initiation of EN could potentially contribute to improved clinical outcomes without increasing the incidence of infection, ventilator-associated pneumonia, and hyperglycemia. [316)]Tolerance to early jejunal administration of nutrition was also reported to be favorable even with reduced intestinal motility;[375 318)] postpyloric feeding tube placement was observed to significantly decrease the rate of late-onset infection. [64)] The method of creating an endoscopic gastrostomy [251)] is also known to significantly reduced the rate of ventilator-associated pneumonia.

J. Disease-Specific Nutrition Support Therapy

**5. Central nervous system disorders**

(2) Cerebral infarction patients

a. Methods for administering nutrition therapy in cerebral infarction patients

CQ5—2—1

Which nutrition administration route should be prioritized: EN or PN?

A5—2—1.

It is recommended that EN be prioritized whenever possible (1E, unknown field). (see Chapter 2, A—CQ3)

CQ5—2—2

Which EN administration route should be prioritized: the gastric or the postpyloric route?

A5—2—2.

There is no evidence available that is specific to cerebral infarction, and so postpyloric administration is suggested over gastric administration in accordance with general principles (2E, unknown field). (see Chapter 2, B—CQ3—1)

Commentary

In a multi-center randomized study of patients with dysphagia hospitalized within seven days of cerebral infarction, there was no significant difference in mortality and neurological outcomes between a group (n=429) in which tube feeding was initiated immediately and a group (n=430) in which it was initiated after at least seven days post-hospitalization. [252)] However, it has been reported that tube feeding via endoscopic

gastrostomy creation significantly reduced the incidence of ventilator-associated pneumonia. [251)]

A single-center randomized study observing the effects of early EN on immunocompetence in cerebral infarction patients[319)] has reported that early EN improved immune condition.

There is no evidence regarding the route of nutrition administration (parenteral or enteral) (CQ1) or the route of EN administration (gastric or postpyloric) (CQ2) that is specific to cerebral infarction. Thus, the recommendation has been made based on general principles.

J. Disease-Specific Nutrition Support Therapy

**5. Central nervous system disorders**

(2) Cerebral infarction patients

b. Methods for nutrition therapy in cerebral infarction patients

CQ5—2—3

Should supplementary specialized nutrition for cerebral infarction patients be administered?

A5—2—3.

The clinical effect of supplementary specialized nutrition is unclear, and so it is suggested that such nutrition should not be administered (2A). (Drafting method G)

*There are no article evaluating clinically important outcomes, so a structured abstract has not been drafted.

Commentary

It has been reported that among cerebral infarction patients (excluding those with subarachnoid hemorrhage) capable of oral consumption, there was no significant difference in mortality or neurological outcomes in a comparison between a group receiving only hospital food and a group that received protein-rich supplementation.[320)] A study of tube-feeding comparing the inclusion of whey and the inclusion of casein for elderly individuals in the acute phase of cerebral infarction did not find a difference in mortality, but it was reported that serum IL-6 decreased significantly and glutathione

increased significantly in the whey group. [160)] It has been noted that EN containing whey could potentially decrease inflammation and increase antioxidant defenses.

In an investigation studying calorie administration and outcomes in the first week in severe cerebral infarction patients, it was reported that survival was the highest in the group administered 8.25-16.5 kcal/kg/day of EN. [321)] Compared to normal tube feeding, administering EN containing abundant glutamine, arginine, and n-3 Polyunsaturated Fatty Acids for two weeks to cerebral infarction patients with a GCS score of no greater than 8 has also been reported to increase CD4+ lymphocytes, increase eicosapentaenoic acid, and decrease arachidonic acid levels; [322)] however, there was no difference in outcomes between study groups. It should be kept in mind that the sample size was small in these studies (n=18).

J. Disease-Specific Nutrition Support Therapy

**5. Central nervous system disorders**

(3) Nutrition therapy during hypothermia therapy

CQ5—3—1

What is the recommended nutrition therapy during hypothermia therapy?

A5—3—1.

There is no special nutrition therapy recommended during hypothermia therapy (unknown field D). (Drafting method G)

*There are no RCTs pertaining to this topic, so a structured abstract has not been prepared.

