Position Statement for Critical Care Nutrition in Hong Kong

Abstract:

Nutrition therapy is an important yet controversial issue in critical care field. There are numerous international guidelines or publications showing different views; therefore, it is difficult to practice critical care nutrition in clinical setting. We believed that by providing appropriate and individualized nutrition therapy, patient's outcome can be improved.

A local position statement was written by the opinion of critical care physicians, intensivists and dietitians in Hong Kong after reviewing available evidence; with the aim to provide recommendations in nutrition therapy in local critical care setting and to stress the importance of appropriate nutrition therapy. The position statement includes recommendation on general aspect and enteral nutrition, on parenteral nutrition and nutrition for specific diseases. A flow chart (Fig. 1) is constructed to provide a pathway for implementing nutritional therapy in clinical practice. The position statement was endorsed by the Hong Kong Society of Critical Care Medicine (HKSCCM) and the Hong Kong Society of Parenteral and Enteral Nutrition (HKSPEN).

A. General information

1. Introduction

What is nutrition therapy?

Nutrition therapy refers to the provision of calories, protein, electrolytes, vitamins, minerals, trace elements, and fluids via oral, enteral or parental routes.

What is the metabolic response to critical illness?

Critical illness induces a highly complex and variable metabolic response. In general, critical illness goes through 3 phases.

The first phase is a period of hemodynamic instability immediately following an acute insult. There is rapid organ dysfunction; fulminant death can occur despites aggressive resuscitation.

The second phase is characterized by severe increase in catabolism. During this phase, fat mobilization is impaired, and muscle protein is broken down into amino acids to serve as the substrate for gluconeogenesis [1]. This phase may last from few days to few weeks.

The third phase begins as critical illness starts to resolve. Anabolism starts to exceed catabolism. Nutrition support provides substrate for the anabolic state, during which the body corrects hypoproteinemia, repairs muscle loss, and replenishes other nutritional stores [2].

Why is nutrition therapy important in critically ill patients?

Nutrition therapy can attenuate metabolic response to stress, prevent oxidative cellular injury, and favorably modulate immune responses. The provision of calories for energy substrate decreases muscle and tissue oxidation, increases mitochondrial function, increases protein synthesis, maintains lean body mass, and enhances muscle function and mobility. Caloric deficits have been associated with organ failure and increased hospital length of stay [3, 4]. Negative nitrogen balance has been associated with development of ICU-acquired weakness [5-7]. Delivery of appropriate nutrition therapy is seen as a proactive therapeutic strategy that may reduce disease severity, diminish complications, decrease length of stay in ICU, and favorably impact patient outcomes.

2. Nutrition Assessment

What does nutrition assessment include?

1. To assess patient's nutrition risk
2. To identify patients who require special attention
3. To determine patient's energy need

How can we assess patient's nutrition risk?

Malnutrition in critically ill patients has always been difficult to define. Objective measurements are needed to classify patients into different risk categories to facilitate subsequent formulation of nutrition plan. There are a lot of nutrition screening tools available to evaluate nutrition status, such as the Mini Nutritional Assessment, the Malnutrition Screening Tool, and the Subjective Global Assessment [8]. However, these tools do not take into account the disease severity. The NUTRIC score has been highly recommended as an effective nutrition screening tool as it considers both nutrition status and disease severity. It was shown to be correlated with mortality and the expected advantage of the score was to be able to show interaction between the score and nutritional intervention regarding outcomes [9, 10]. Critically ill patients are recommended to undergo nutrition screening by the NUTRIC score within 48 hours of ICU admission.

What are the populations of critically ill patients who require special attention?

Patients with renal disease, liver disease, acute pancreatitis, and major burns require some specific nutritional interventions [11-14]. These patients should be taken care of by a multi-disciplinary team to improve clinical outcomes. More details are covered in the later section of "Specific Conditions".

How can we determine the energy needs in critically ill patients?

In critically ill mechanically ventilated patients, energy expenditure should be determined by using indirect calorimetry. However, the use of indirect calorimetry is subjected to availability. There are also variables in ICU that affect timing and accuracy of indirect calorimetry, including the presence of air leaks, high fractional inspiratory oxygen, and excessive movement [15]. The ICALIC (International Multicentric Study Group for Indirect Calorimetry) group has issued a position paper on the use of

indirect calorimetry in nutrition therapy in 2017, and the group has provided product concept and specifications in the design of a new metabolic cart, in the hope of developing an accurate metabolic system which is simple to use and able to solve all typical pitfalls of indirect calorimetry [16].

When indirect calorimetry is not available or not possible, a simple weight-based equation (25-30kCal/kg/day for BMI <30 kg/m2 and 11-14kCal/kg/day for BMI 30 kg/m2 or above) can be used to determine energy expenditure, as recommended by the SCCM/ASPEN guidelines [17]. Alternatively, another simple weight-based equation (20-25kCal/kg/day) may be used, using the actual body weight for patients with BMI <25kg/m^2, and an adjusted body weight for those with BMI >25 kg/m^2 (Adjusted body weight = Ideal body weight + [Actual body weight – Ideal body weight] x 20%) [28].

There are numerous predictive equations published in the literature, but no single equation is more accurate in ICU setting [18-23]. Predictive equations are even less accurate in obese and underweight patients [24-27]. The poor accuracy of predictive equations is related to many unstable variables affecting expenditure in critically ill patients, such as weight, body temperature, and medications. The only advantage of using weight-based equations over other predictive equations is simplicity.

Whether measured by indirect calorimetry or estimated by predictive equations, energy expenditure should be re-evaluated once there is change in patient's clinical condition.

3. Formulation of Nutrition Therapy

What should be considered when formulating nutrition therapy?

1. Route: oral, enteral, or parental
2. Time of initiation
3. Dose, formula and rate
4. Monitoring: adequacy, tolerance, complications

What is the preferred route of nutrition therapy?

Oral diet is always recommended in all patients able to eat. If oral intake is not possible, enteral nutrition (EN) is recommended over parental nutrition (PN) in critically ill patients. When comparing EN and PN, EN is associated with less infectious complications, shorted length of ICU and hospital stay [28].

What are the contraindications to enteral nutrition?

1. Uncontrolled shock
2. Uncontrolled hypoxemia
3. Uncontrolled acidosis
4. Uncontrolled upper gastrointestinal bleeding
5. Gastric aspirate > 500ml over 6 hours

6. Bowel ischemia
7. Bowel obstruction
8. Abdominal compartment syndrome
9. High-output fistula without distal feeding access

When should nutrition therapy be initiated?

