Nutrition in Paediatric Patients

Module 10.4.

Title of the Module: Principles of feeding in PICU

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Learning Objectives:

- To describe nutritional assessment of the PICU patient;
- To describe principles of energy expenditure in the critically ill child;
- To describe the acute stress response;
- To describe the hyperglycaemic response;
- To describe treatment of hyperglycaemia with insulin;
- To present the concept of early enteral nutrition;
- To present the principles of gastric versus transpyloric feeding;
- To discuss principles of parental feeding administration.

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Key Messages:

- In critically ill children energy expenditure does not change in the first week after admission and can vary markedly within the same disease between individual patients;
- Critically ill children are in a catabolic state, characterized by three major metabolic changes; increased protein turnover with enhanced hepatic protein synthesis and muscle protein breakdown with negative protein balance, increased lipolysis, insulin resistance causing hyperglycaemia;
• Enteral nutrition is the preferred route in patients with a working gastro-intestinal tract. Enteral nutrition can be initiated within 24 hours in the majority of the children and within 48 hours it is possible to achieve an appropriate intake of energy and protein;
• The main advantages of enteral over parenteral nutrition include preservation of gastrointestinal function, cost, manageability, and safety;
• An increased protein intake cannot reverse protein breakdown but can improve nitrogen balance by enhancing protein synthesis;
• Specific nutrients, such as glutamine, antioxidants, fish oils, and arginine are called pharmaconutrients and have profound effects on underlying inflammatory, immunological, metabolic, and other pathophysiological processes in the critically ill.

1. Nutritional assessment of the critically ill child

1.1. General

Critical illness greatly influences one’s nutritional status, and assessment of nutritional status should therefore be an integral part of patient care. During a child’s intensive care (ICU) stay, however, attention is mostly focused on the primary medical problem, e.g. haemodynamic instability, serious infection, congenital anomaly, and not on the child’s nutritional status.

Critically ill children are at high risk of developing nutritional deficiencies and altered nutritional status. Much more than adults, critically ill children are at high risk of clinical depletion because they have limited body reserves of fat and protein, higher energy expenditure, and increased energy requirements for growth and development in the recovery phase after critical illness.

Studies performed in the 1980s revealed that about 20% of the children admitted to a paediatric intensive care unit were in poor nutritional state. Despite improvements in intensive care technology, feeding possibilities and increased awareness of the significance of adequate nutritional support, the prevalence of malnutrition over the last 30 years still remains high, at up to 45%. The fact that the incidence has not gone down may be explained by certain developments in the care for critically ill children in recent years. As a result of these developments, more and more children with chronic disease or major congenital anomalies survive to an older age, and these individuals are more likely to be in poor nutritional state on admission to the ICU than are previously healthy children. One has also to take into account the high prevalence of underlying growth-affecting disease in those with acute malnutrition.

The acute effects of malnutrition include poor wound healing, higher risk of infections due to poor immune defence, reduced gut function, longer dependency on mechanical ventilation and longer hospital stay. Considering that malnutrition might also jeopardize future growth and development, it seems all-important to identify on admission to the ICU, those children with pre-existing poor nutritional status and those at risk for developing malnutrition, with a view to tailoring their nutritional care.

1.2. Principles of nutritional assessment

Nutritional assessment is defined as a structured way to establish the nutritional status and energy requirements of a child by objective measurements in relation to specific disease-indications, whereby an adequate nutritional treatment can be developed and monitored. In general a multidisciplinary setting is preferred, including physicians, dieticians and nurses. Different data must be interpreted together in order to perform a comprehensive nutritional assessment:
A. General evaluation (including dietary and medical history and physical signs)
B. Severity of illness assessment and risk for malnutrition assessment,
C. Assessment of body composition,
D. Measurement of nutrient balance
E. Laboratory studies including measurement of inflammatory activity, functional
assessment and the estimation of energy requirements

1.3. Energy Expenditure

Measuring energy expenditure
Measuring energy expenditure allows for a more accurate monitoring of the child’s varying
energy needs in the course of critical illness. In the research setting, total and resting
energy expenditure can be estimated by using the following methods: indirect calorimetry,
doubly labelled water (DLW), whole-body calorimetry, thermic effect of food assessment,
and heart rate monitoring. The DLW method is the one mostly used in research and
evaluates energy expenditure (EE) over a longer period of time. As the technique is not
readily available, its use to estimate EE and adjust energy intake in clinical practice is of
limited value and restricted to the research setting. Measuring EE by indirect calorimetry is
however applicable clinically, in the intensive care unit, and more accurate than estimating
individual EE from standard predictive equations.