Commentary

There are no RCTs that may serve as references for nutrition therapy during hypothermia therapy. In a study [323] using an indirect calorimeter to measure the total energy expenditure during hypothermia therapy in cerebral infarction patients (n=10), an average of 1,549 kcal was expended before introducing hypothermia therapy; this value decreased significantly to 1,157 kcal on the third day following the initiation of hypothermia therapy. In addition, according to a study on tube-feeding and tolerance during hypothermia therapy of patients after cardiac arrest, [324] when EN was supplied during the hypothermic state (32-34ºC, 24 hours) until return to normal body temperature, 83% of patients tolerated gastric nutrition (1 kcal/mL, 10 mL/h). However, the complication of vomiting was observed in 9.6% of the subjects during the

hypothermic period (32-34ºC) and in 19.2% of the subjects during the restored temperature period (approximately 36.5ºC). Even in post-cardiac-arrest syndrome patients undergoing hypothermia therapy, nutrition administration is possible; however, after the body temperature reaches 32-34ºC, reducing the rate of nutrition administration should be considered.

## 6. Obesity

CQ6

How should nutrition therapy be implemented in critically ill patients with obesity?

A6.

We suggested high-protein and hypocaloric target is for obese patients with a BMI of at least 30 (2C). (Drafting method A)

It is suggested that the target amount of energy administered be 60-70% of the value measured by an indirect calorimeter or the estimated energy expenditure, or 20-25 kcal/kg/day at an ideal body weight, and the target amount of protein/amino acid administered be 1.2 g/kg (actual body weight)/day (2C). (Drafting method A)

Commentary

Critically ill, obese patients are at a high risk for insulin resistance, infection, and thrombosis, compared to patients with a normal BMI.[325)] Thus, reducing body weight in such patients may improve insulin sensitivity, ameliorate the disease condition and also improve prognosis. In addition, it is believed that sufficient protein administration may help maintain the nitrogen balance and promote wound healing. [326)] A retrospective study noted that for BMI>40, administering 2 g/kg ideal body weight/day of protein was not sufficient.[325)]

According to one observational study of patients with morbid obesity, a low-caloric, high-protein group was found to have improved mortality and duration of hospitalization compared to a high-protein, eucaloric group. One case series study did not find an increase in complications in a hypocaloric, high-protein group compared to the previous study results, and a separate case series study found that the nitrogen balance was positive in a hypocaloric, high-protein group; no problems were found with wound healing in the study groups. However, a RCT of patients administered nutrition as above did not find a significant difference between the two groups. [327)] In addition, an observational study, found that hypocaloric, low-protein therapy for high-BMI patients negatively impacted the 60-day outcomes. [81)]

Based on the above articles, performing hypocaloric, high-protein nutrition therapy at the very least did not worsen the prognosis for obese individuals, and may conceivably have improved outcomes.

For the estimation equation of energy consumption, the Penn State University 2010 predictive equation had the smallest error in indirect calorimetry results among the estimation equations in patients with BMI greater than 30 or 45. [328)] In addition, the modified Penn State University equation had the lowest error for patients aged above 60 years and in those with a BMI of over 30.[328)]

Based on the above, the target energy to be supplied to such patients should be 60-70% of the measurement results from an indirect calorimeter, or of the estimated results using the Penn State University 2010 predictive equation; for subjects aged 60 and over, the modified Penn State University equation should be used for the energy estimation

using the above method, or a target energy value of 20-25 kcal/kg/day with respect to the patient's ideal weight, [327] or 11-14 kcal/kg/day using the patient's actual weight should be used.

Two studies (an observational study of only 13 postoperative patients with TPN management and a study of patients managed by home PN) have reported that supplying 11-14 kcal/kg/day using the patient's actual weight led to an improvement in the nitrogen balance without a deterioration in the prognosis. However, because the subjects of the above mentioned studies differed significantly from the target subjects for these guidelines, this evidence has been characterized as extremely weak.
The aforementioned study[327] in which there was no difference between management with 22 kcal/kg/day of ideal body weight and management with more energy included 30 hospitalized cases, 13 of which were ICU cases. Therefore, these studies are a weak basis for the recommendations in this CQ.

The targets for protein and amino acid administration are 1.2 g/kg (actual body weight)/day[327] or 2.5 g/kg (ideal body weight)/day for patients with BMI>40, or at least 2 g/kg (ideal body weight)/day for those with a BMI that falls between 30 and 40 (30<BMI<40).[326]

In addition, patients with a history of bariatric surgery are expected to be deficient in iron, copper,[325] zinc, selenium, thiamine, folate, vitamin $B_{12}$, and vitamin D; thus, it is noted that individualized evaluation is necessary.