If enteral nutrition is not contraindicated, it should be initiated early within 24- 48 hours of ICU admission. In patients with uncontrolled shock, hypoxemia or acidosis, enteral nutrition can be delayed. Early EN is associated with reduced infectious complications, but no difference in mortality is documented [29]. There will be further discussion in the later section of "Enteral Nutrition".

When enteral nutrition is not feasible, timing for initiation of parental nutrition depends on patient's nutritional risk. In low risk patients, PN should be withheld over the first 5 to 7 days following ICU admission. In high risk patients, initiation of early low dose PN should be carefully considered and balanced against the risks of overfeeding and refeeding, which may outweigh the expected benefits [17].

What is hypocaloric feeding? What is overfeeding? Does the dose matters?

Hypocaloric feeding is an energy provision below 70% of the defined target; while overfeeding is an energy administration of 110% above the defined target.

Undernutrition or over-nutrition is deleterious to clinical outcome according to observational studies [30, 31]. The optimal dose of enteral nutrition appeared to be between 70 and 100% of measured energy expenditure [31, 32].

During the initial acute phase, there is a risk of relative overfeeding due to endogenous energy supply which covers most of the energy needs [33].

How does nutrition formula make a difference in clinical outcomes?

Numerous enteral and parental formulas are available in the market, such as disease-specific (diabetes), organ specific (pulmonary, renal, hepatic), elemental, or immune-modulating. Please refer to the more detailed discussion in relevant sections under "Enteral Nutrition" and "Parental Nutrition".

What should be monitored when ICU patients receiving nutrition therapy?

Critically ill patients have rapidly changing clinical conditions. Their nutrition demands vary at different phases of illness. At the same time, tolerance to nutrition therapy may be hampered by critical illness. Intolerance to enteral feeding can be reflected by vomiting, abdominal distension, high gastric residual volume, or diarrhea. Intolerance impedes the delivery of adequate nutrition, and should be actively managed [34].

Less than half of critically ill patients ever reach their target goal energy intake during ICU stay [35, 36]. Adequacy of energy, protein, and other micronutrients should be monitored regularly. Nutrition therapy has to be adjusted according to patient's need.

Complications, such as hyperglycemia, aspiration, or infections, are not uncommon. Strategies should be applied to minimize these complications; or if complication occurs, it should be managed as soon as possible.

B. Enteral Nutrition

1. Timing of initiation of EN

Enteral feeding has been proven to have a role in maintaining functional and structural integrity of the gut, and modulation of stress and systemic immune response [37-41]. Loss of functional integrity leads to increased bacterial challenge, risk for systemic infection, and greater likelihood of multiple-organ dysfunction syndrome [42, 43].

Multiple randomized controlled trials have been conducted in comparing early initiation of enteral nutrition with late initiation, with regards to outcomes in infections and mortality. Meta-analysis of 8 trials by Heyland et al. found a non-significant trend towards reduced mortality [44] for early initiation of EN, while a meta-analysis of 12 trials by Marik et al. found significant reduction in infectious morbidity (RR = 0.45) and reduction in hospital LOS (mean= 2.2 days) for early initiation of EN within 36 hours [45]. Meta-analysis of 6 trials by Doug et al. showed a significant reduction in pneumonia (OR= 0.31) and mortality (OR = 0.34) for early EN initiation within 24 hours [46]. The meta-analysis by ASPEN 2016, including a total of 21 RCTs, found a significant reduction in mortality (RR = 0.70) and infectious morbidity (RR = 0.74) for early EN initiation [17].

However, during the first 48 hours of admission to the intensive care unit, the patient may be at the height of his/her critical illness. There is evidence that in cases with shock, there is increased risk for subclinical ischemia/reperfusion injuries involving the intestinal microcirculation [47]. Reignier et al. have demonstrated in the NUTRIREA-2 trial that early isocaloric enteral nutrition in cases with shock was associated with a greater risk of digestive complications including ischaemic bowel when compared to early isocaloric parenteral nutrition, although there were no significant differences in mortality [48]. Therefore, EN should not be initiated in patients who are profoundly hypotensive or in patients for whom escalating doses of catecholamine agents are required to maintain hemodynamic stability. Safety of initiating EN in patients on stable low doses of vasopressors was demonstrated in a retrospective review by Khalid et al., with the benefits of lower ICU mortality and hospital mortality [49]. EN may be initiated as soon as shock has stabilized; Heighes et al. have suggested using a shock Index of =<1 for at least 1 h (Shock Index = heart rate/SBP] as a surrogate of haemodynamic stability for initiation of EN [50]. For patients on vasopressor therapy receiving EN, any signs of gastrointestinal intolerance should be closely scrutinized in view of possible gut ischemia, and in such cases EN should be withheld until symptoms resolve.

Conclusion:

We recommend enteral feeding to be initiated within 24–48 hours in the critically ill patient. However,

in the setting of hemodynamic compromise or instability, EN should be withheld until the patient is fully resuscitated, with stable or decreasing vasopressor requirement.

2. Which route is preferable for EN?

Whether to deliver EN through gastric or post pyloric route is controversial. Three meta-analyses [51-53] concluded that post pyloric feeding was superior to gastric feeding in reducing the risk of pneumonia in critically ill patients, without showing any difference regarding other outcomes including mortality, ICU length of study or mechanical ventilator days. However, the studies included were small studies with heterogeneity in terms of the technique for insertion of feeding tube, definition of pneumonia and the amount of nutrient delivery. According to a letter to the editor, a subgroup analysis was performed based on the analysis by Deane and colleagues [52], and the results suggested that post pyloric feeding was associated with a reduction in the incidence of pneumonia in trauma patients only (relative risk (RR) 0.67, 95% confidence interval (CI) 0.52 to 0.87; P=0.003) but no reduction in the medical or surgical ICU population or both (RR 0.68, 95% CI 0.58 to 1.26; P=0.43). From this subgroup analysis, it suggested that the effects of post pyloric feeding versus gastric feeding on clinical outcomes may vary significantly in different patient population.

Delivery of nutrition into the small bowel may be preferable to gastric delivery as the small bowel has greater absorptive capacity and is less subject to impaired motility. However according to one of the largest randomized trial of 181 mechanically ventilated adults [54], early nasojejunal nutrition did not increase energy delivery and did not appear to reduce the frequency of pneumonia, however the rate of minor gastrointestinal haemorrhage was increased, therefore the authors concluded that the routine placement of a nasojejunal tube in such patients is not recommended.