Indirect calorimetry
Indirect calorimetry provides non-invasive, reliable, repeatable and affordable
measurements of actual EE – i.e. resting EE (REE) in non-ventilated children and total daily
EE (TDEE) in ventilated children. Quantification of EE is also important for diagnostic
purposes in the critically ill child, because it can reveal hyper- or hypometabolic conditions
directly related to the individual prognosis. The greatest asset of indirect calorimetry is its
potential in designing a nutrition regimen that exactly meets the patient’s energy
requirements while avoiding the complications of overfeeding.
Several factors commonly present in the ICU population might affect measured EE and must
be taken into account when interpreting the outcome; for example fever can increase EE,
while sedatives, anaesthesia and muscle relaxants may decrease it in some patients.
The second parameter obtained from indirect calorimetry, the respiratory quotient (RQ),
may help in evaluating substrate utilization and/or nutritional support, and in determining
overfeeding and underfeeding. Fat oxidation results in an RQ of 0.7, whereas protein and
carbohydrate oxidation result in RQ's of 0.83 and 1.0 respectively. Net lipogenesis is shown
by an RQ >1.0 which is indicative of overfeeding.
Indirect calorimetry is being widely used as a research tool to determine energy
requirements. In most ICUs, however, its routine use is hampered by limited space at the
bedside, the cost of multiple metabolic carts, and the lack of trained staff to operate these
monitors. In addition, several criteria need to be fulfilled before accurate indirect calorimetry measurements can be performed, some of which are described below:
- Regular and correct calibration of the calorimeter
- A sufficient period of measurement to achieve steady VO\textsubscript{2} and VCO\textsubscript{2} levels.
- Endotracheal tube leakage < 10%
- Inspired oxygen fraction (FiO\textsubscript{2}) stable and below 60%
- Steady haemodynamic, respiratory and metabolic states to ensure that respiratory gas
  exchange is equivalent to tissue gas exchange

Estimating EE
In clinical practice the use of equations based on weight and sex to estimate REE (e.g.
Schofield equation) can be helpful to guide nutritional support. None of these equations will
predict EE with acceptable precision for use in the individual, especially in disease states.
Nevertheless in absence of equipment to measure EE it is advocated to use the Schofield equation for age and weight to calculate REE.

Calculation of resting energy expenditure (kcal) according to Schofield based on age and weight.

Table 1

<table>
<thead>
<tr>
<th>Age</th>
<th>Boys</th>
<th>Girls</th>
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<tbody>
<tr>
<td>0-3 y</td>
<td>60.9 x (kg) – 54</td>
<td>61.0 x (kg) – 51</td>
</tr>
<tr>
<td>3-10 y</td>
<td>22.7 x (kg) + 495</td>
<td>22.5 x (kg) + 499</td>
</tr>
<tr>
<td>10-18 y</td>
<td>17.5 x (kg) + 651</td>
<td>12.2 x (kg) + 746</td>
</tr>
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</table>

2. The acute stress response

2.1. General

Critical illness can be defined as a life threatening medical or surgical condition. It mostly results from infection, sepsis and trauma. These conditions are accompanied by similar physiological and biochemical responses, which have been termed the systemic inflammatory response syndrome (SIRS). The associated major metabolic changes are also known as the acute stress response. The acute stress response is a universal reaction, and from an evolutionary point of view these response are required for the “fight, flight, fright” reaction when encountering a threat, to mobilize fuels for tissues that are activated. Both the clinical and the metabolic responses after trauma are an integral part of the natural adaptation following injury that serves to facilitate recovery.