This section has been drafted in light of the ASPEN Clinical Guidelines: Nutrition Support of Hospitalized Adult Patients With Obesity [329] and the Guidelines for the

Provision and Assessment of Nutrition Support Therapy in the Adult Critically Ill Patient. [11)]

It is important to note that the definition of obesity differs between Japan[330)] and that in other countries worldwide, [331)] but there is agreement that exceeding a BMI of 25 represents a deviation from the normal range. The possibility has been raised that Japanese populations may develop obesity-related diseases at lower BMIs than do western populations. [330)] For this reason, caution is needed when using data from other countries to produce a recommendation. However, at the present time, no data on morbid obese patients can be found in the field of intensive care in Japan, and so data from other countries have been cited to produce the current recommendations.

## Nutrition Support Therapy for Children

A. Nutritional therapy

### 1. Necessity of nutritional support

CQ1

What are the impacts of malnutrition on clinical outcomes and what are the best practices for nutritional management for these children?

A1.

1) Malnutrition may affect patient prognosis (2C). (Drafting method F—1)

2) However, the best practices for nutritional management for critically ill children have not been formulated (unknown field, C). (Drafting method F—1)

Commentary

Malnutrition in pediatric hospital patients has been associated with duration of hospital stay and disease progression. [332,333)] The rate of malnutrition in children with severe illness has not changed greatly in recent years. [334,335)] Leite et al.[333)] have evaluated the relationship between malnutrition and clinical outcomes using physical measurements for nutritional evaluations, and have found that the mortality rate was significantly higher in the malnutrition group. In addition, a prospective study of children (385 cases) aged 2 years or older admitted to a pediatric ICU (PICU) has found a significant increase in the duration of mechanical ventilation in children with malnutrition.[336)]

Both insufficient and excessive energy administration are observed frequently in

children with critical pathophysiology. Therefore, evaluation and optimization of nutrition status, amount of nutrition to administer, and method of administration would assist in achieving favorable clinical progress. In addition, sufficient administration of nutrition to children in the ICU is important for growth, even if the duration of PICU stay is short. However, high-quality evidence is lacking to manage malnutrition in the field of pediatric intensive care, and there remain many unanswered questions. This section has been addressed in the ASPEN/SCCM2009 guidelines.[337)]

B. Assessment of malnutrition

**1. Evaluating nutritional status**

CQ1

What are the best practices for screening of malnutrition?

A1—1.

We suggested regular evaluations of nutritional status after ICU admission. (2D). (Drafting method F—1)

A1—2.

We suggested a nutrition administration plan be customized for each individual (2D). (Drafting method F—1)

**2. Markers of nutritional status**

CQ2

What are the evaluation indicators of nutritional status in critically ill patients?

A2.

There are no objective evaluation indicators of nutritional status in critically ill patients. (unknown field, D). (Drafting method F—1)

Commentary

For children with critical illness, it is desirable that nutrition be evaluated as the disease condition progresses. When evaluating nutrition, physical measurements are the

most familiar and quantitative markers of nutrion.[338] Although weight measurements do have value as markers of nutritional state in children, when in the ICU, it is necessary to consider factors affecting body fluid status such as the use of fluid therapy and diuretics. Malnutrition may affect clinical outcomes, and it is important to perform regular evaluations of nutrition in children admitted to the ICU, including a pre-admission evaluation in cases of planned admission. Among the blood test variables used for nutritional evaluation, albumin has been commonly used. In critically ill patients, however, this parameter is reported to be affected by many factors including the administration of albumin preparations, the change in circulating blood volume due to dehydration or fluid therapy, and hepatic dysfunction. Therefore, serum albumin concentration cannot be used as a reliable marker of nutrition. Transthyretin is often used in conjunction with transferrin and retinol-binding proteins as a marker of relatively short-term protein nutritional status.[339] In critical illness, however, the synthesis of albumin and Transthyretin declines as their priority in protein synthesis in the liver changes in a metabolic response to stress,[340] rendering them unreliable markers of nutritional status.[341] This section has been addressed in the ASPEN/SCCM2009 guidelines.

C. Energy expenditure

**1. Estimating energy expenditure**

CQ1

Which methods should be used to estimate energy expenditure?