The preferable route for EN in patients suffering from acute pancreatitis will be addressed in the section of “specific conditions”.

Conclusion:

A general recommendation for post pyloric feeding in critically ill patients is not justified.

3. What to give?

i. Macronutrients and micronutrients

Amount of energy

In critically ill mechanically ventilated patients, energy expenditure should be determined by using indirect calorimetry. When indirect calorimetry is not available, a simple weight-based equation can be used to determine energy expenditure. Predictive equations have poor accuracy in estimating energy expenditure in critically ill patients [15].

Undernutrition or over-nutrition is deleterious to clinical outcome according to observational studies

[30, 31]. The optimal dose of enteral nutrition appeared to be between 70 and 100% of measured energy expenditure [31, 32].
Evidences are inconsistent concerning whether a specific threshold of enteral nutrition delivered within the first week of hospitalization affects mortality, length of stay or mechanical ventilation days in critically ill patients [55-59].

Amount of protein
A prospective observational study in mechanically ventilated patients demonstrated that achievement of both protein (1.3 g/kg protein provided) and energy targets was associated with a 50% decrease in 28-day mortality [60].

Addition of glutamine to standard enteral feeds or to an immunomodulatory formula did not improve hospital mortality [61].

Amount of fat
Specific lipids such as omega three showed no significant difference in ventilator-free days or 60-day mortality [62].

Amount of micronutrients
Antioxidant vitamins (including vitamins E and ascorbic acid) and trace minerals (including selenium, zinc, and copper) may improve patient outcome, especially in burns, trauma, and critical illness requiring mechanical ventilation. The results of numerous clinical trials showed that antioxidant and trace element supplementation was associated with a significant reduction in overall mortality [63-76]

Use of probiotics has shown benefit in the ICU setting when commercially available products are provided, reducing ventilator-associated pneumonia, and likelihood to acquire antibiotic-associated diarrhea, pseudomembranous colitis, and possibly overall infections. However, the benefits of probiotics appear to be widely variable, species-specific, and may be dose-dependent, all of which should be taken into account when deciding which product to use [77].

Conclusion:
Amount of energy should be tailor-made to individual patient; indirect calorimetry should be used if the technology is available. Achieving both protein and energy targets can improve patient outcome. No evidence for addition of glutamine to enteral formula. No specific lipid is shown to improve survival in critically ill patient receiving enteral nutrition. Antioxidant vitamins and trace minerals may be beneficial in selected group of critically ill patients. The benefits of probiotics appear to be widely variable and should be considered case by case.

ii. Disease specific formulae

Disease specific formula- DM

Intensive glucose control was shown to increase mortality among adults in the ICU; a blood glucose target of 180mg or less per deciliter resulted in lower mortality than did a target of 81 to 108mg per deciliter [78].

Improved glycemic control can be achieved with a disease-specific enteral formula low in carbohydrates and high in monounsaturated fatty acids (MUFAs), fish oil, chromium, and antioxidants in insulin-treated type 2 diabetes. 105 patients with HbA1C >= 7.0% and/or fasting blood glucose (FG) > 6.7 mmol/L (>120 mg/dL) requiring enteral tube feeding due to neurological dysphagia received 113 kJ (27 kcal)/kg body weight of either test formula (Diben) or an isoenergetic, isonitrogenous standard formula (control) for up to 84 days. Long-term tube feeding with a disease-specific enteral formula was safe and well tolerated in type 2 diabetic patients with neurological disorders. When compared with a standard diet, TI requirement decreased significantly with less hypoglycemia whereas FG and AG were significantly lowered, resulting in improved glycemic control [79].

Conclusion:

Tight glucose control is unnecessary in the ICU, we should aim to prevent hypoglycaemia and diabetic ketoacidosis.

Disease specific formula- fish oil and antioxidant

The OMEGA trial studied the effect of a 24-h dose of 'fish oil/antioxidant' cocktail given in a twice-daily bolus in patients suffering from acute lung injury. The results showed that the fish oil group had fewer ventilator-free days, fewer ICU-free days and more days with diarrhea. The OMEGA trial was ultimately discontinued prior to completion due to indication of futility. The confounding factors included the fish oil supplement was delivered as a large bolus dose given twice a day (120 ml of fish oil cocktail as a single enteral push) [80].

The INTERSEPT study (Investigating Nutritional Therapy with eicosapentaenoic acid: gammalinolenic acid and Antioxidants Role in Sepsis Treatment) was a multicenter RCT designed and fish oil/antioxidant combination was administered continuously in a complete enteral nutrition formula versus a standard (non-high fat) formula for 7 days. This intention-to-treat study showed that patients on fish oil/antioxidant feeding developed less severe sepsis and/or septic shock than patients fed the control diet but no difference in mortality. Furthermore, patients in the fish oil/antioxidant group required statistically less use of mechanical ventilation and had shorter ICU and hospital LOS [81].

Septic ICU patients with APACHE II scores of ≥10 received either an enteral feed enriched with arginine, mRNA, and ω-3 fatty acids from fish oil or a common use, high protein control feed. The mortality rate was reduced for the treatment group compared with the control group and bacteremias were also

reduced in the treatment group [82].

Conclusion:
Studies showed conflicting results regarding the use of fish oil and antioxidants in critically ill patients. Further RCTs are required to address this issue.

4. Enhancing the delivery of EN

Monitoring of tolerance

Gastrointestinal (GI) intolerance is common in critically ill patients [83], and intolerance to EN has been observed in approximately 33% of patients in Asia [84]. ICU length of stay has been shown to increase with greater number of symptoms of GI intolerance [85]. A greater number of symptoms of GI intolerance is associated with failure of EN delivery and hence warrant increased vigilance. Presence of multiple symptoms of GI intolerance and the associated enteral underfeeding are both shown to be associated with increased mortality in a retrospective observational study by Blaser et al. [86].

Tolerance may be determined by physical examination, any passage of flatus and stool, absence of patient complaints such as pain or abdominal distention and radiological investigations. GI intolerance is usually defined by vomiting, abdominal distention, complaints of discomfort, high NG output, high gastric residual volumes (GRV), diarrhea, reduced passage of flatus and stool, or abnormal abdominal radiographs. However in a survey by Metheny et al., majority of nurses rely solely on measuring GRVs [87]; however the sole use of GRV as monitoring of GI tolerance is demonstrated to be flawed.