Depending on the severity of initial insult, pronounced neuroendocrine and metabolic alterations will occur. A key feature is increased sympathetic nervous system activity, resulting in increased levels of adrenaline and glucocorticoids. Subsequently, immune cells are activated and pro-inflammatory cytokines secreted, which trigger further metabolic changes. In addition, insulin secretion is increased as well as the counter regulatory hormones glucagon, catecholamines, cortisol and growth hormone. As a result, glucose production is increased via increased glycogenolysis and gluconeogenesis, and insulin resistance develops, leading to hyperglycaemia. Also, fat is mobilized (lipolysis) and fat oxidation and ketone body formation are increased, while muscle protein breakdown is stimulated to provide amino acids for protein synthesis in proliferating cells, the production of acute phase proteins and other peptides (eg cytokines) and for gluconeogenesis. Thus, protein turnover is increased resulting in net protein loss.

In critically adult patients the metabolic response to injury and sepsis is characterized by an ebb and flow phase. In the ebb phase there is a hypometabolic response with decreased energy expenditure, poor tissue perfusion, mild protein catabolism, and with elevated blood glucose, catecholamines, glucocorticoids and glucagon but low insulin. The duration of this phase is relatively short - 8-12 hours. In the flow phase there is a hypermetabolic response with increased energy expenditure, normal tissue perfusion, profound protein catabolism and elevated blood glucose levels, catecholamines, glucocorticoids, glucagon and insulin. The duration of this phase is 7-10 days. It is questionable whether this response is present in critically ill infants and children.

Concerning energy metabolism several studies have shown that in critically ill children energy expenditure does not change in the first week after admission and can vary
markedly within the same disease between individual patients. Only temperature will affect energy expenditure significantly, by 7-10% per degree Celsius.

2.2. Hormonal alterations

Critical illness is hallmarked by striking alterations in the hypothalamic-pituitary-peripheral hormone axes (neuroendocrine axes), according to a biphasic pattern. The peripheral effector hormone levels are reduced in both phases of critical illness, although the aetiology is different, with peripheral target organ resistance in the acute phase and relative hypopituitarism in the prolonged (chronic) phase.

The hypothalamic-pituitary-adrenal axis shows a biphasic, but somewhat different response as compared with the other axes, with cortisol as effector hormone being high in both phases. The responses of the neuroendocrine axes during prolonged critical illness overall have been linked to the development of a characteristic hypercatabolic state, resulting in feeding-resistant muscle wasting, and the severity of the disturbances has been associated with the high risk of morbidity and mortality of the patients. Not only excessive activation of the hypothalamic-pituitary-adrenal axis, but also adrenal insufficiency contributes to morbidity in critically ill children. The time course of the changes of the different hormonal axes in critically ill children depends not only on the severity of illness but also on the primary diagnoses.

2.3. Substrate alterations

Critically ill patients are in a catabolic state, characterized by three major metabolic changes. First, there is an increased protein turnover with enhanced hepatic protein synthesis and muscle protein breakdown. Second, during critical illness there is increased lipolysis, or the breakdown of triglycerides to free fatty acids (FFA) and glycerol. Third, insulin resistance causes hyperglycaemia due to ongoing endogenous glucose production (glycogenolysis and gluconeogenesis) and blunted peripheral uptake. Although plasma substrate levels may be increased, their availability to peripheral tissues may be blunted (because of factors such as insulin resistance and inhibition of lipoprotein lipase), while plasma levels of other substrates (e.g. specific amino acids, cholesterol) may be insufficient to meet metabolic demands.

3. Principles of feeding

3.1. Glucose and treatment of hyperglycaemia

Energy requirements of the human body, and especially the brain, depend on glucose as the major fuel. Plasma glucose levels are the resultant of a balance between exogenous glucose intake and endogenous glucose production (glycogenolysis and gluconeogenesis) on the one hand and glucose utilization (oxidation or storage as glycogen and triglycerides) on the other.