A1.

It is suggested that estimates of energy expenditure be made based on the results of indirect calorimeter measurements or calculations using predictive equations (2C). (Drafting method F—1)

**2. Determining the energy supply to administer**

CQ2

How should the target amount of energy intake be determined?

A2.

Sufficient evidence does not exist regarding the optimum amount of energy to be supplied (unknown field, C). (Drafting method F—2)

Commentary

The amount of energy requirement changes greatly as a result of surgery, trauma, or other invasive experiences, and is affected by the magnitude and duration of the invasive experience. In many cases, a catabolic response is normally induced. Rising levels of insulin-antagonistic hormones in blood induce insulin resistance, leading to catabolism of fat and protein stored within the body to supply the required energy and

necessary substrates to the metabolic stress response underway. [342)] Children under mechanical ventilation in the ICU experience a variety of metabolic states depending on pathophysiology and circumstances, but most of them are in hypermetabolic state in early stage. [343)] In critical pediatric burn patients, ensues following injury, and the resting energy expenditure (REE) estimated using a standard calculation formula falls short of the actual REE. [344)] If appropriate energy is hypermetabolism not supplied during this period, a large amount of reserved energy in body mass may be eliminated, which may further worsen an existing state of malnutrition. Although there is no conclusive evidence in the field of pediatric intensive care to show that administering low-energy nutrition has a negative impact on clinical outcomes, Larsen et al.[345)] have reported that administering low-energy nutrition after pediatric open-heart surgery resulted in prolonged ICU stay and mechanical ventilation. However, critically ill children under ventilation management administered sedatives may have a smaller true amount of energy expenditure due to reduced activity and a temporarily arrested growth state. In this case, using an energy estimation formula produced for healthy children, and further determining the amount of energy administration taking into consideration the effects of invasion could lead to excessive administration.[346)] Excessive administration leads to unfavorable outcomes including prolonged mechanical ventilation and ICU stay through deleterious effects such as increased carbon dioxide production, liver dysfunction due to fatty liver and cholestasis, and increased infectious complications due to hyperglycemia. [347,348)] For these reasons, REE measurements using an indirect calorimetry are desirable when measuring the amount of energy expenditure

in pediatric patients in critically ill condition[349,350)]. It has been reported that REE measurements using an indirect calorimeter are feasible in children with a variety of critical illnesses. [351-353)] However, the equipment is expensive and difficult to use on a routine basis.

Studies investigating the appropriate amount of energy to administer to children with critical illnesses are lacking. Future studies are awaited on the recommendable amount of energy supply. This section has been addressed by the ASPEN/SCCM2009 guidelines.

D. Macronutrients: carbohydrates, protein, and fat

## 1. Dosage of Macronutrients

CQ1

What is the dosage for carbohydrates, protein, and fat?

A1.

Sufficient evidence does not exist regarding the recommendable amount of each of the nutrients to be supplied (unknown field, C). (Drafting method F—2)

Commentary

It is not always possible to determine the recommended energy dose and the recommended dose for the three major nutrients of carbohydrates, protein, and fat.

Glucose is the most important energy substrate for the whole body and particularly for the brain. Glycogen stores in the body are limited and easily depleted during invasive experiences; gluconeogenesis is thus necessitated in such conditions. However, gluconeogenesis cannot be suppressed by administering exogenous carbohydrates during this period, and exogenous carbohydrates administration may result in hyperglycemia.

Protein breakdown and synthesis are promoted during critical illness and after surgical invasion, but breakdown is predominant.

These may result in a negative protein balance, which causes skeletal muscle wasting, decrease in body weight, and in immune dysfunction. In children, proteolysis rises by

25% postoperatively, and if sepsis occurs, nitrogen discharge from urea increases. [354,355] Administration of protein (amino acids) in a critically ill state is considered necessary for wound healing and for promoting immune responses. However, if there is renal dysfunction or hepatic dysfunction, excessive protein administration should be avoided. When a high dose of protein such as at 4-6 g/kg/day is administered, adverse effects such as azotemia, metabolic acidosis, and neurodevelopmental abnormalities have been reported. [356] According to the ASPEN guidelines for the recommended dose of amino acids to administer,[337] 2-3 g/kg/day for ages 0-2, 1.5-2 g/kg/day for ages 2-13, and 1.5 g/kg/day for ages 13-18, have been indicated. A study of pediatric intensive care patients has found that compared to administration of standard milk, the effects of administering an enteral nutriment with increased protein and energy per mL led to a significant improvement in nitrogen balance. [357,358] Boltrán et al. [359] have compared the effects of administering an enteral nutriment enriched in protein alone with that of administering standard EN in 41 children aged one month to 16 years; a significant increase in retinol-binding protein was found in the group receiving protein-enriched nutriment. However, such reports have been focused on improving nitrogen balance and other nutrition parameters, and have not discussed ICU outcomes. Thus, further study is required on whether EN enriched with protein is beneficial for pediatric intensive care patients.

Similar to that of carbohydrates and proteins, metabolism of fats is also promoted by invasive experiences, [360] and it has been reported that the rate of fat oxidation rises during critical illness in children. [361] When a fat emulsion is administered to children in

critically ill condition, the risk of essential fatty acid deficiency decreases; additionally, the increased production of carbon dioxide may be suppressed. [362)] There is no evidence for the manner in which fat emulsions should be administered to critically ill children. In the ASPEN guidelines, 1 g/kg/day has been recommended as the initial dose, with a subsequent increase in dosage (2-4 g/kg/day) while monitoring blood triglyceride concentrations.

E. Route of nutritional administration

## 1. Determining the route of nutritional administration

CQ1

Which route of administration should be preferred, EN or PN?

A1-1.

We suggested to use EN if the gastrointestinal tract is functional (2D). (Drafting method F-1)

A1-2.

We suggested to eliminatie barriers for EN (2D). (Drafting method F-1)

## 2. Selection of feeding tube position

CQ2

For EN, should administration be performed at postpyloric rather than gastric?

A2-1.

We suggested to select jejunal (postpyloric) rather than gastric route to attain prompt target energy. (2B). (Drafting method F-1)

A2-2.

We suggested to use jejunal (postpyloric) administration be performed if gastroesophageal reflux or delayed gastric emptying exists (2D). (Drafting method F-1)

Commentary

Choosing the appropriate route to administer nutrition is important. If gastrointestinal function is normal, EN is preferable. EN does not increase risk of infection associated with PN, and is a highly cost-effective. [363)] In pediatrics, there are no RCTs focusing on the optimum route of administering nutrition, while EN has been successfully implemented in children with a variety of critical illnesses. [364,365 )] In addition, in a large-scale, prospective cohort study conducted recently, the 60-day mortality was decreased when EN administration approached the target value. [366)] However, the ideal timing and dose of PN has unclear neither for adults nor pediatrics.

Interruption of of EN is frequently required during any procedures or withdrawal from mechanical ventilation. Taylor et al. [367)] have studied nutrition administration in pediatrics admitted to the PICU for at least three days, and have reported 264 instances of discontinuation associated with any treatment. Lyons et al. [368)] have reported that even when postpyloric administration of EN was continued before and after endotracheal extubation, there was no increase in respiratory or gastrointestinal complications such as aspiration, and the necessary amount of energy could be supplied in a majority of cases. When implementing EN for pediatric critical illness, it is important for medical care providers to recognize any interruptions in EN, and to restart administration as soon as possible.

For children receiving EN in the ICU, gastric administration is simple and is widely used. Horn et al. [369)] have investigated intermittent and continuous EN administration, and have found no significant difference between the two methods in the incidence of gastrointestinal complications. Continuous administration is used as a standard method

for jejunal (postpyloric) administration. Intermittent administration is not ordinarily used for jejunal (postpyloric) administration, as it has been associated with a risk of dumping syndrome. Meert et al. [123] have conducted an RCT in PICU patients, and have compared a continuous gastric administration group with a continuous jejunal administration group. They found that although the continuous jejunal administration group reached the target energy amount significantly faster, there was no difference between groups in days in ICU or in days on mechanical ventilation. Given the differences in experience at each facility and the paucity of the effect on clinical outcomes, the evidence does not recommend any particular administration route as a default option. When gastric administration is difficult, jejunal (postpyloric) administration may be attempted. This section has been addressed by the ASPEN/SCCM2009 guidelines.

F. Immunomodulating diet

## 1. Immunomodulating diet

CQ1

Should an immunomodulating diet be administered?

A1.

We suggested that immunomodulating diet should not be administered (2B). (Drafting method F-2)

Commentary

An immunomodulating diet is a general term used for nutrition containing one or more of the following components: arginine, glutamine, nucleic acids, n-3 Polyunsaturated Fatty Acids, selenium, and zinc. This type of diet has been used with the aim in reducing infectious complications and controlling the inflammatory response. However, previous reports have not achieved uniform results and have not been conclusive. Briassoulis et al. [370] have conducted an RCT of 50 children under mechanical ventilation in a PICU. The intervention group was administered EN containing arginine, glutamine, zinc, vitamin E, β-carotene, copper, selenium, andn-3 polyunsaturated fatty acids, but no significant improvement was found in days in ICU stay, mortality, or days on mechanical ventilation in this intervention group. Similarly, other studies evaluating the administration of an immunomodulating diet to pediatric patients with septic shock [371] and severe head trauma [372] have not reported any difference in mortality or days in ICU

in the intervention groups. Albers et al. [373] have conducted an RCT to assess the effects of a glutamine infusion on clinical outcomes in pediatric post-gastrointestinal-surgery patients, and have found that although there was no increase in complications, no significant improvement in clinical outcomes was obtained. Carcillo et al. [374] have conducted a multicenter RCT using nutrition supplemented with added zinc, selenium, glutamine, and metoclopramide on 293 children staying at PICU for at least 72 hours; the control group was administered a placebo. The results showed that there was no difference in infectious complications between the two groups. There is thus no clear evidence for recommending the administration of an immunomodulating diet.

G. Blood glucose management

## 1. Target blood glucose level

CQ1

How should the target blood glucose level be set?

A1.

We recommend to set a target blood glucose level of 215 mg/dL or below and not applying intensive insulin therapy (1A). (Drafting method G)

Commentary

Hyperglycemia has been shown to correlate with poor outcomes in critically ill children.[348, 375,376] Several adult studies have suggested improved clinical outcomes by strictly controlling blood glucose levels in response to hyperglycemia using insulin (tight glycemic control [TGC], or intensive insulin therapy [IIT]). Vlasselaers et al.[377] have used IIT (50-80 mg/dL for ages under 1 year, and 70-100 mg/dL for ages 1 and older) in 700 patients in a PICU, and have found a decrease in mortality in the intervention group. However, in this study, hypoglycemia was observed in 25% of the IIT group (a subsequent study[378], however, did not find a difference in neurological findings or cognitive testing between the two groups). In contrast, Agus et al.[379] have studied the effects of IIT (controlling blood glucose levels to 80-110 mg/dL) in 980 pediatric post-cardiac-surgery patients aged 0-36 months, and found that there was no improvement in days on mechanical ventilation or days in ICU stay in the intervention group. A similar

result was reported from the use of IIT in children other than cardiac surgery, and no improvement in outcomes was reported in the IIT group. [380)] The clinical evaluation of IIT in pediatric intensive care patients is thus still inconclusive.

In most large-scale studies of pediatric patients, insulin has been administered when the blood glucose levels exceeding 215 mg/dL in the control group. Thus, active intervention for blood glucose levels is likely unnecessary below this value. Thus, it is reasonable to keep a target blood glucose value of no greater than 215 mg/dL.

H. Protocol of EN administration and nutritional support team

## 1. The significance of protocol of EN administration and nutritional support team (NST)

CQ1

What is the significance of EN protocol and nutritional support team?

A1.

We suggested support by a nutritional support team (NST) and the use of active EN protocol as a means for more rapid attainment of the energy targets (2D). (Drafting method F-1)

Commentary

In Japan, NSTs have getting become popular, while its effect on outcomes in patients in the PICU is unclear. The degree of NST involvement with patients admitted to the PICU has been reported to be associated with an increase in EN administration, and the risk of mortality has been reported to be lower in pediatric patients for whom the number of days of EN administration was more than half of the days in the ICU.[381 ) ] In contrast, another study has reported that there was no difference in time to achieve the target energy and protein doses due to involvement of NSTs. [382)]

In critically ill children, a nutritional administration protocol may be beneficial for the attainment of early EN. [383)] Petrillo-Albarano et al. [384)] have performed a prospective study of EN protocols, and found a significant decrease in time to reach the target

energy dose and a decrease in gastrointestinal complications such as diarrhea and constipation when established nutrition administration protocols were implemented. This section has been addressed in the ASPEN/SCCM2009 guidelines.