Conclusion:
We recommend daily monitoring of gastrointestinal tolerance of EN by a multimodal method.

Role of Gastric Residual volume (GRV)

GRV is a common and traditional practice to assess gastrointestinal (GI) tolerance in critically ill patients. In the past, it was believed that larger GRV is associated with higher rates of aspiration and ventilator associated pneumonia (VAP). The accuracy of GRV is limited by the method of measurement, size of feeding tube and position of the tip of feeding tube. The problem of GRV includes prolonging the time to reach energy target and consumption of nursing time.

There are 3 randomized controlled trials (RCTs) comparing GRV with higher (ranging from >250ml to >500ml) or lower threshold (ranging from >150ml to >200). Pinilla et al. found that there was no statistical difference in the frequency of gastrointestinal (GI) tolerance in terms of high GRV, emesis or diarrhea [88]. Also there was reduced time to achieved target with GRV >250ml. McClave et al. found that there was no statistical difference in the frequency of regurgitation or aspiration when using higher (>400ml) or lower (>200ml) threshold of GRV [89]. REGANE study by Montejo el. at found that

the mean enteral nutrition (EN) volume ratio (EN received/ EN prescribed) was greater in the higher threshold group in the first week of intensive care unit (ICU) stay [90].
Reignier et al. conducted a randomized, noninferiority, open-label, multicenter trial to compare the monitoring of GRV with threshold of 250ml (control group) versus no monitoring of GRV (intervention group) in the risk of VAP [91]. They found that VAP occurred in 16.7% in the intervention group and 15.8% in the control group (difference, 0.9%; 90% CI, -4.8% to 6.7%). There were also no significant between-group differences in other ICU-acquired infections, mechanical ventilation duration, ICU stay length, or mortality rates. They concluded that among adults requiring mechanical ventilation and receiving early enteral nutrition, the absence of gastric volume monitoring was not inferior to routine residual gastric volume monitoring in terms of development of VAP.

ASPEN guideline 2016 suggested that GRV not be used as part of routine care to monitor ICU patients receiving EN [17]. Also for those ICU where GRV is still utilized, holding EN for GRV <500ml in the absence of other signs of intolerance should be avoided. ESPEN 2019 guidelines recommend delaying EN only when GRV is more than 500ml over a 6 hour period [28].

Conclusion:
Routine monitoring of GRV is not necessary, its utilization should be considered case by case.

Avoiding inappropriate cessation of EN
Multiple studies have shown that patient intolerance only represents a relatively small proportion of EN cessation time [35, 36, 92-95]. Up to 25% of cessation time were due to fasting after midnight for diagnostic tests and procedures [93, 94]. Technical issues requiring repositioning/replacing the enteral access device also account for up to 25% of cessation time [93, 94]. In one observational study in Malaysia by Lee et al., only about 20% of cessation time were due to true intolerance [95]. The other causes of EN cessation should be scrutinized and unnecessary interruption of EN should be avoided in order to enhance the amount of EN delivered.

Diarrhea is another common cause of cessation of EN; clinicians frequently stop EN when persistent diarrhea [96]. However, there are other causes of diarrhea apart from the EN formulation [96], and most episodes of nosocomial diarrhea are self-limiting [97]. ASPEN 2016 guidelines have suggested, based on expert opinion, that EN should not be automatically interrupted for diarrhea, but rather be continued while the cause of diarrhea were being evaluated [17].

Conclusion:
We recommend minimizing unnecessary cessation of EN due to reasons other than GI intolerance.

Initiatives to reduce aspiration risk
Elevating the head of the bed 30°–45° was shown to significantly reduce risk of pneumonia [98, 99].

Reducing the level of sedation/analgesia when possible (use of a nurse-driven sedation protocol) and minimizing transport out of the ICU for diagnostic tests and procedures were also associated with less aspiration risk [100, 101].

Conclusion:

To reduce risk of aspiration, we recommend employing a semirecumbent position (head of bed elevated 30°–45°), minimizing the level of sedation, and minimizing unnecessary transport out of ICU for critically ill patients while on EN.

Developing feeding protocols

Implementation of feeding protocols in the ICU with defined goal rates and specific orders for handling GI intolerance have been shown in multiple RCTs to be successful in increasing overall percentage of energy delivered [102-107].

ASPEN aggravated 2 studies [102, 107] in their 2016 guidelines paper [17] and concluded that the use of nurse-driven EN protocols to increase EN delivery had a positive impact in terms of patient outcome, with reduction of the incidence of nosocomial infections.

Volume-based feeding protocols utilizing a daily volume target instead of hourly rates have also been shown to increase volume of nutrition delivered [107-109]. Furthermore, top-down protocols where multiple different strategies were employed at initiation of EN (including volume-based strategy, use of prokinetics, postpyloric feeding etc.), with removal of individual strategies as tolerance improves over time, were also shown to enhance volume of EN delivered [107]. PEPUp protocol is one of such top-down protocol which have been shown to be safe (without increase in rates of vomiting, regurgitation, aspiration, and pneumonia) and associated with enhanced protein and caloric delivery [58, 107, 110].

Conclusion:

We recommend the use of a nurse-driven feeding protocol for enhancing the volume of EN delivered, with consideration being given for the use of a volume-based or top-down feeding strategy.

Use of continuous infusion of EN

Continuous infusion of EN was shown in one prospective RCT to have a trend towards decreased mortality [111], and in several RCTs to have greater volume of EN delivered when covered to bolus infusion [112-116].

Aggressive bolus infusion of EN was shown in one study to increase aspiration risk [117]. However there are examples in literature where bolus feeding were tolerated in the critically ill population [118, 119].

Conclusion:

We recommend the use of a continuous infusion of EN, especially those already shown to be

intolerant to bolus gastric EN.

Prokinetics

In the meta-analysis included in the ASPEN 2016 guidelines paper [17] covering 3 RCTs, the use of metoclopramide have been shown to be associated with reduced GRVs (RR = 1.87); however patient outcome benefits cannot be demonstrated. There are some individual reports of superiority of erythromycin as a prokinetic agent over metoclopramide [120]; overall there is a lack of conclusive evidence [121].

Use of prokinetics are not without risks. Both erythromycin and metoclopramide were associated with a prolonged QT interval [122] and tachyphylaxis [120]. Erythromycin has been associated with bacterial resistance unless given for a short duration at a low dose [123]. Metoclopramide on the other hand is associated with tardive dyskinesia, especially in the elderly.

Combination of the two prokinetics erythromycin and metoclopramide demonstrated improved GRVs in the expense of increase in watery diarrhea [124, 125]. No patient outcome benefits can be demonstrated.

Opioid antagonists may have a role in improving gut motility. In one study by Meissner et al., use of enteral naloxone to reverse the effects of opioid narcotics at the level of the gut when compared to placebo, was shown to increase the volume of EN delivered, with reduction in GRVs and also reduction the incidence of VAP [126].

Conclusion:

We recommend the use of either metoclopromide or erythromycin in selected cases with proven GI intolerance, or as part of a top-down feeding strategy.

C. Parenteral Nutrition

1. Timing of initiation of supplementary PN

Optimal timing for the initiation of PN still remains controversial [127]. Theoretically supplementary PN (SPN) should be initiated in critically ill patients when energy needs are not covered by EN. However, balancing the risks and benefits of PN, exact timing to initiate PN remains debatable. Multiple randomized control trials failed to show mortality difference between early PN versus late PN [128-130]. ESPEN guidelines in 2019 recommends that PN should not be started until all strategies to maximize EN tolerance have been attempted. And in patients who do not tolerate full dose EN during the first week in ICU, the safety and benefits of initiating PN should be weighed on a case-by-case basis [28]. ASPEN guidelines suggested to initiate exclusive PN as soon as possible, when EN is not feasible, for high nutrition risk or severely malnourished adult critically ill patients. While for low nutritional risk patients, exclusive PN should be withheld over the first 7 days following ICU admission [17].

Conclusion:

Supplementary PN should be initiated if and only if EN is not tolerated despite all strategies. Evidence showed late start of PN up to one week following ICU admission is not inferior to early initiation of PN in terms of mortality.

2. What to give?

Parenteral nutrition is an admixture of solutions containing dextrose, amino acids, electrolytes, vitamins, minerals, and trace elements. Lipid emulsion may be infused separately or added to the mixture. Mixing all three macronutrients, a so-called total nutrient admixture, or 3-in-1 parenteral nutrition, is favored by most experts [131]. Exact composition and infusion rate should be tailored to the nutritional and fluid needs of each patient by a multidisciplinary team of physicians, nutritionists, pharmacists, and nurses [132].

Patients requiring PN in the ICU may benefit from a feeding strategy that is hypocaloric (≤20 kcal/kg/d or no more than 80% of estimated energy needs) but provides adequate protein (≥1.2 g protein/kg/d). This strategy may optimize the efficacy of PN in the early phases of critical illness by reducing the potential for hyperglycemia and insulin resistance, and may reduce infectious morbidity, duration of mechanical ventilation, and hospital LOS [133].

Critically ill patients generally required protein of 1.2 to 1.5 g/kg/day [134]. For specific subgroups of patients like major burns, obese and traumatic brain injury, protein requirement may be up to 2.5g/kg/day [17, 134]. Each gram of protein supplies 4 kcal calories but each gram of hydrated mixed amino acid (AA) in PN products only provide 3.4 kcal calories and 0.83g protein substrate due to peptide bond formation during the dehydration process. Every 6.25g protein supplies 1g nitrogen. Premixed ready-to-use PN products are convenient and potentially cost-effective, but their fixed

nutrient composition is a drawback. They are commonly provided in volumes calculated to match the patient's calorie requirement, with may result in under-provision of amino acids in specific subgroups such as burns and obese patients [135]. In the commercially available PN products, proteins are supplied as an amino acid (AA) solution which is a mixture of essential and nonessential amino acids ranging from 3% to 10%. Specific formulas are available for higher levels of the branched chain amino acids (BCAA) which may be useful for patients with liver disease. However, these special formulations are very expensive, and their efficacy has not been thoroughly documented through research. In patients with hepatic encephalopathy already receiving first-line therapy (antibiotics and lactulose), there is no evidence to date that adding BCAAs will further improve mental status or coma grade [136, 137].

Energy requirements of a critically ill patient estimated to be 25-30 kcal/kg/day which are mostly provided by carbohydrate and fat. In PN, carbohydrates are supplied in the form of dextrose which can range from 5% to 70%. Dextrose in solution has 3.4 kcal per gram rather than 4 kcal per gram as in dietary carbohydrates, because a non-caloric water molecule is attached to dextrose molecules. The recommended dextrose administration should not exceed 5mg/kg/min [28].

Lipid emulsions in PN are composed of soybean and/or safflower oil, glycerol, and egg phospholipid which are sources of essential fatty acid (EFA) and energy. Since intravenous lipids are isotonic and calorically dense, they are a good source of calories for hypermetabolic patients, or patients with volume or carbohydrate restrictions. Usually, lipid emulsions are composed of long chain triglycerides (LCT). Medium chain triglycerides do not require carnitine for oxidation and therefore may be more easily used for energy in the stressed patient. MCTs produce greater numbers of ketones than LCTs, and ketones can be a secondary source of energy for peripheral tissues. The exact amount required is unknown.

The optimal ratio between dextrose and lipid calories has to be controlled, and may vary from 50:50 to 75:25. In terms of improving nitrogen balance, a high ratio is suggested [138]. However, administration of marked amounts of dextrose will lead to hyperglycaemia while high fat administration can lead to lipid overload, and especially unsaturated fat to impaired lung function and immune suppression [139]. Close monitoring of glucose, triglycerides and liver function tests may guide the optimal ratio for administration [140].

Non-Protein Calorie to nitrogen ratio (NPC: N ratio) of 100-200kcal/g of nitrogen is often used as a clinically feasible indicator of nitrogen balance to prevent muscle loss [141].

Conclusion:
Exact composition and infusion rate should be tailored to the nutritional and fluid needs of each individual patient by a multidisciplinary team of physicians, nutritionists, pharmacists, and nurses.

3. How to select an appropriate vascular access for PN administration?

PN could be administrated centrally or peripherally. Central PN administration remains to be the most common practice in Hong Kong ICUs. The leading complications of central PN administration include central line-associated blood stream infection (CLABSI) and deep vein thrombosis (DVT) [142]. Subclavian vein is the preferred site for non-tunneled catheters to lower the risk of CLABSI [143]. Other methods to reduce the risk of CLABSI and DVT include using a single-lumen central catheter with smaller caliber [144]. Multi-lumen catheters receive more frequent manipulation than single-lumen catheters, which likely accounts for the increased rates of CLABSI reported with multi-lumen catheters [145, 146]. Large caliber catheters are also more likely to induce endothelial trauma, inflammation, stasis and turbulent blood flow which lead to thrombus formation [147]. However, if multi-lumen central catheters must be used for PN, one lumen of the device should be dedicated exclusively for the PN administration [144, 146, 148]. Using a dedicated lumen reduces the potential for microbial contamination by limiting the frequency of manipulation, and avoids the coinfusion of potentially incompatible medications with the complex PN mixture [144].

For all newly inserted central catheters, correct position should be confirmed radiologically before PN administration [144]. Although the tip position remains a topic of debate, the tip of the catheter should be ideally positioned in the distal third of the superior vena cava (SVC) near the junction with the right atrium [149, 150]. Placing the tip too deep into the right atrium will potentially lead to cardiac dysrhythmia, perforation and tamponade [151, 152]. Positioning the tip in the upper portions of SVC are known to elevate the risk for thrombotic complications [153-155]. In the upper SVC, left-sided catheters carry an added risk for DVT because the tip often abuts the vessel wall, where motion of the catheter may cause repeated trauma to the endothelium [156, 157].

Peripherally administrated PN avoid the complications of central venous catheter placement. Unfortunately, critically ill patients rarely have sufficient peripheral venous integrity to allow infusion of relatively hypertonic nutrient admixtures without disrupting the nutrition regimen or other drug therapies. Frequent reposition of the peripheral iv catheters every 72-96 hours, suggested by the Centres for Disease Control and Prevention to reduce blood stream infection and phlebitis, is an important barrier to administering peripheral PN [149, 156].

Improvements in the design of different catheters e.g. peripheral midline catheters (which can remain in place for 29 days) or peripherally-inserted central catheter (PICC) (which may last up to months or years), may offer an alternative.

Conclusion:

The selection of vascular access should be individualized. Choose the smallest caliber with fewest number of lumens necessary for individual patient's needs. Dedicate one lumen for PN administration whenever possible.

4. How to monitor and assess progress towards therapeutic goals, the need to adjust the PN prescription and when to wean PN?

Monitoring and assessment should be performed regularly from both clinical and laboratory aspect. Clinical monitoring parameters include physical examination of muscle and fat stores, fluid status, functional status, body height, weight, and signs of micronutrient abnormalities. Intake and output records, review vital signs, wound healing and vascular access for PN should be evaluated [144, 150, 158]. Laboratory monitoring parameters include frequent glucose, electrolytes and acid-base measurement until stable. Blood count, liver function test, clotting profile, lipid profile, serum proteins should be assessed at least weekly. Micronutrients including iron, zinc, selenium, manganese, copper, chromium, vitamins, folate, TSH and carnitine should be monitored as clinically indicated [144, 150, 158]. A multidisciplinary team including clinicians, pharmacists, dieticians can minimize PN-related errors and improve patient outcomes [159].

Before attempting to wean PN, the bowel function has to be improved to a certain level. Generally, if 50-75% of energy and protein need could be provided orally or through EN, PN can be withdrawn gradually. The weaning process could be rapid, in a short period without significant modification. However, a longer weaning period may be necessary for patients with complicated hospital course and the malnourished. In the transition period, more frequent monitoring of both clinical and laboratory parameters is necessary. A weaning protocol can help to prevent overfeeding and fluid overload [160].

Conclusion:

Consider a multidisciplinary team to review and monitor patient's clinical status and response to PN. Consider using a weaning protocol during transition from PN to EN. Modify PN prescription when oral intake / EN achieves 50-70% of requirements for energy, protein and micronutrients.

5. Should parenteral glutamine be used?

Improved short-term survival with glutamine supplementation is shown in single centre trials published before 2003 [161]. But trials published after 2003 did not show mortality difference. The REDOX trial, a multi-centre large RCT showed higher mortality for patients who received glutamine [162]. Another large study of parenteral glutamine use in ICU patient failed to demonstrate an outcome benefit in terms of infectious complications and mortality [163]. Conflicting evidences failed to guide the use of glutamine.

Conclusion:

Parenteral glutamine supplementation should not be used routinely.

D. Specific diseases

1. Acute Hepatic Failure :

Whenever available, indirect calorimetry should be used to measure resting energy expenditure (REE). A total energy supply of 1.3 x REE is recommended for patients with chronic liver disease [164]. Energy requirement in critically ill patients with liver disease are highly variable, hence difficult to predict by simple equations, and therefore best determined by IC [165]. In cirrhotics without ascites, the actual body weight should be used for the calculation of the basal metabolic rate. In patients with ascites the ideal body weight should be used [164]. When weight-based equation is used, energy and protein requirements are based on the same recommendations as for other critically ill patients.

Three subtypes of acute liver failure can be classified according to their clinical course. In hyper-acute liver failure, onset of hepatic encephalopathy (HE) occurs within 7 days of the onset of jaundice. In acute liver failure the interval is 8 to 28 days. While in sub-acute liver failure, this interval is between 29 and 72 days.

In patients with severe hyper-acute hepatic failure with encephalopathy and highly elevated arterial ammonia (> 150 µ mol/l) who are at risk of cerebral edema, nutritional protein support can be deferred for 24-48 hours until hyperammonemia is controlled. As protein administration may further elevate ammonia level and exacerbate cerebral edema, ammonia level should be monitored once it is commenced [164].

In the other two subtypes of acute liver failure, early nutrition is necessary [164]. Patients with mild HE can be fed orally as long as cough and swallow reflexes are intact. Patients with acute liver failure who cannot be fed orally should receive EN. PN should be used as a second line treatment in patients who cannot be fed adequately by oral and/or EN.

Low dose EN should be started independent of the grade of HE. According to the ESICM guidelines, low dose EN should be started when acute, immediately life-threatening metabolic derangements are controlled with or without liver support strategies, independent on grade of encephalopathy. Arterial ammonia levels should be monitored [29]. Standard enteral formula can be used in ICU patients with acute and chronic liver failure.

There is no evidence of additional benefit of branched –chain amino acid (BCAA) formulation on coma grade in ICU patients with hepatic encephalopathy who is already receiving first –line therapy with luminal –acting antibiotics and lactulose [136, 137, 166].

2. Acute Renal Failure:

To determine the energy requirement in patients with acute renal failure, it is best measured by indirect calorimetry (IC). If IC is not available, energy needs can be determined by the use of a weight-based equation (25-30 kcal/kg/day). Meanwhile, protein requirement followed the standard ICU recommendations ie 1.2-2 g/kg actual body weight per day [17].

For patients receiving frequent hemodialysis or CRRT, it is recommended to receive an increase in protein up to a maximum of 2.5 g/kg/day [17].

In continuous renal replacement therapy (CRRT), there is a loss of about 0.2g amino acids/ L filtrate; giving a total daily loss of 10-15 g amino acids, hence a protein loss of 5- 10 g /day has to be added [167]. Patient on CRRT may require at least an additional of 0.2 g/kg/day totally up to 2.5 g/kg/day protein [168-170]. At least one RCT has suggested that an intake of 2.5 g/kg/day is necessary to achieve positive nitrogen balance in this group of patients [169].

3. Pulmonary Failure:

Current evidence does not support the routine use of high-fat / low –carbohydrate formulations in an attempt to lower the respiratory quotient, hence carbon dioxide production. However, effort should be made to avoid overfeed the patient as lipogenesis would lead to increase CO2 production which can be tolerated poorly by patient prone to hypercapnia [171-174]. There are conflicting data regarding the routine use of an enteral formula with an anti-inflammatory lipid profile (e.g. omega-3 fish oils, borage oil, and anti-oxidants) in patients with ARDS/ALI and sepsis in reducing organ failure, duration of mechanical ventilation, ICU LOS or hospital mortality compared with the use of a standard enteral formulation [62, 80, 175-178].

4. Acute pancreatitis

i. Parenteral Nutrition (PN) or Enteral Nutrition (EN)

If clinically feasible, enteral nutrition is preferable over parenteral nutrition. A Cochrane review of 8 trials with a total of 348 patients with acute pancreatitis showed a reduction in death, multi-organ failure, systemic infection, need for operative intervention and hospital length of stay for patients receiving EN compared with those receiving PN. A subgroup analysis of patients with severe acute pancreatitis receiving EN had a lower risk of death and multi-organ failure compared with those patients on PN [179]. A subsequent meta-analysis of 8 RCTs including 381 patients with severe acute pancreatitis also showed improvement in major complications and death with EN when compared with PN [180].

ii. Enteral Nutrition (EN) vs oral nutrition

Studies have not demonstrated the superiority of EN over oral nutrition, in terms of complications between the two groups [181, 182]. The PYTHON trial compared early EN within 24 hours of admission with oral diet after 72 hours in patients with high risk of complications. Two hundred and eight patients were randomized with a primary composite end point of major infection or death. The primary end-point occurred in 30% of the early EN group vs 27 % of the on demand group and the difference was not statistically significant. Hence there was no superiority of early nasoenteric feeding compared with oral feeding after 72 hours [183].

iii. Timing of enteral nutrition (EN)

The available data support the initiation of EN in patients with severe acute pancreatitis within 48 hours, if clinically feasible. A retrospective review of 197 patients with severe acute pancreatitis demonstrated reduced mortality, development of infected necrosis, respiratory failure, and need for ICU admission in patient receiving early EN, within 48 hours of admission when compared to those receiving delayed EN, after 48 hours [184]. Subsequent studies have also demonstrated improved outcomes with early initiation of EN [180, 184-190]. A Cochrane review of 11 RCTs by Petrov et al. demonstrated improved outcomes with respect to multi-organ failure, pancreatic infectious complications, and mortality in patients with acute pancreatitis receiving EN within 48 hours of admission compared with those receiving PN [191].

IV. Gastric Nutrition vs Jejunal Nutrition

For patients with severe acute pancreatitis, there is no difference in tolerance or clinical outcomes between feeding by gastric and jejunal route. The RCT conducted by Eatock et al. of early nasogastric vs nasojejunal feeding in patients with severe acute pancreatitis found no statistically significant difference in inflammatory markers or pain scores between the groups [192] . A subsequent RCT in patients with severe acute pancreatitis also found no difference in LOS, need for surgical intervention, or death between the two routes of feeding [193]. These two studies and a third RCT [194], comprising a total of 157 patients, were used to conduct a meta-analysis. The author reported no significant differences between the two groups in their relative risk of mortality, diarrhea, exacerbation of pain, and meeting energy balance [195].

V. Types of EN formula

Use a standard polymeric formula when initiating EN in patients with severe acute pancreatitis. A meta-analysis compared the effect of immune-mediating enteral nutrition with standard enteral nutrition revealed a modest benefit in mortality with immunonutrition. However, there was no difference in infectious complications, systemic inflammatory response syndrome, or organ damage. They also noted no clear benefit of enteral formula with fiber or probiotic supplementation [196] . Similar findings were also noted in a separate systemic review which showed that polymeric formulations were not less tolerated compared with oligomeric fomulations. Moreover, no specific benefit was noted with immunonutrition or probiotics [197].

5. Burns:

Indirect calorimetry (IC) is recommended to determine energy requirements whenever it is available. The energy requirements after major burns are significantly increased above basal resting energy expenditure (REE) and the increase varies with time, and grossly proportional to the burned body surface area [198].

Without IC, the Toronto equation, which is based on multiple regression analysis of an important number of calorimetric studies, is a well validated alternative for adult patient suffering from acute burn injury [199, 200].

TORONTO FORMULA:

For all patients:

REE (kcal) = -4343 + (10.5 x %TBSA burned) + (0.23 x kcals) + (0.84 x Harris Benedict) +
(114 x T ©) – (4.5 x days post-burn)

TBSA = total body surface area burned

Kcals = calorie intake in past 24 hours

Harris Benedict = basal requirements in calories using the Harris Benedict equation with no stress factors or activity factors

T ©= body temperature in degree Celsius

Days post-burn = the number of days after the burn injury is sustained using the day itself as day zero

Protein requirement is suggested to be in the range of 1.5-2 g/kg/day [4, 5, 6]. Study showed that protein intake above 2.2 g/kg/day has no further beneficial effects on net protein synthesis [7]. This recommendation is based on the 2001 American Burn Association guidelines, the 2013 ESPEN guidelines in major burns, as well as the 2016 SCCM and ASPEN guidelines [17, 201, 202].

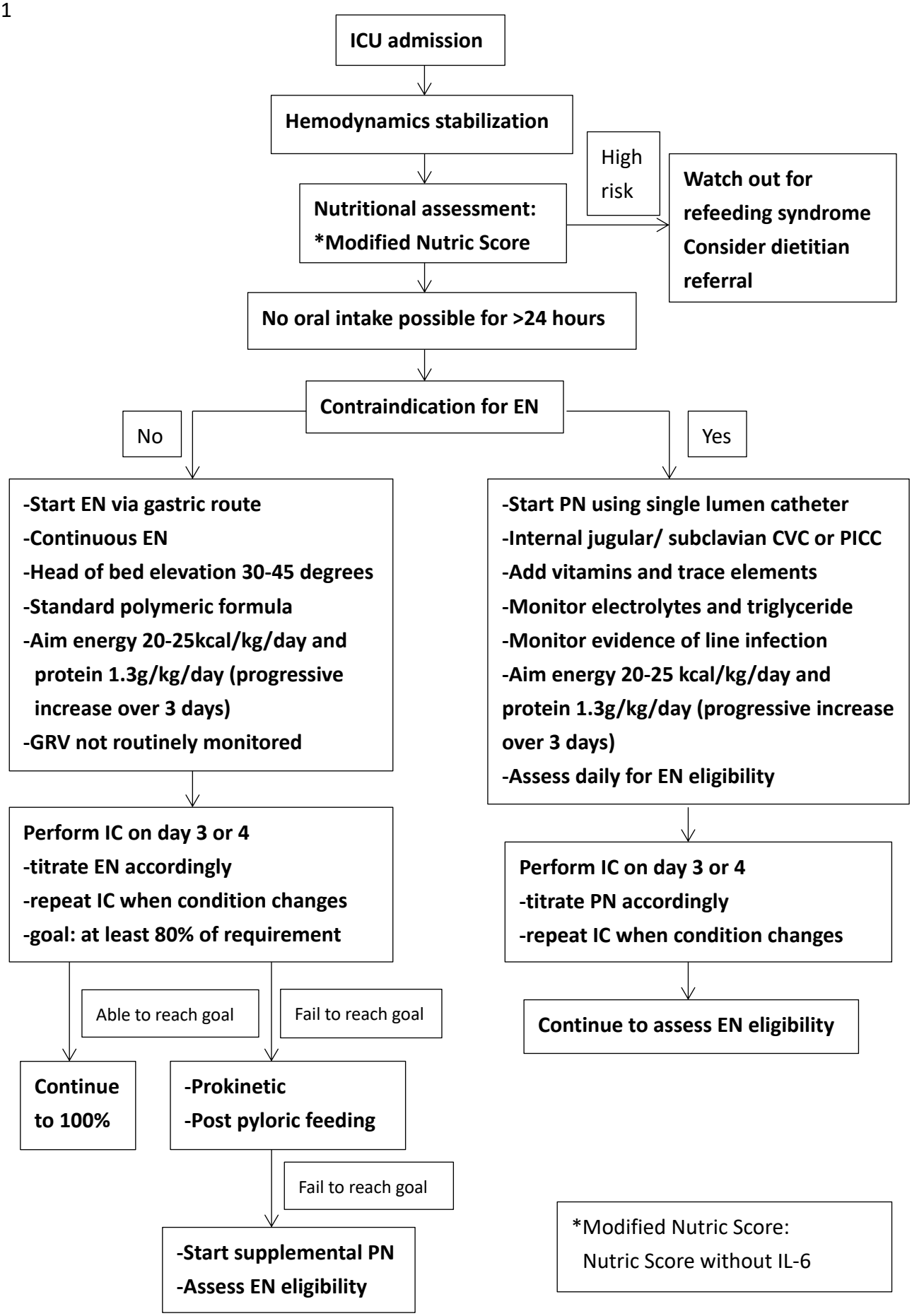
Very early initiation of EN (within 4-6 hours of injury if possible) is suggested [203]. Very early enteral feeding (within first 6-12 hours) after injury by the gastric route is associated with numerous clinical and biologic advantages, such as attenuation of the stress hormone levels, of the hypermetabolic response [204] , results in increased immunoglobulin production [205], reduction of stress ulcers, as well as reducing the risk of malnutrition and of energy deficit [206, 207].

Supplement of vitamins C and E, copper, selenium and zinc have been shown to improve wound healing. Using doses of vitamin C and E 1.5 -3 times higher than recommended daily intakes had been shown to decrease oxidative stress and improved wound healing [208].
Three trace elements have been shown to be particularly important in immunity and wound healing: copper (Cu), selenium (Se) and zinc (Zn) [209, 210]. They are lost in large quantities with the exudative losses at open burn wounds. Systemic review has shown a reduction in infectious complications and length of ICU stay with their supplementation [211].

Glutamine supplementation has repeatedly shown in studies, systemic review and meta-analyses to have beneficial effects in reducing infectious complications (mainly gram negative infections) and also mortality in patients with major burn injuries[212, 213, 214] . This higher requirement is secondary to exudative losses as analysis of burn exudates shows that glutamine is lost in larger amounts than any other amino acid [215]. Therefore, it is recommended that for burns > 20% body surface area, additional enteral doses of glutamine (0.3-0.5g/kg/d) should be administered for 10-15 days as soon as EN is started [28].

EN should be provided to burns patients with functional GI tracts and for whom volitional intake is inadequate to meet estimated energy needs. PN should be reserved for those whom EN is not feasible or not tolerated. Studies have supported that when early EN were compared to PN, though PN patients received significantly more energy, it was associated with higher infectious rate and mortality [205, 216].

Fig. 1


ICU admission
Hemodynamics stabilization
Nutritional assessment:
*Modified Nutric Score
High risk
Watch out for refeeding syndrome
Consider dietitian referral
No oral intake possible for >24 hours
Contraindication for EN
No
Yes
-Start EN via gastric route
-Continuous EN
-Head of bed elevation 30-45 degrees
-Standard polymeric formula
-Aim energy 20-25kcal/kg/day and protein 1.3g/kg/day (progressive increase over 3 days)
-GRV not routinely monitored
-Start PN using single lumen catheter
-Internal jugular/ subclavian CVC or PICC
-Add vitamins and trace elements
-Monitor electrolytes and triglyceride
-Monitor evidence of line infection
-Aim energy 20-25 kcal/kg/day and protein 1.3g/kg/day (progressive increase over 3 days)
-Assess daily for EN eligibility
Perform IC on day 3 or 4
-titrate EN accordingly
-repeat IC when condition changes
-goal: at least 80% of requirement
Perform IC on day 3 or 4
-titrate PN accordingly
-repeat IC when condition changes
Able to reach goal
Fail to reach goal
Continue to 100%
-Prokinetic
-Post pyloric feeding
Continue to assess EN eligibility
Fail to reach goal
-Start supplemental PN
-Assess EN eligibility
*Modified Nutric Score:
Nutric Score without IL-6

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