Initial screening for hypo- and hyperglycaemia should be performed in all critically ill children. Both low as well high blood glucose levels and also variability of glucose levels worsen outcome and should be treated; however there is ongoing debate on how tightly glucose should be controlled. Hyperglycaemia with high plasma insulin concentrations is the result of insulin insensitivity that occurs during stress. Both insulin resistance and (relative) β-cell dysfunction play a role in the occurrence of hyperglycaemia in critically ill children. The gold standard for quantifying insulin sensitivity in vivo is the hyperinsulinaemic euglycaemic clamp technique. This is a complex and invasive technique, and therefore not easily applied in studies with critically ill children. So far, methods to quantify insulin...
sensitivity are used in the research setting and not for bedside use in the paediatric intensive care. But routine glycaemic control should be considered as standard care. Large randomized outcome studies of tight glucose regimen with insulin therapy in the critically ill paediatric population are limited to one published trial. This study showed an improved outcome, despite an increase in hypoglycaemia (blood glucose <2.2 mmol/L = <40 mg/dl) and severe hypoglycaemia (blood glucose <1.7 mmol/L = <30 mg/dl).

**Glucose recommendation**
Adequate glucose intake depends on age and clinical situation, such as prematurity and critical illness. The ESPGHAN guidelines state that critically ill children should receive a maximum of 5mg/kg/min parenteral glucose, which is lower than in healthy peers. It was stated by others that for children < 30 kg a glucose intake of 4-6 mg/kg/min is recommended whereas for children > 30 kg an intake of 2-4 mg/kg/min is recommended.

<table>
<thead>
<tr>
<th>Glucose intake iv</th>
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<tbody>
<tr>
<td>ESPGHAN</td>
</tr>
<tr>
<td>Max 5 mg/kg/min</td>
</tr>
<tr>
<td>&lt; 30 kg</td>
</tr>
<tr>
<td>4-6 mg/kg/min</td>
</tr>
<tr>
<td>&gt; 30 kg</td>
</tr>
<tr>
<td>2–4 mg/kg/min</td>
</tr>
</tbody>
</table>

### 3.2. Protein

Proteins are made of amino acids as their building blocks. Almost the entire amino acid pool (98%) resides in proteins, which are in a constant process of degradation and synthesis, the so-called protein turnover. Protein turnover allows a continuous flow of amino acids to be available for necessary new proteins. In addition, specific amino acids serve “non-protein” actions. Amino acids act as precursors for the biosynthesis of substrates such as nitric oxide and polyamines, and as signalling molecules in signal transduction pathways. They also regulate energy metabolism, help protect against oxidative stress, and protect endothelial function cells.

Protein requirements of critically ill children are higher than in healthy children. The catabolic effects of illness lead to negative nitrogen balance and loss of lean body mass, which have deleterious effects on outcome. An increased protein intake cannot reverse protein breakdown but can improve nitrogen balance by enhancing protein synthesis. There is a close interrelationship between protein and energy metabolism. A lack in energy supply will enhance an already increased protein catabolism during critical illness. However, an increase in the energy supply will not promote nitrogen retention unless the protein supply is adequate, and conversely an increased protein supply will be useless if energy is limiting. The ESPGHAN guidelines show a consensus regarding the total amount of parenteral protein substrates that critically ill children should receive. However, there is a wide range within these recommendations (Table 2).

To estimate appropriate daily intake, urinary nitrogen excretion data can be used to calculate at least the nitrogen equilibration.

Equation

\[ \text{Protein excretion per day} = 6.25 \times \text{urinary urea nitrogen in total amount of urine output in} \]
\[ \text{24 hours (mmol N of excreted urea)} \]
### Recommendations for parenteral amino acids

#### Table 2

<table>
<thead>
<tr>
<th>Age</th>
<th>Parenteral amino acids g/kg/day</th>
</tr>
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<tbody>
<tr>
<td>0-2 month</td>
<td>1.5-3.0</td>
</tr>
<tr>
<td>3-5 month</td>
<td>1.0-2.5</td>
</tr>
<tr>
<td>6-11 month</td>
<td>1.0-2.5</td>
</tr>
<tr>
<td>1-13 yr</td>
<td>1.0-2.0</td>
</tr>
<tr>
<td>14-18 yr</td>
<td>1.0-2.0</td>
</tr>
</tbody>
</table>

Some specific amino acids may help to modulate key processes such as immunity, inflammation, endothelial health and oxidative stress. Glutamine and arginine are the most promising nutrients.

Glutamine is the most abundant amino acid in plasma and has numerous metabolic functions. It is an important fuel for rapidly dividing cells, is a precursor for glutathione, protect intestinal mucosa and augments cellular immune functions. One meta-analysis in critically ill adult patients revealed a reduction in mortality. Recent meta-analyses do not show definite benefits from glutamine. Also a recent randomized study with enteral supplemented glutamine, zinc, selenium and other antioxidants was negative. Amongst critically ill children, parenteral or enteral glutamine might be beneficial in those with burns and after trauma. Optimal doses are probably 0.3-0.5 g/kg/d given iv or enterally.

Arginine is an important amino acid for the immune system, because it is a fuel for leucocytes. Also, it is a precursor of nitric oxide (NO), which is needed, amongst other things, for killing bacteria. In addition, it has a role in wound healing and cell regeneration, and in vasodilatation as a precursor of NO. Arginine supplementation has led to inconsistent results in clinical studies with critically ill adult patients, possibly because of the potential toxic effect of arginine as a substrate for inducible nitric oxide synthase. Increased NO production might deteriorate microcirculation and organ dysfunction. Studies of arginine metabolism in critically ill children are lacking and it is not known if arginine supplementation might be beneficial.

### 3.3. Lipids

In enteral nutrition lipids can be provided not only as triglycerides but also as phospholipids, mainly to provide some long or very long-chain fatty acids. In addition, another important lipid component is represented by the lipid-soluble vitamins (A, D, E, and K). The infusion of lipid emulsions allows a high energy supply, facilitates the prevention of high glucose infusion rates and is indispensable for the supply of essential fatty acids. Lipid intake should usually provide 25-40% of non-protein calories in fully parenteral fed patients. The quantitatively dominant lipids in enteral and parenteral nutrition are triglycerides (triacylglycerols, neutral lipids; glycerol esterified with three fatty acids). The physical, chemical and metabolic properties of triglycerides are determined by their fatty acid content. Saturated, monounsaturated and polyunsaturated fatty acids differ in their metabolic and physiological properties. While saturated fatty acids serve primarily as an energy source, polyunsaturated fatty acids play an important role as components of structural lipids, for example in biological membranes. Some polyunsaturated fatty acids of
the n-6 series (linoleic acid and metabolites), and some polyunsaturated fatty acids of the n-3 series (α-linolenic acid and metabolites) cannot be synthesised de novo by higher organisms and are, thus, essential nutrients.

A number of factors decrease the rate of clearance of IV fat emulsions and increase the level of serum triglycerides:
- Malnutrition (lower levels of lipoprotein lipase)
- Lipolytic effect of drugs (like steroids)
- Lipid containing drugs (like Propofol, Amphotericin B)
- Metabolic stress and organ dysfunction

**Lipid recommendation (ESPGHAN)**

<table>
<thead>
<tr>
<th>Age</th>
<th>Lipids iv g/kg/day</th>
</tr>
</thead>
<tbody>
<tr>
<td>To prevent fatty acid</td>
<td></td>
</tr>
<tr>
<td>deficiency</td>
<td></td>
</tr>
<tr>
<td>Infants</td>
<td>3-4 g/kg/day</td>
</tr>
<tr>
<td>Older children</td>
<td>1.5 g/kg twice a week</td>
</tr>
<tr>
<td>As energy source</td>
<td></td>
</tr>
<tr>
<td>Infants</td>
<td>3-4 g/kg/day</td>
</tr>
<tr>
<td>Older children</td>
<td>2-3 g/kg/day</td>
</tr>
<tr>
<td>Reduction of lipids</td>
<td>Triglyceride level</td>
</tr>
<tr>
<td>Infants</td>
<td>&gt;250 mg/dl (&gt;2.9 mmol/L)</td>
</tr>
<tr>
<td>Older children</td>
<td>&gt;400 mg/dl (&gt;4.6 mmol/L)</td>
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Parenteral lipid emulsions based on soybean oil have been widely used for several decades. Soybean oil contains high concentrations of polyunsaturated fatty acids (PUFA, around 60% of the total fatty acids; ratio of linoleic acid (n-6) to α-linolenic acid (n-3) approximately 8:1). Lipid emulsions based on soybean oil are nowadays considered to be from the first generation.

The second and third generation lipids were designed to reduce the amount of linoleic acid (n-6), to increase the ratio n-3 to n-6 and aim to modulate metabolic reactions

**Lipid generations**

1. First generation
   a. soybean oil, very rich in ω-6 PUFA
2. Second generation
   a. MCT/LCT mixtures and olive oil containing emulsions
3. Third generation
   a. soybean-LCT, MCT, olive oil and fish oil, supplemented with Vitamin E
3.4. Micronutrients, vitamins and pharmaconutrients

Micronutrients and vitamins are critical in both health and disease. Deficiencies occur frequently during critical illness. Certain micronutrients have antioxidant properties and a role during critical illness. A complex system of special enzymes, their cofactors (selenium, zinc, iron and manganese), sulfhydryl group donors (glutathione), and vitamins (E and C) form a defence system to counter the oxidant stress seen in the acute phase of injury or illness. Critically ill patients may have variable deficiencies of micronutrients in the course of the disease. As hypocalcaemia, hypomagnesaeemia and hypophosphataemia commonly occur in the critically ill, it is essential to determine their levels. Low plasma levels of selenium and zinc will be present as well, but in daily practice it might be difficult to perform laboratory measurements of these micronutrients. In prolonged critical illness it is wise to assess levels of vitamins and carnitine sequentially, as decreased nutrient intakes and increased requirements may easily lead to deficiency states.

Specific nutrients, such as glutamine, antioxidants, fish oils, and arginine are called pharmaconutrients and these nutrients have profound effects on underlying inflammatory, immunological, metabolic, and other pathophysiological processes in critically ill patients. There is however limited evidence for the use of these pharmaconutrients in critically ill children. Children with burns and trauma are likely to benefit from glutamine and arginine supplementation. An enteral formula containing antioxidants plus the omega-3 and omega-6 fatty acids has shown improvements in clinical outcome compared with an isocaloric, isonitrogenous control in adults with acute respiratory distress syndrome and sepsis. This formula might also be recommended in older children with ARDS. Adequately powered randomized clinical trials using pharmaconutrients are required.

3.5. Parenteral versus enteral

Whenever enteral nutrition is tolerated, it is the preferred route of nutrition. It supports both the functional and structural integrity of the gut, through maintaining tight junctions between intra-epithelial cells, stimulating blood flow, inducing release of trophic endogenous agents, maintaining villous height, supporting the mass of secretory IgA-producing immune cells of the gut-associated lymphoid tissue and contributing to mucosal-associated lymphoid tissue.

Early enteral nutrition is safe and well tolerated in most critically ill children even with vasoactive medications, and improves protein metabolism and caloric deficits. Constipation and diarrhoea are common in PICU patients and guidelines to prevent or manage constipation and diarrhoea can improve EN tolerance and delivery. Gastric residual volumes are commonly used to assess enteral feeding tolerance, but it is unclear whether they are reliable for this purpose (in critically ill adults they are not). Whether enteral feeding should be given by a gastric tube or a transpyloric tube depends on the tolerance. However, it has been shown that a transpyloric feeding tube can increase the delivery of enteral nutrition to critically ill children but is unable to impede tracheal aspiration of gastric fluids. It should be emphasized to avoid or reduce unnecessary fasting due to procedures if the patient is on transpyloric feeding (eg preoperative, pre-extubation, imaging).

When enteral nutrition is contra-indicated or insufficiently tolerated, parenteral nutrition may be used to supplement or replace enteral nutrition. Recently, in adults a large randomized controlled study evaluated whether early parenteral nutrition to supplement enteral nutrition if energy goals are not met, was more beneficial than initiating supplemental parenteral nutrition after 1 week. It appeared that the late initiation resulted in reduced morbidity as compared to the early initiation. No such comparisons have been done in children, but results may differ in children, because they have less energy reserves and a shorter acute stress response.
4. Summary

In this module we discuss various aspects of the alterations of the metabolism of critically ill children and the consequences for enteral and parenteral nutrition. Principles of nutritional assessment are described and methods to calculate energy expenditure are given. Indications, contraindications and recommendations for the administration of enteral and parenteral nutrition are described.

5. References: