LIFE LONG LEARNING SYSTEM FOR TRAINING MEDICAL DOCTORS AND STUDENTS IN NUTRITION

STUDY MANUAL
Educational Modules
Volume 1

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Life Long Learning System:
Nutrition at the Level of Molecular Medicine

Leonardo da Vinci Programme
Pilot Project: BG-03-B-F-PP-166039

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PREFACE

Life Long Learning system for the training of medical doctors and students in nutrition

The development of a Life Long Learning (LLL) system in nutrition is timely since the essential role of nutrition in human health is becoming increasingly recognized and, as a consequence, the need for a proper education in nutrition to improve patient care has arisen.

Increasing awareness of the role of nutrition in the prevention and treatment of human disease has made clinical nutrition one of the fast growing fields in medicine during the past two-three decades. The unprecedented expansion of human knowledge and education, leading to differentiation in the levels and degree courses, makes it necessary to shift educational activities to lifelong learning, and to satisfy a growing proportion of specialists including health related professionals seeking for the programmes for additional qualification in a special field.

The intent of this manual is to allow students and physicians as well as other medical specialists to learn and understand recent achievements of nutritional science and to apply them to patient care in the areas of prevention and treatment of disease.

The Study manual for users of LLL system in nutrition contains:

• A core curriculum developed with the consensus of European partners according to the requirements of modern education in nutrition;
• A module catalogue;
• The modules developed for the system.

The main objective of this manual is to present the basic principles of clinical nutrition and metabolism and their application in clinical practice. It is constructed in a way that introduces the learner step by step into a modern training content. The first part of the Study manual is the Module catalogue which contains a list of modules with the corresponding system code and credits. The modules are presented in a summarized version with key messages, contents and learning objectives, providing an overview of the training content and enabling the selection of modules of interest.

The second part of the Study manual provides the educational modules of the LLL system in nutrition printed in volumes.

The first and the second volumes developed in 2005 contain 29 modules out of 105 of the module catalogue developed by a network of European partners and ESPEN with the support of the European Commission, Directorate-General for Education and Culture Leonardo da Vinci Programme.

Publishing of the educational modules of LLL system in nutrition is planned as a periodic annual edition according to the educational programme of ESPEN and partners network.

This volume contains the modules that were presented at live session as a LLL course related to 27th ESPEN Congress in Brussels, August 26-27, 2005.
Chapter 1

Topic 17
Nutritional Support in the Perioperative Period
Nutritional Support in the Perioperative Period

**Module 17.1**

**The Stress Response and its Effects on Metabolism**

CHC Dejong

**Learning Objectives**

- Understand the mechanisms behind the stress response in surgical patients and how this may relate to impaired or enhanced recovery after surgery;
- How does the surgical stress response lead to hypermetabolism?
- What does this mean for protein metabolism?
- How can certain aspects of the stress response and its effects on protein metabolism be avoided and how can it be treated?
- Insights into the relationship between hypermetabolism, alterations in protein metabolism and complications in surgery.

**Contents**

1. What is meant by the surgical stress response?
2. Clinical symptoms
3. How does hypermetabolism result from the surgical stress response?
4. Protein kinetics
5. Does the gut play a role?
6. Proactive approach to prevent unnecessary aspects of the surgical stress response

**Key Messages**

- The stress response after surgery is a useful phenomenon;
- However, if uncontrolled, it leads to auto-cannibalism;
- Reduction of magnitude of surgical impact or its effects may be useful (small incisions, epidural);
- The counter regulatory hormones and inflammatory response to surgery cause insulin resistance;
- Insulin is the main anabolic hormone;
- To avoid catabolism, insulin resistance must be avoided;
- Patients should not be fasted unnecessarily. Modern fasting guidelines recommend patients to drink clear fluids up until 2 hours and allow solids 6 hours before anaesthesia and surgery;
- Depleted patients should be replenished;
- Albumin is not a measure of nutritional status.
1. What is meant by the surgical stress response?

In modern medicine, elective and acute surgical procedures are a more and more common phenomenon. Particularly for elective surgery it can be said that this constitutes a predictable form of trauma, and we now know that such trauma elicits a series of events called the “stress response”, that may adversely affect the patient’s health and capability to recover.

Unlike accidental trauma, however, the moment when the organism is affected can be anticipated and therefore, if we know the details of the “stress response”, adequate measures could be taken to streamline the physiological response of the organism to surgical trauma.

The “stress response” is a phenomenon extensively studied since the thirties of the past century and includes changes in the metabolism of all nutrients including the macro-nutrients fat, carbohydrate and protein. It is initiated and orchestrated by a multitude of neuro-endocrine and cytokine mediators and release of stress hormones, such as catecholamines, cortisol and glucagons, and induces a catabolic response leading to a negative nitrogen balance (1) (Fig. 1, Fig. 2).

This negative nitrogen and energy balance indicates that the body loses protein and this occurs for 50% in muscle and 50% in fat (2) (Fig. 3).

The loss of muscle mass does not only interfere with muscle function, but also with the ability of the organism to raise substrate to fuel host response, necessary in the defence against disease (3).

In the following, we will stipulate why this stress response is detrimental on the one hand and useful on the other.

---

**Effects of major surgical trauma on homeostasis of the organism**

- Wound causes pain, resulting in stress
- Stress is accompanied by neurohumoral changes: fight or flight
- Open wound: fluid loss
- Healing: anabolism

**Effects of surgical trauma on homeostasis of the organism**

Surgical trauma is accompanied by a negative nitrogen balance

Nitrogen balance is more negative than during pure fasting

**weight loss following surgical trauma**

- Where?
  - Muscle
  - Fat
- Why?
  - Reduced food intake
  - Increased energy expenditure and nitrogen loss
  - Metabolic ‘Error’ in Protein/Fat metabolism

---

Fig. 1

Fig. 2

Fig. 3
1. What is meant by the surgical stress response?

In modern medicine, elective and acute surgical procedures are a more and more common phenomenon. Particularly for elective surgery it can be said that this constitutes a predictable form of trauma, and we now know that such trauma elicits a series of events called the "stress response", that may adversely affect the patient's health and capability to recover. Unlike accidental trauma, however, the moment when the organism is affected can be anticipated and therefore, if we know the details of the "stress response", adequate measures could be taken to streamline the physiological response of the organism to surgical trauma.

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In the following, we will stipulate why this stress response is detrimental on the one hand and useful on the other.

2. Clinical symptoms

Two different phases have classically been distinguished by Sir David Cuthbertson after most forms of trauma, including surgery: an initial short hypodynamic 'ebb' phase and a later hyperdynamic 'flow' phase (4). The clinical picture accompanying the hyperdynamic phase consists of several characteristics: tissue edema (representing shifts in the body fluid compartment) (Fig. 4), increased cardiac output, hyperthermia, hypermetabolism, catabolism leading to muscle atrophy, biochemical alterations and an ongoing acute phase response:

- Tissue edema results from vasodilatation and increased capillary leakage. This implies that more fluid, plasma proteins, leukocytes, macrophages and electrolytes leave the vascular compartment and accumulate in the tissues. Increased capillary leakage is probably mediated by pro-inflammatory cytokines.
- Vasodilatation implies that intravascular volume decreases, which induces shock if adequate resuscitation is not achieved. Meanwhile intracellular volume decreases and this furnishes part of the volume necessary to replenish intravascular and extravascular extracellular volume (Fig. 5, Fig. 6).
- Increased cardiac output is induced by vasodilatation.
- Hyperthermia leads to, but is also caused by increased energy expenditure, oxygen uptake and substrate utilization during the stress response. This requires increased delivery by increased cardiac output, or increased extraction.
- Changes in protein breakdown and synthesis lead to net catabolism, but tissue edema may hide muscle atrophy.
• Biochemically the expansion of total body water leads to dilution of solutes including important electrolytes, but is also reflected in a low haematocrit.
• The ongoing “acute phase protein response” is illustrated by rises in CRP and fibrinogen (positive acute phase proteins), and a drop in albumin (negative acute phase proteins) (5, 6).

3. How does hypermetabolism result from the surgical stress response?
Surgical trauma and the resulting stress response leads to an increase in energy expenditures of about 15-25% above predicted healthy resting values. The increase in energy expenditure is caused amongst others by an upward resetting of thermoregulation that mediates an increase in energy production through enhanced activity of the sympathetic nervous system. Also, an increase in sympathetic activity may stimulate metabolic rate by enhancing substrate cycling between non-esterified fatty acids and triacylglycerol and glucose and glucolytic products. The wound is also an area of increased metabolic activity (Fig. 7), and contributes to substrate cycling. Lactate produced in the wound is transported to the liver where it is converted to glucose in the Cori cycle, an energy consuming process. Activated inflammatory cells in the wound have a high oxygen consumption and release of a number of cytokines (e.g. IL-1β and TNF-α) which mediate central upward resetting of metabolic activity. Finally, increased protein breakdown via energy-consuming pathways may contribute.

The stress response is always accompanied by catabolism at the whole body level
Normally, following surgical trauma, the body is in negative nitrogen balance, reflecting loss of body protein (7-9) (Fig. 2). Body weight drops and muscle atrophy becomes apparent, even when the patient has been receiving adequate nutrition. Interestingly, the response to surgical trauma is quite different from that to pure starvation. During pure starvation all organs lose mass (10). Following surgical trauma however some organs (muscle, adipose tissue, skin) are catabolic (11) (protein degradation exceeds synthesis). Other organs, however, such as the wound itself are anabolic (12). The whole immune system is anabolic including the liver. This is achieved by an increase in muscle protein degradation whereas muscle protein synthesis hardly changes. “Centrally” increased uptake of amino acids is achieved in liver by an increase in protein synthesis, whereas protein degradation increases to a lesser extent. Thus, during the stress response, only peripheral tissues (muscle, adipose tissue, skin) are catabolic whereas central tissues (liver, immune system, wound) are anabolic (13, 14) (Fig. 8).

- Immobilization
- Muscle protein breakdown
- Protein synthesis in liver, wound and immune system
- Anabolism and catabolism occur simultaneously
- Overall result: Body weight loss

Surgical trauma – Protein kinetics
As the amino acid composition of the protein synthesized centrally differs considerably from the ones broken down in muscle, this contributes to nitrogen loss. In this context, it has been calculated that seven grams of muscle protein would have to be broken down to furnish the amino acids for hepatic synthesis of 1 gram of fibrinogen (15) (Fig. 9). However, the atrophying action of the stress response on muscle has been viewed as a useful adaptive process, meant to furnish fuel and building blocks to organs that play a vital role in the healing process after trauma and disease (14).

It is remarkable that muscle catabolism can hardly be inhibited by furnishing nutrition as long as the stress response continues. However, emerging evidence suggests that if the stress response is minimized, metabolism supported towards anabolism and nutrition is provided, healing of wounds can be accomplished at least as well while recovery is enhanced (see modules 17.2 and 17.6).

### 4. Protein kinetics

Proteins are continuously synthesized and broken down. Several authors have reported increased protein turnover after trauma, including an increase in whole body protein synthesis and an even more pronounced increase in protein breakdown (2, 16). Protein breakdown can take place via at least three routes (Fig. 10, Fig. 11, Fig. 12), but it is currently believed that the energy consuming ubiquitin proteasome pathway plays a crucial role in this respect, in concert with the calpain system (17, 18). This occurs also in the absence of food intake, but net whole body catabolism is more pronounced after surgical trauma than in the pure fasted state.
The continuous process of simultaneous protein synthesis and breakdown serves several useful purposes (19-21). Modest changes in protein synthesis or breakdown or both, allow for the net effect to be catabolic or anabolic. In addition, a high flux through pathways makes it possible to rapidly respond to changing needs.

As said, the sum of the central anabolic actions and the peripheral catabolic actions is negative in the sense that at the whole body level body protein is lost. This process is therefore inefficient in terms of nitrogen economy because the overall effect is net catabolism of the whole organism.

5. Does the gut play a role?

It has been proposed that temporary hypoperfusion of the splanchnic area may affect intestinal barrier function (Fig. 13). This would then lead to increased permeability and translocation of bacteria or their products (Fig. 14), contributing to a systemic inflammatory response and/or sepsis.
A generalized systemic inflammatory response in itself may induce gut leakiness contributing to a vicious cycle detrimental to the host.

Equally, a state of malnutrition as reflected by a low Quetelet index (Fig. 15) may lead to inappropriate gut permeability (Fig. 16). In this context, it should be stressed that albumin in itself is not a good marker of nutritional status. Since early enteral nutrition has been shown to be safe and beneficial to the gut, it seems logical to administer food via the enteral route as soon as possible after surgery (Fig. 17). It may well be that high fat enteral nutrition or probiotics will turn out to have added value in this context (22, 23).

6. Proactive approach to prevent unnecessary aspects of the surgical stress response

From the above, the strategies to dampen the surgical stress response and its effects are self-evident:

- surgical trauma should be minimized (length of incision, technique);
- afferent painful stimuli should be minimized to prevent the stress response. The use of epidural analgesia and/or local wound infiltration with a local anesthetic may be useful;
- stressing the patient preoperatively should be avoided (no unnecessary starvation);
- the anabolic effects of insulin should be facilitated by reducing insulin resistance (See module 17.2);
- depleted patients should be fed during 7-10 days preoperatively. Protein synthesis rates should be stimulated by nutritional support to synthesize new muscle protein and to meet the demand of crucial visceral protein and proteins in wounds, white cells and macrophages. So essentially, new therapeutic interventions should be more tailored to organ needs and thereby supply organs with their specific needs.
References

Nutritional Support in the Perioperative Period

Module 17.2

Insulin Resistance and Glucose Control

Olle Ljungqvist

Learning Objectives

- Understand the mechanisms behind insulin resistance (IR) and how this may relate to recovery;
- How IR affects glucose metabolism?
- How IR can be avoided and how it should be treated?
- Insights to the relationship between hyperglycaemia and complications in surgery.

Contents

1. How insulin resistance develops?
2. Metabolic and clinical outcomes from treating insulin resistance
3. Changes in glucose metabolism
4. Proactive approach to insulin resistance
5. Treating insulin resistance with insulin
6. Modern fasting guidelines

Key Messages

- The counter regulatory hormones and inflammatory response to surgery cause insulin resistance;
- Resistance to insulin develops within minutes and remains for days to weeks;
- Insulin resistance is the cause of hyperglycaemia;
- Hyperglycaemia increases complications and mortality in postoperative critically ill patients, and has been associated with prolonged length of stay in uncomplicated surgery;
- Treatment with insulin during TPN to maintain normoglycaemia also normalizes FFA levels, substrate oxidation and nitrogen losses;
- Insulin resistance can be avoided or minimized by the use of epidural anaesthesia and analgesia, minimal invasive surgery and by preoperatively preparing metabolism with carbohydrates instead of overnight fasting;
- Preoperative carbohydrate loading as opposed to overnight fasting has been shown to reduce nitrogen losses, retain lean body mass and improve muscle strength;
- If insulin resistance has developed and hyperglycaemia is present, available data suggests that insulin should be given to keep blood glucose levels between 4.5 and 6.1 mM in postoperative critically ill patients;
- Modern fasting guidelines recommend patients to drink clear fluids up until 2 hours and allow solids 6 hours before anaesthesia and surgery.
1. How insulin resistance develops

Surgery and trauma initiates the release of stress hormones and cytokines (1). Catecholamines, cortisol, glucagon and growth hormone independently cause IR, and potentiate each other. Cytokines such as Interleukin 6 and TNF-α also cause insulin resistance. IR affects all parts of metabolism and also other endocrine systems. Hyperglycemia and elevations of FFA levels are typical signs of insulin resistance. Protein breakdown increases and negative nitrogen balance is also associated with insulin resistance.

2. Metabolic and clinical outcomes from treating insulin resistance

When the effectiveness of insulin is reinstated by the use of iv insulin, these metabolic disturbances are reversed (2). More importantly, in critically ill surgical patients, this treatment was shown to reduce mortality by over 40%, due to reductions in sepsis, need of assisted ventilation, renal failure and polyneuropathy (3) (Fig. 1). Other studies have suggested that the degree of insulin resistance is an independent factor explaining the variation in length of stay after uncomplicated surgery (1) (Fig. 2, Fig. 3).
1. How insulin resistance develops
Surgery and trauma initiates the release of stress hormones and cytokines (1). Catecholamines, cortisol, glucagon and growth hormone independently cause IR, and potentiate each other. Cytokines such as Interleukin 6 and TNF-α also cause insulin resistance. IR affects all parts of metabolism and also other endocrine systems. Hyperglycemia and elevations of FFA levels are typical signs of insulin resistance. Protein breakdown increases and negative nitrogen balance is also associated with insulin resistance.

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3. Changes in glucose metabolism
Within minutes of the trauma, changes in all parts of metabolism begin to occur. The overall reaction is a change to catabolism. Hyperglycaemia develops due to a simultaneous increase in glucose production, while glucose uptake in insulin sensitive cells (mainly muscle and fat tissue) becomes resistant to the action of insulin. In muscle, the main target tissue for insulin, this hormone has reduced capacity to stimulate specific glucose transporting proteins facilitating glucose uptake, and glycogen formation is also blocked. This change may remain for several weeks after a colorectal operation and seems associated with muscle function (4).

It is interesting to note that the changes occurring in glucose metabolism after surgery in otherwise healthy patients are very similar to those developing over years in patients with diabetes mellitus type 2 (5) (Fig. 4). The degree of IR is related to the magnitude of the operation (1) and remains for about 2-3 weeks after uncomplicated medium size upper abdominal surgery (6) (Fig. 5, Fig. 6).
4. Proactive approach to insulin resistance

There are a few known ways to proactively minimize postoperative insulin resistance (Fig. 7). The placement and activation of a thoracic epidural before the onset of the operation has been shown to reduce postoperative IR by about 40% in abdominal surgery (7). This was associated with marked reductions of circulating catecholamine and cortisol levels.

Minimal invasive surgical techniques also reduce postoperative insulin resistance markedly, probably by reducing the level of traumatic injury to the body (8) (Fig. 8). Pain is another factor that increases insulin resistance in itself (9). This is yet another argument for the use of continuous epidural analgesia after major surgery, since this has been shown to provide better pain control than intravenous opioids (10) including PCA (11).

Finally, it has been shown that preparing metabolism for the stress of surgery by boosting insulin sensitivity using a carbohydrate load instead of remaining in the overnight fasted state results in an approximately 50% reduction in insulin resistance in a several surgical procedures and in hip replacement (12) (Fig. 9). The latter method is by far the best studied, and has been shown to affect both of the two main driving forces behind hyperglycaemia.
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Finally, it has been shown that preparing metabolism for the stress of surgery by boosting insulin sensitivity using a carbohydrate load instead of remaining in the overnight fasted state results in an approximately 50% reduction in insulin resistance in several surgical procedures and in hip replacement (12) (Fig. 9).

The latter method is by far the best studied, and has been shown to affect both of the two main driving forces behind hyperglycaemia. Preoperative carbohydrates reduce glucose production and enhances glucose uptake (13). When this treatment is combined with epidural analgesia for several days after major colorectal surgery, insulin resistance can be minimized to levels seen after laparoscopic cholecystectomies. In this situation, it is possible to provide complete enteral nutrition while glucose levels remained below 6.1 mM without any need of exogenous insulin (14) (Fig. 10).

In addition to these effects on glucose metabolism, preoperative carbohydrate treatment has been shown to affect protein metabolism and muscle function by reducing nitrogen losses (15) (Fig. 11), retaining lean body mass (16) (Fig. 12) and improving muscle strength (4) (Fig. 13).

Preoperative CH0 + EDA maintains normoglycemia during enteral feeding

![Graph showing the maintenance of normoglycemia](Fig. 10)

Soop M et al, Br J Surg, 2004

Preoperative 20% glucose infusion and urea losses

Prospective randomized trial comparing the effects of 20% glucose infusion (5 mg/kg/min), known to increase insulin levels as after a meal, and a 5% glucose infusion (1 mg/kg/min) overnight before abdominal surgery.

![Graph showing urea losses](Fig. 11)

Crowe Br J Surg 1984

Preoperative CH0 retains lean body mass

![Graph showing changes in lean body mass](Fig. 12)

Yuill et al: Clin Nutr 2005
From a nutritional point of view, the report indicating reduced PONV after laparoscopic cholecystectomies comparing preoperative oral carbohydrates to overnight fasting (18) is interesting (Fig. 14), while there was no significant difference to placebo in this or in another study of similar kind (19).

5. Treating insulin resistance with insulin

In postoperative patients with a need of ventilatory support in the ICU, tight control of blood glucose levels (4.5 - 6.1 mM) has been shown to reduce drastically complications and mortality (Fig. 15). Further studies showed that it was the prevailing glucose level and not primarily the insulin given that had the effect. Importantly, a post hoc analysis showed that normoglycaemia (blood glucose < 6.1 mM) gave the best effect on overall outcomes including mortality. Even glucose levels between 6.1 and 8.3 mM was associated with increased mortality and morbidity (20). This suggests that normoglycaemia should be the target glucose level for these patients. To what extent hyperglycaemia exists in the ordinary postoperative patient, and how this may affect outcomes remains to be investigated.

Preoperative oral CHO retains quadriceps muscle function

Prospective randomized trial, comparison between patients given CHO alone or CHO and amino acids (same result) versus overnight fasted patients

![Graph showing effect of preoperative oral CHO on quadriceps muscle function](image)

Observed late (12-24h) PONV

Laparoscopic cholecystectomy

<table>
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<th>Yes</th>
<th>Totals</th>
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<tbody>
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<tr>
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<td>8</td>
</tr>
<tr>
<td>Totals</td>
<td>159</td>
<td>13</td>
</tr>
</tbody>
</table>

P = 0.05, Chi square, CHO vs, fasted

![Table showing observed late PONV](image)

Hyperglycemia & risk of ICU mortality

![Graph showing hyperglycemia and ICU mortality](image)

P < 0.01

Death in ICU

<table>
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<th>% risk</th>
</tr>
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<tr>
<td>&lt; 6.1 mmol/L</td>
</tr>
<tr>
<td>6.1-8.3 mmol/L</td>
</tr>
<tr>
<td>&gt; 8.3 mmol/L</td>
</tr>
</tbody>
</table>

6. Modern fasting guidelines

Over the last 2 decades the traditional routine of overnight fasting before elective surgery has been questioned, challenged and proven not to provide any additional safety over allowing patients to drink freely of clear fluids up until 2 hours before elective anaesthesia and surgery (21) (Fig. 16).

In fact, many of the most common preoperative discomforts primarily thirst and to some extent headaches and hunger, can be avoided when the patient is allowed to drink in the morning before surgery.

Many European and North American Anaesthesia Societies have therefore updated their fasting guidelines and generally recommend that patients drink clear fluids up until 2 hours before anaesthesia. Solids, however, empty from the stomach much slower, and should not be taken later than 6 hours before anaesthesia. Patients with known slow gastric emptying for any reason should best be treated with more restriction, and generally be kept fasted for longer periods of time to reduce the risk of aspiration.

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16. Hausel et al.


Nutritional Support in the Perioperative Period

Module 17.3

Nutritional Support in the Perioperative Period

Ken Fearon

Learning Objectives

- Understand the principles behind nutritional care for elective surgical patients;
- Recognise key issues that allow restoration of oral food intake quickly and safely following major surgery;
- Understand the specific issues surrounding provision of nutritional support for malnourished/complicated patients in the post-operative period.

Contents

1. Principles of post-operative care
2. Promotion of oral food intake for patients not at nutritional risk
3. Nutritional support for malnourished patients
4. Use of artificial nutritional support
5. Summary

Key Messages

- Restoration of normal gastrointestinal function is a key aspect of postoperative care and is promoted by the use of enhanced recovery programs;
- Early oral feeding improves outcomes and should be facilitated;
- The malnourished patient are at high risk of postoperative complications;
- Nutritional support should be considered on an individual basis for all patients undergoing major surgery.
1. Principles of post-operative care

For normally nourished patients, one of the key objectives of postoperative care is restoration of normal GI function to allow adequate food intake and rapid recovery. Normally nourished patients clearly have no pre-existing nutritional deficit and thus if GI function is restored shortly after surgery there should be no risk of developing nutrition-related morbidity/mortality.

In contrast, malnourished patients are at increased risk of postoperative complications and mortality, yet artificial nutritional support in itself can be associated with major complications.

Thus if outcome is to be improved in malnourished patients not only must restoration of GI function be as rapid as possible but the quality of care surrounding any targeted artificial nutritional support must be of the highest standards.

2. Promotion of oral food intake for patients not at nutritional risk

Oral intake should be commenced as soon as possible after surgery.

A meta-analysis of controlled trials (11 studies with 837 patients) of early enteral feeding versus “nil by mouth” after GI surgery, concluded there is no clear advantage to keeping patients nil by mouth after elective GI resection (1). Early feeding reduced both the risk of any type of infection and the mean length of stay in hospital. However the risk of vomiting increased in patients fed early.

For patients with an anastomosis in the upper GI tract, ingestion of solid food may have to be delayed for several days (e.g. until contrast studies confirm an intact oesophageal anastomosis).

Following colorectal operations where the GI tract remains functional solid food can be commenced without adverse effect on the first postoperative day (2). Patients may find liquid supplements easier to take in the first instance.
The following key issues should be addressed if restoration of oral food intake is to be achieved quickly and safely:

- **Avoiding routine nasogastric intubation**
  To promote a return to normal dietary intake, the presence of a nasogastric (NG) tube should be avoided. Avoiding routine nasogastric decompression after abdominal surgery significantly reduces the incidence of fever, atelectasis and pneumonia (3).

- **Provision and access to appetising food**
  Patients should not be fasted for any longer than necessary, either for investigations or surgery. Studies in hospital patients have shown that up to 20% of meals are missed while patients attend or are fasted for investigative or therapeutic interventions, whilst 40% of the content of meals delivered to the patient is discarded (4). The provision of appetising hospital food and access to sufficient nursing staff to help patients who have difficulty in eating is a key issue in helping patients return to a normal food intake.

- **Postoperative nausea and vomiting**
  The control of postoperative nausea and vomiting is essential if patients are to resume normal oral fluid and dietary intake. The regular use of anti-emetics according to a strict protocol and with an emphasis on targeting high risk patients is strongly recommended.

- **Prevention of postoperative ileus**
  The effect of early enteral feeding on ileus is controversial. The only manoeuvre proven to reduce the incidence of post-operative ileus is the use of epidural analgesia during and after surgery (5).

- **Use of oral nutritional supplements**
  Patients who are malnourished either at the time of, or shortly following, major abdominal or vascular surgery have a more rapid recovery of nutritional status, physical function and quality of life, if given nutritional advice and prescribed routine oral supplements in the immediate postoperative period and following two months (6).
  The evidence supporting the short term routine use of oral supplements in patients who are not malnourished is not clear (7, 8).

- **Multimodal enhanced recovery programmes**
  Use of early oral or artificial enteral nutrition at a time when gastrointestinal function has not returned to a suitable level can be associated with abdominal distension, vomiting and respiratory embarrassment (9). In contrast, multimodal enhanced recovery programmes (with a focus on pain control, early mobilisation and promotion of gastrointestinal function) are associated with an early return of oral nutrition in the postoperative period (10, 11). Patients care pathways should therefore, be designed to take account of a multimodal approach (12) (see Module 17.6).

### 3. Nutritional support for malnourished patients

Protein/calorie undernutrition can vary from mild (e.g., <5% weight loss) to severe (e.g., >15% weight loss, BMI <18 kg/m², albumin <30 g/l) and can occur in patients undergoing surgery for benign or malignant disease. The need for nutritional support should be considered in relation to each patient's nutritional status and surgical pathology. Patients who are identified as malnourished should be referred to the unit dietician for further assessment and management.
- **Malnutrition and surgical risk; screening tools**
  Patients who are malnourished are at increased risk of postoperative complications (13, 14). A variety of strategies have been suggested for screening patients for malnutrition in the community, but it is not clear whether their implementation reduces morbidity or mortality.

- **Malnutrition in benign disease**
  There is no evidence that malnourished patients with benign disease and requiring surgery (e.g. Crohn's disease) benefit from prolonged preoperative artificial nutrition support. Such patients are best treated by surgical correction of their pathology followed by intensive nutritional support in the postoperative period.

- **Malnutrition in malignant disease**
  There is some evidence to suggest that severely malnourished patients with cancer benefit from perioperative total parenteral nutrition (TPN) (15). This benefit does not pertain to cancer patients with mild or moderate malnutrition, where a meta-analysis has shown that perioperative TPN has no benefits in terms of mortality (16).

Upper GI cancer patients are often given postoperative enteral feeding either via a jejunostomy or fine-bore nasoenteral feeding tube. This allows maintenance of nutritional status should the patient develop a postoperative complication that retards normal progression towards oral nutrition (e.g. an anastomotic leak). A meta-analysis has demonstrated that enteral nutritional support supplemented with immunomodulatory nutrients results in a significant reduction in the risk of developing infectious complications but has no effect on mortality (17). The cost-effectiveness of such a strategy has not been clearly established. Immunonutrition may be given preoperatively as well as postoperatively (18).

In summary mild or moderately malnourished cancer patients should proceed with surgery and only receive artificial nutritional support if specifically indicated. All malnourished cancer patients should be considered for nutritional advice and oral supplements in the postoperative period and for a period following peroperative TPN.

**Fig. 4** Heyland et al 1998, *JAMA, 280: 2013, 9*
4. Use of artificial nutritional support

Generally, if oral nutritional is not re-established within five to seven days postoperatively, enteral or parenteral feeding should be considered (see Module 17.4).

5. Summary

It is vital to consider a patient’s nutritional status throughout their surgical journey and to optimise the function and use of their GI tract whenever possible.

References

16. Heys, S.D. et al., Enteral nutritional supplementation with key nutrients in patients with
Nutritional Support in the Perioperative Period

Module 17.4

Nutritional Goals in the Perioperative Period

Learning Objectives

· To learn about common methods used to assess nutritional state in preoperative patients;
· To review caloric and protein requirements before and after surgery;
· To decide what is the most appropriate route of nutrition in various surgical diseases.

Content

1. Nutritional assessment in the preoperative patient
2. Caloric and protein requirements before and after surgery
3. Routes of nutrition in the surgical patient

Key Messages

· Only in intestinal failure should parenteral feeding be used;
· Subjective global assessment (SGA) is a simple and highly accurate "nutritional" test to predict postoperative complications;
· Preoperative parenteral feeding in malnourished patients for five to ten days is associated with a reduction in postoperative morbidity. Preoperative oral or enteral nutritional support in malnourished patients needs further evaluation;
· Postoperative caloric and protein requirements are not highly elevated in modern surgical care;
· Early oral nutrition is safe after lower gastrointestinal surgery, and decreases infectious morbidity and enhances recovery;
· Parenteral feeding in the postoperative patient who cannot be fed orally or enterally for a prolonged period has not been evaluated. Expert groups recommend waiting for at least five days before total parenteral nutrition is started in well-nourished patients.

Module 17.4

Nutritional Goals in the Perioperative Period

Mattias Soop

Learning Objectives

- To learn about common methods used to assess nutritional state in preoperative patients;
- To review caloric and protein requirements before and after surgery;
- To decide what is the most appropriate route of nutrition in various surgical diseases.

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- Early oral nutrition is safe after lower gastrointestinal surgery, and decreases infectious morbidity and enhances recovery;
- Parenteral feeding in the postoperative patient who cannot be fed orally or enterally for a prolonged period has not been evaluated. Expert groups recommend waiting for at least five days before total parenteral nutrition is started in well-nourished patients.
1. Nutritional assessment in the preoperative patient

Even in modern surgical practice as many as 25% of surgical patients have been reported to be malnourished on admission (1). There is little doubt that malnutrition adversely affects outcome from surgery (2). Preoperative parenteral feeding in malnourished patients for five to ten days is associated with a reduction in postoperative overall complication rates from approximately 40% to 30% (3) (Fig. 1). Therefore, it is important to identify patients who are malnourished before surgery.

Unfortunately, all tests available in clinical practice today to assess nutritional status are also affected to various degrees by the metabolic abnormalities that are associated with most surgical disease, such as malignant and inflammatory conditions. For example, serum concentrations of proteins (e.g. albumin) are affected more by physiological stress than by malnutrition (see also module 17.1).

The Subjective Global Assessment (SGA) (4) and experimental muscle function tests are the tests with the best track record in predicting postoperative complications of all current tests for malnutrition. The SGA is based on a careful history and physical examination and this simple and inexpensive assessment predicts postoperative morbidity with high accuracy (2).

Although it would be of great use to follow the nutritional state in the postoperative patient day-by-day, this is made virtually impossible by the fluid shifts and acute stress responses to surgery. Body weight, for instance, normally increases by 5-10% due to fluid retention, masking any loss of body cell mass (see also module 17.1). One pragmatic way to ensure adequate postoperative nutritional intake is to keep a careful daily record of all nutritional intakes. The daily caloric intake is compared to calculated or measured energy expenditure, and adjusted if necessary.

2. Caloric and protein requirements before and after surgery

There is good evidence that five to ten days of total parenteral nutrition (TPN) at 30-35 kcal·kg⁻¹·day⁻¹ and 0.16-0.20 g nitrogen·kg⁻¹·day⁻¹ before major abdominal surgery in malnourished patients decreases overall postoperative morbidity (5-7) (Fig. 2).

Although similar beneficial effects would be expected from preoperative oral nutritional support in patients who tolerate it, no trials testing this hypothesis have been reported.

Routine TPN in the postoperative phase, in contrast to preoperative TPN, has been found to significantly increase postoperative morbidity in meta-analysis (3, 8).
A field of current intense investigation is so-called immunonutrition with various specific nutrients such as arginine, glutamine, nucleotides and omega-3 fatty acids, given before or after surgery and often in various combinations. A recent meta-analysis found that such immunonutrition significantly reduced morbidity in critical illness, but not after elective surgery (10). In malnourished patients, preoperative immunonutrition has been associated with decreased postoperative morbidity and quicker recovery (11).

### 3. Routes of nutrition in the surgical patient

It has been firmly established that the enteral route should be used for total or partial nutritional support as tolerated, as this route is associated with lower complication rates than the parenteral (12). Additional caloric needs are covered via the parenteral route. Contrary to traditional belief, early (<24 h postop) feeding above a bowel anastomosis has not been associated with an increased risk of anastomotic dehiscence; indeed there was a near-significant risk reduction in a recent meta-analysis of trials comparing early feeding with late reintroduction of oral diet after gastrointestinal surgery (13) (Fig. 4).

Significant reductions of postoperative infectious complication rates and lengths of hospital stay were found with early feeding compared to the traditional gradual reintroduction of diet (13). Patients with an anastomosis in the upper gastrointestinal tract, however, are a subgroup for which trials of early oral intake of nutrients are lacking. Therefore, it may be prudent to feed these patients via a feeding jejunostomy or, perhaps more safely (14), via a naso-jejunal tube through the anastomosis.

In patients with gastrointestinal paralysis for any reason, partial or total parenteral nutrition must be initiated. Although no data has been reported on the effects of delayed TPN in prolonged postoperative ileus, expert groups recommend waiting at least five days before starting TPN in well-nourished patients, as too aggressive parenteral nutrition will increase complications in this group (3, 8). In malnourished patients, however, parenteral nutrition should be started earlier in postoperative ileus (8).
Nutritional Support in the Perioperative Period

Module 17.5

The Traumatized Patient

CHC Dejong

Learning Objectives

· Understand the mechanisms behind the metabolic effects of trauma;
· How does the stress response after traumatic injury lead to hypermetabolism?
· What does this mean for protein metabolism?
· Can certain aspects of the stress response after acute non-surgical trauma be avoided and how can they be treated?
· Insights into the relationship between hypermetabolism, alterations in protein metabolism and complications in surgery for trauma.

Contents

1. Introduction
2. What happens after trauma?
3. Clinical symptoms
4. Protein kinetics
5. Why is there increased protein degradation during trauma?
6. Minimizing unwanted effects of trauma and its treatment: hypothermia
7. Proactive approach to prevent unnecessary aspects of the surgical stress response
8. What is the actual substrate mix used by the body after trauma?
9. What metabolic goals should be achieved in traumatized patients?
10. Assessment of efficacy of treatment

Key Messages

· Trauma leads to overall catabolism in the body;
· Anabolism occurs in splanchnic organs, immune system and in wounds;
· Nutrition should support these processes;
· Specific nutrients like glutamine may be considered.

References

Nutritional Support in the Perioperative Period

Module 17.5

The Traumatized Patient

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- Understand the mechanisms behind the metabolic effects of trauma;
- How does the stress response after traumatic injury lead to hypermetabolism?
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- Anabolism occurs in splanchnic organs, immune system and in wounds;
- Nutrition should support these processes;
- Specific nutrients like glutamine may be considered.
1. Introduction

This module discusses the effects of acute un-anticipated traumatic injury on human metabolism. This is to make a distinction with surgical trauma as well as with the critically ill. In elective surgery, the trauma inflicted by the surgical procedure is foreseeable and therefore, appropriate measures can be taken to counteract any unwanted effects of the host response to trauma. This is not the case in acute traumatic injury, such as a long bone fracture due to a traffic accident (Fig. 1, Fig. 2).

It is not intended to give an extensive review of various types of trauma, such as single versus multiple injuries blunt versus penetrating, hypothermia versus burns or fractures versus soft tissue trauma. The scope is to focus on skeletal muscle injury and its effects on metabolism.

2. What happens after trauma?

From observations in traumatized wild animals in their natural surroundings, three distinct features become clear. The animal retreats into a hiding place and exhibits little mobility. A second striking phenomenon is anorexia, not exclusively due to the inability to catch food, but also present when easy access to food is offered. Finally the animal exhibits a catabolic state, reflected in loss of weight, largely consisting of loss of muscle (Fig. 3, Fig. 4).

When the trauma is not too extensive, the traumatized area heals, whereafter the animal resumes normal activity, starts eating and regains muscle mass and function. In the following, we will explain why these adaptations after trauma are a logic and obligatory event.
The response of the human being to acute trauma is essentially the same as in animals. It differs from surgical trauma in that it is unanticipated and therefore, many of its effects can not be prevented, although we can treat them.

Accidental trauma may range from a simple long bone fracture to any combination of injuries in multiple trauma victims (Fig. 5). As such, symptoms may vary widely and many organs may be affected. The general principle in treating these patients is to protect life and preserve function of vital organs. Once this has been achieved, nutritional support may be started. Obviously, the route of administration may be affected by the specific trauma (1, 2).

3. Clinical symptoms

Symptoms of accidental injury are mainly related to the local effects of trauma, such as a fracture, and the systemic effects of a particular injury (3). Pain and shock are two dominant features, that initiate and sustain a chain of adverse events, that may be described as the stress response.

Two different phases are distinguished in shock after trauma: an initial hypodynamic phase and a later hyperdynamic phase (4).

The initial hypodynamic phase may be quite pronounced after trauma and leads to hypoperfusion of all organs. Subsequent transmembrane fluid shifts will lead to intracellular dehydration and subsequent acidification, which precludes adequate cell function including regulation of protein turnover (5) (Fig. 6).
Also, hypovolemic shock affects intestinal barrier and this may facilitate translocation of bacteria or their components and a subsequent generalized inflammatory response (6-8) (Fig. 7).

The clinical picture of the stress response, including increased capillary leakage, the development of tissue edema, increased cardiac output and vasodilatation is generally considered a harmful side effect of trauma. It leads to compromised alveolar diffusion of oxygen, to intravascular hypovolemia, renal insufficiency and many other disturbances of organ function (3).

4. Protein kinetics

During acute disease and following trauma, growth is inhibited and the organism becomes catabolic, which is specifically exemplified by muscle breakdown and atrophy (9). It is now clear that the neuroendocrine response including the cytokine response to disease leads to an obligatory loss of muscle that cannot be blocked by nutrition alone (10). In fact, the normal response to moderate trauma or disease includes immobility, anorexia, and catabolism (Fig. 8).

Muscle tissue disappears, but at the site of injury or in tissues such as liver and the immune system, there is protein accumulation that is modulated by pro-inflammatory cytokines. Although the individual is anorectic, the anabolic accumulation of tissue in the liver, immune system, and site of injury can only occur with substrate that is derived from other tissues such as muscle. This is an easily detectable situation, and it clearly indicates that muscle catabolism during acute trauma or disease is a useful adaptive phenomenon because the substrate derived from this catabolism is utilized for the healing response. As a consequence, modulation of the "catabolic" hormonal pattern with the intention of blocking muscle catabolism should not block the anabolic actions in the wound and immune system (11).

During pure starvation, the reutilization of amino acids derived from protein degradation is efficient. Essential amino acids are degraded to a very limited degree and are reused for protein synthesis. Whole-body protein turnover decreases, and very little protein is lost at the whole-body level.
Trauma – Amino acid kinetics

- Muscle protein breakdown
- Muscle: BCAA conversion to glutamine and alanine
- Glutamine consumption in gut, liver, wound and immune system
- As BCAA are essential amino acids, this process means catabolism
- Overall result: Body weight loss

Following trauma, amino acids derived from muscle catabolism are not released in the circulation as such, but a large part, especially the branched-chain amino acids (BCAAs) are irreversibly degraded to yield other amino acids such as glutamine and alanine, which are avidly used at the site of injury and in the liver and immune system (11) (Fig. 9). This precludes efficient reutilization of amino acids and obligatorily leads to increased protein catabolism at the whole-body level.

5. Why is there increased protein degradation during trauma?

In traumatized animals, muscle protein synthesis rates are not decreased, but remain stable or are even slightly increased. In view of the fact that muscle protein loss occurs, this must imply that muscle protein degradation increases to an even greater degree. However, muscle protein turnover contributes only 40% to total body protein turnover and this figure may even be less in the stressed condition. It has already been mentioned that in the stressed condition liver protein synthesis is greatly enhanced. The increase in muscle protein degradation may furnish amino acids from peripheral tissues to central tissues to sustain synthesis of crucial proteins. Visceral protein synthesis is increased in response to trauma and these proteins are functional like e.g. clotting factors, fibrinogen, complement factors and many others.

6. Minimizing unwanted effects of trauma and its treatment: hypothermia

More often than not, a laparotomy is part of the treatment of major trauma patients. The open abdomen is a site of major fluid and heat loss, and this is potentially harmful to the patient. Prevention of (intraoperative) hypothermia reduces the severity of the endocrine-metabolic response and sympathetic reflexes, and changes the fibrinolytic-coagulatory balance resulting in reduced bleeding. Several randomised trials have demonstrated that preservation of normothermia by infusion of fluids, heated to body temperature and using an upper body forced-air heating cover reduces wound infections, cardiac complications and bleeding, and transfusion requirements (12).

7. Proactive approach to prevent unnecessary aspects of the surgical stress response

Increased whole body protein degradation partly reflects the increased degradation of muscle protein, and partly increased turnover of visceral proteins, that play crucial functional roles in the response to trauma and other diseases. Protein synthesis rates should be stimulated by nutritional support to synthesize new muscle protein and to meet the demand of crucial visceral protein and proteins in wounds, white cells and macrophages. So essentially, new therapeutic interventions should be more tailored to organ needs and thereby supply organs with their specific needs.
8. What is the actual substrate mix used by the body after trauma?

One of the major reasons why reutilization of amino acids derived from muscle proteolysis leads to net catabolism at the whole-body level is that the increased glutamine and alanine efflux from muscle following trauma (13) is derived in part from the irreversible degradation of the BCAAs. This precludes reutilization of BCAAs for protein synthesis and leads to a catabolic rate that is more pronounced than during starvation unaccompanied by disease or trauma. The observation that more glutamine (and alanine) is released from peripheral (muscle) tissues (14) implies that more glutamine is consumed in central organs such as liver, immune system, and possibly the site of injury (Fig. 9).

9. What metabolic goals should be achieved in traumatized patients?

As stated, the acutely traumatized organism increases its protein turnover and becomes catabolic. Although plasma concentrations of albumin decrease, fractional synthesis rates of albumin and fibrinogen increase after trauma (11). The accumulation of white cells, macrophages, granulation tissue, collagen, and bone matrix at fracture sites is also proof of increased synthetic processes at the site of injury and in the immune system following trauma. These considerations imply that one of the metabolic goals of therapeutic intervention should be to support increased protein turnover.

Another goal is to exogenously furnish the specific nonessential amino acids that the previously healthy organism produces in excess after trauma and acute illness. Glutamine would seem to be a good candidate for this in the traumatized patient, because it has been shown to reduce complications in trauma victims (15) (Fig. 10).

Early enteral nutrition may be beneficial if tolerated (Fig. 11). Finally, we should preserve the differential changes in protein kinetics as observed in the previously healthy organism subject to trauma or acute disease.

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**Multiple Trauma – Glutamine-enriched enteral nutrition**

- Reduction in morbidity (28%) in multiple trauma patients
- May be mediated via arginine production in the kidney

Fig. 10

Houdijk et al, Lancet 1998;352:772-776

**Early enteral feeding and gut permeability**

Early enteral feeding may have beneficial effects on intestinal permeability (as assessed by the lactulose/mannitol test)

![Graph showing early enteral feeding and gut permeability](image_url)

Fig. 11

*Intensive Care Med 1999;25:157-161*
Endeavors to inhibit net muscle catabolism in patients with burns by the use of growth hormone have been reasonably successful (16) and therefore, preservation of the central anabolic responses and inhibition of muscle catabolism may be a future treatment option, but only when this does not interfere with the central response.

10. Assessment of efficacy of treatment

Essentially, growth stops when organisms are traumatized (11) and all substrate is directed to the healing response. Although the response to trauma is obligatorily catabolic despite nutritional support, nutrition may limit nitrogen losses by increasing the protein content of the food to 1.5 g of protein/kg/24 h limits nitrogen losses. Glutamine enrichment may limit nitrogen losses and may improve outcome for trauma patients (15). The increased flux and rate of appearance of glutamine from peripheral to central tissues after trauma is such that supplementing the nutritional regimen with as much as 20 or even 40 g/d can still be considered in the physiological range and safe. Clinically, it is clear that healthy granulation tissue, solid epithelialization of granulating defects, growth of hair, loss of tissue edema, and regaining of muscle tonicity are all convincing signs of benefit.

References

Facilitating Oral or Enteral Nutrition in the Postoperative Period

Learning Objectives

· To review the causes of postoperative gastrointestinal paralysis;
· To learn in some detail about the perioperative interventions that have been shown to promote postoperative gut function;
· In particular, to learn about the uses of epidural analgesia and multimodal analgesia to promote bowel function, the importance of fluid balance, and the role, if any, of prokinetic drugs;
· To review additional interventions which may be of use.

Content

1. Postoperative gastrointestinal paralysis
2. Thoracic epidural analgesia
3. Avoidance of opioids
4. Perioperative fluid balance
5. Other interventions to limit postoperative ileus
6. Gastrointestinal function after colonic surgery in enhanced-recovery protocols

Key Messages

· Postoperative ileus is preventable;
· The main alterable causes are inhibitory sympathetic activity, manipulation of the bowel, exogenous and endogenous opioids and fluid overload;
· Mid-thoracic epidural analgesia promotes postoperative bowel function by blocking inhibitory reflexes, catecholamine release and eliminating the need for systemic opioid analgesia;
· NSAIDs and paracetamol reduce the need for opioids once the epidural analgesia is discontinued;
· Maintaining postoperative fluid balance, rather than fluid overload, helps prevent postoperative ileus;
· Prokinetic drugs have no current role in postoperative ileus, apart from magnesium oxide, which may be beneficial;
· Combining several of the above interventions in an enhanced-recovery protocol, it is possible to maintain a normal gastrointestinal transit time after colonic surgery.

References

Nutritional Support in the Perioperative Period

Module 17.6

Facilitating Oral or Enteral Nutrition in the Postoperative Period

Mattias Soop

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- Prokinetic drugs have no current role in postoperative ileus, apart from magnesium oxide, which may be beneficial;
- Combining several of the above interventions in an enhanced-recovery protocol, it is possible to maintain a normal gastrointestinal transit time after colonic surgery.
1. Postoperative gastrointestinal paralysis

Paralysis of the gastrointestinal tract has been a major problem in traditional surgical care, limiting the tolerance to oral or enteral nutrition (1). The time to recovery of gastrointestinal function has often been cited as 2-5 days. Delayed oral or enteral nutrition significantly delays recovery and increases the risk of infectious complications as compared to early reintroduction of feeding (2).

The causes of postoperative gastrointestinal paralysis are multifactorial. The main causes are inhibitory sympathetic activity in response to pain and dissection in the peritoneum, local release of inhibitory neurotransmitters in response to manipulation of the bowel, a direct inhibitory effect of exogenous and endogenous opioids, and fluid overload. Most of these effects can be influenced by perioperative interventions, minimising or even eliminating postoperative ileus (3).

2. Thoracic epidural analgesia

Catecholamine release occurs during and after surgery both systemically from the adrenal medulla in response to apprehension and pain, and locally from sympathetic nerve endings in response to dissection in the visceral peritoneum. The adrenal medulla is innervated via segments T5-T11, the small bowel via T9-T12 and the colon via T11-L2. Not surprisingly, an epidural block with a local anaesthetic at a mid-thoracic level effectively decreases circulating concentrations of catecholamines (4, 5) and significantly shortens the duration of postoperative ileus (6) as compared to systemically administered opioids (Fig. 1).

Peritoneal dissection and postoperative ileus

Peritoneal dissection triggers sympathetic viscerovisceral reflexes, inhibiting motility

A mid-thoracic epidural block inhibits afferent and efferent limbs

Local anaesthetic must be used; not opiates alone

Mid-thoracic epidural is required for sympathetic block of the intestinal tract

"Sympathectomy with local anaesthetic requires mid-thoracic placement."

"Low-thoracic epidural was not shown to be beneficial on postoperative ileus."

"Not surprisingly, studies using low-thoracic epidurals have not demonstrated the positive effects of epidural analgesia on ileus."

Fig. 1

Fig. 2 Miedema Lancet Oncology 2003; Baig Dis Colon Rectum 2004; Holte Br J Surg 2000
As is apparent from the innervation of the adrenal medulla and the bowel, the epidural block must be mid-thoracic rather than low-thoracic or lumbar (7-9) to achieve this sympathetic block (Fig. 2). Thus, this requires a more cephalad level of epidural block than that required for analgesia alone in lower abdominal or pelvic surgery. To increase the analgesic effect of epidurally administered local anaesthetics, opioids are often added to the epidural infusate. Although the addition of a low dose of opioids to the epidural infusate may contribute to postoperative ileus, the effect is small (7) and it allows for a lower dosage of epidural local anaesthetic, minimising lower limb paralysis.

3. Avoidance of opioids

The gut paralytic effect of opioids is four times as strong as their analgesic effect (10). One benefit of epidural analgesia is that it eliminates the need for postoperative systemic opioid analgesia. When epidural analgesia is discontinued, non-steroidal anti-inflammatory drugs (NSAIDs) and paracetamol reduce the need for opioid analgesia and can be expected to decrease postoperative ileus.

However, even though the systemic administration of opioids can be avoided by multimodal analgesia based on epidural analgesia, NSAIDs and paracetamol, endogenous opioid production is significant in the postoperative period (11). Locally active oral opioid receptor antagonists, although still experimental, have been shown to significantly decrease postoperative ileus (12).

4. Perioperative fluid balance

It is traditional to substitute real and perceived fluid losses during and after surgery liberally. This practice, which originated in trauma surgery, has recently been shown to be detrimental to gastrointestinal function (13) and postoperative morbidity (14) in elective surgery. From animal studies, it is clear that such fluid overload causes oedema and paralysis of the stomach wall. In humans, a perioperative fluid regime aiming at maintaining fluid balance rather than the traditional fluid overload has been shown to significantly decrease the time to return of bowel function and discharge following colonic resection (13) (Fig. 3).

In colonic surgery, routine preoperative bowel preparation is now known to confer no clinical benefits, and in fact increases the risk of anastomotic dehiscence (15). Preoperative overnight fasting has also been shown to confer no benefits (see module 17.2). Epidural-induced vasodilatation is preferably treated by vasopressants rather than fluid boluses (16).

5. Other interventions to limit postoperative ileus

Preoperative patient education and coaching has been shown to confer multiple benefits to postoperative recovery as compared to general reassurance, among those an earlier return of bowel function (17). This is a simple, inexpensive intervention that is easily implemented.
Prokinetic drugs have had a disappointing track record in affecting postoperative ileus (10). Metoclopramide, although still popular, has been shown to have no effect on postoperative ileus (10). A postoperative laxative agent have been shown to significantly shorten the time to return of bowel function in a double-blinded study in patients after appendicectomy (18) (Fig. 4). Postoperative bowel stimulation with magnesium oxide has now been part of enhanced-recovery protocols in elective colonic surgery for several years without an increase in complications (19). Surgical technique may influence the duration of postoperative gastrointestinal paralysis. Interestingly, mere manipulation of the small bowel causes the same distribution and duration of postoperative intestinal ileus as does extensive dissection of the right or left colon in a primate model (20). Thus, efforts to minimise the magnitude of the surgical trauma, such as the use of minimal abdominal wall incisions, may be beneficial on postoperative bowel function. Laparoscopic colonic surgery may promote gastrointestinal function as compared to open surgery (10), although no such benefit was seen in a recent blinded study within an enhanced-recovery protocol (21). Routine postoperative nasogastric drainage not only prevents oral feeding, but has been shown not to be of any benefit and should be abandoned after elective laparotomy (22).

6. Gastrointestinal function after colonic surgery in enhanced-recovery protocols

Enhanced-recovery protocols combine several of the interventions described above. The effect on postoperative gut function is impressive. Gastrointestinal transit was unaffected by colonic resection in a protocol combining thoracic epidural analgesia and postoperative magnesium oxide, as compared to healthy controls (3). Such protocols allow for oral intake of solid food and oral nutritional supplements early after surgery (23).

References


Chapter 2

Topic 18

Nutritional Support in Intensive Care Unit (ICU) Patients
Learning Objectives

- Understand the mechanisms of the physiologic response to stress;
- Understand the effects of the critical illness on energy metabolism;
- Understand the effects of the critical illness on the adaptation to starvation;
- Propose rules for energy supply in critically ill patients.

Contents

1. Physiologic response to stress
2. Metabolic response: energy metabolism
3. Energy requirements
4. Adaptation to fasting

Key Messages

- The critical illness induces extensive physiological changes, involving energy metabolism and substrate utilization;
- Resting energy expenditure is increased in patients with severe trauma, sepsis and burns;
- Numerous factors influence resting energy expenditure in critically ill patients: type and severity of illness, organ failure, supportive therapies;
- Precise energy requirements are difficult to determine in critically ill patients. Indirect calorimetry allows more a precise estimate of energy requirements, but simple rules are usually used in clinical practice;
- Prolonged hypocaloric feeding is associated with clinical complications; energy balance should be calculated in the most ill patients;
- Adaptation to fasting is blunted, ketosis is suppressed.
1. Physiologic response to stress

Extensive physiological changes occur in critically ill patients, particularly in those suffering from sepsis, trauma and burns. All the body systems are involved, particularly the circulation, the endocrine, metabolic and immune systems. This response is mainly activated from tissue inflammation and from the central nervous system. It plays a key role for the adaptation of the organism to the various forms of stress, including surgery, trauma and many types of critical illnesses, as shown by the inability of patients with cortico-adrenal failure to face minimal stress.

Tissue injury induces an acute local inflammatory response which activates macrophages and endothelial cells which in turn activate cascades of inflammatory mediators, including cytokines, coagulation factors, kinins and others endogenous substances. Both pro-inflammatory cytokines (TNF-α IL-1 and IL-6) and anti-inflammatory cytokines (IL-4 and IL-10) are released to insure an adequate adaptation to the inflammatory stress (Fig. 1, Fig. 3).

The neuro-endocrine response is characterised by the activation of the sympatho-adrenal system, hypothalamo-pituitary axis and other endocrine glands. It leads to the release of the stress hormones epinephrine, norepinephrine, cortisol, vasopressin, growth hormone and glucagon (Fig. 2).

There is a synergy between the sympatho-adrenal system and the pituitary-adrenal axis: activation of the sympathetic system leads to a parallel stimulation of the corticotropic axis and vice-versa.

**Fig. 1**


**Fig. 2**


**Fig. 3**

Rossner MJ et al, J Neurosurg 1994; 81: 76
The overall response is a dynamic process, allowing a rapid and prolonged adaptation to stress: adrenergic, growth hormone and vasopressin response time are very short (seconds), while the corticotropic response has a delay of some hours. Factors triggering this response include mental and psychological stress, exercise, pain, hypovolemia, hypothermia, hypoglycemia, and severe metabolic and electrolytes disorders. The magnitude of the neuro-endocrine response is related to the type of injury and severity of stress. The neuro-endocrine response plays a critical role in maintaining the circulation and perfusion of vital organs, as well as the energy metabolism (Fig. 3). The thyroid axis is down regulated during acute stress, leading to the sick euthyroid syndrome. This may decrease energy metabolism during prolonged stress and critical illness.

2. Metabolic response: energy metabolism

The metabolic response to stress is extensive, involving all the major pathways of metabolism. The overall response is characterized by an enhanced metabolic rate associated with increased release of endogenous substrates for energy metabolism and increased inter organ substrate exchanges.

Insulin resistance leads to increased plasma glucose concentration and gluconeogenesis and endogenous glucose production. Lipolysis is activated with concomitant release of fatty acids for energy metabolism.

In healthy resting subjects, the main determinant of basal energy expenditure is the fat-free mass (FFM) (Fig. 4). FFM includes the tissues with the most active metabolic rate, mainly skeletal muscle and viscera. In subjects with normal FFM, REE amounts to 20 kcal/kg per day, or 1400 kcal for a 70 kg subject. The specific contribution of the different organs and tissues to REE is highly variable, ranging from 5 kcal/kg per day for fat tissue to 500 kcal/kg for the myocardium (Fig. 5). As a whole the vital organs, that account for only 5% of body weight, consume 60% of REE.

Except during the initial phase after injury (the ebb phase), the energy metabolism is stimulated after the initial resuscitation (flow phase). During this flow phase, resting energy expenditure (REE) is increased in critically ill patients, amounting to 120-150% of normal basal values after severe trauma or sepsis.
Resting metabolic rate is even higher in patients with major burns, reaching 140-170%.
Stress hormones, pro-inflammatory cytokines and other mediators mainly cause such hypermetabolism. Infusion of the stress hormones cortisol, glucagon and epinephrine in healthy subjects induces metabolic changes mimicking important aspects of the metabolic response to injury (Fig. 6, Fig. 7).
The duration of the flow phase varies according to the evolution of the acute illness: it is short lasting after major uncomplicated surgery (days), lasts several weeks after major trauma and sepsis and even months after major burns until the full skin healing.
Variability of REE is extensive, both between different diagnosis categories of patients and over time in a given patient (Fig. 8).
In healthy subjects, the metabolic rate is increased by feeding, cold exposure, exercise and by growth in children (Fig. 9). Additional factors influence REE in acutely ill patients (Fig. 10, Fig. 11). The main factors include body temperature, organ failure, pain and supportive and drug therapies. Fever increases metabolic rate by 10-15% per degree C, hypothermia does the reverse. Pain, respiratory failure, acute liver failure are all associated with hypermetabolism. Mechanical ventilation in patients with respiratory failure, sedation, opiates, muscular relaxants, decrease the metabolic rate, while catecholamines increase the metabolism.

### Conditions affecting energy expenditure in healthy subjects

<table>
<thead>
<tr>
<th>Condition</th>
<th>REE Change</th>
</tr>
</thead>
<tbody>
<tr>
<td>Basal metabolic rate</td>
<td>-10 %</td>
</tr>
<tr>
<td>Sleeping</td>
<td>-5 - 10 %</td>
</tr>
<tr>
<td>Nutrition</td>
<td>+3 - 20 %</td>
</tr>
<tr>
<td>Exercise</td>
<td>+100 - 1500 %</td>
</tr>
<tr>
<td>Pregnancy</td>
<td>+10 %</td>
</tr>
<tr>
<td>Growth</td>
<td>+5 - 15 %</td>
</tr>
</tbody>
</table>

Fig. 9

### Conditions affecting energy expenditure in ICU patient

<table>
<thead>
<tr>
<th>Condition</th>
<th>REE Change</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fever (per °C)</td>
<td>+10 to 15 %</td>
</tr>
<tr>
<td>Sepsis</td>
<td>+20 to +60 %</td>
</tr>
<tr>
<td>Trauma</td>
<td>+20 to 50%</td>
</tr>
<tr>
<td>Burn</td>
<td>+40 - 80%</td>
</tr>
<tr>
<td>Treatments</td>
<td></td>
</tr>
<tr>
<td>• Mech. Ventilation (resp. failure)</td>
<td>-25 - 35 %</td>
</tr>
<tr>
<td>• Nutritional support (Burn)</td>
<td>+20 %</td>
</tr>
<tr>
<td>Agitation</td>
<td>+50 - 100%</td>
</tr>
</tbody>
</table>

Fig. 10

### Drugs affecting EE in the ICU patient

<table>
<thead>
<tr>
<th>Drug</th>
<th>Condition</th>
<th>Change</th>
</tr>
</thead>
<tbody>
<tr>
<td>Opiates</td>
<td>Analgesia</td>
<td>-9%</td>
</tr>
<tr>
<td></td>
<td>Post-op rewarming</td>
<td>-26%</td>
</tr>
<tr>
<td></td>
<td>Post-op shivering</td>
<td>-59%</td>
</tr>
<tr>
<td>Sedation</td>
<td>Mechanical ventilation</td>
<td>-20 - 55%</td>
</tr>
<tr>
<td>Barbiturates</td>
<td>Brain injury</td>
<td>-32%</td>
</tr>
<tr>
<td>Musc. relaxants</td>
<td>Brain injury</td>
<td>-42%</td>
</tr>
<tr>
<td>Catecholamines</td>
<td>Circ failure</td>
<td>+32%</td>
</tr>
<tr>
<td>ß-blockers</td>
<td>Head injury</td>
<td>-6%</td>
</tr>
<tr>
<td></td>
<td>Burn (adult)</td>
<td>-7%</td>
</tr>
</tbody>
</table>

Fig. 11

*Chiolero R, Nutrition 1997;13(9 Suppl):45S-51S.*
Physical activity is usually low in critically ill patients, but may be significant in agitated patients (Fig. 12). Beta-blockade in burn and trauma patients has been associated with decrease in resting energy expenditure (Fig. 13) and in protein catabolism (Fig. 14, Fig. 15).
There is little information on the change of the regional metabolic rate induced by the critical illness. Inflammatory diseases stimulate the regional metabolism, as shown by studies performed in patients with acute pneumonia, which show increased \( \text{O}_2 \) consumption in the lung (Fig. 16). Coma is associated with decreased brain \( \text{O}_2 \) consumption during the initial phase of brain injury.

3. Energy requirements

Clinical assessment of energy expenditure is difficult in critical care and requires the use of sophisticated techniques (see Table 1). Several equations allow the calculation of resting metabolic rate in healthy subjects, based on body weight, height, gender and age (Table 2, Fig. 17).

**Harris-Benedict equations**

These equations are gender specific and are based on body weight (kg), height (cm) and age (yr). They predict the resting energy expenditure (+ 10%) in subjects with normal body composition.

- **Male:** \( \text{REE} \) (kcal/day) = 66.5 + (13.8 x body weight) + (5.0 x body height) – (6.8 x age)
- **Female:** \( \text{REE} \) (kcal/day) = 655.1 + (9.6 x body weight) + (1.8 x body height) – (4.7 x age)
It underestimates resting energy expenditure in most surgical patients. Correction factors for stress have been proposed, but they have been found to be inappropriate for clinical practice, fostering excessive feeding (Fig. 18).

In clinical practice, simple rules are used to estimate REE in critically ill patients:

- 20-25 kcal/kg per day in patients with low or moderate stress;
- 25-30 kcal/kg per day in patients with marked stress: multiple injury, brain injury, severe sepsis;
- 35-40 kcal/kg per day or more in patients with major stress, like extensive burns.

In patients with complicated evolution, requiring prolonged nutritional support, it is recommended to perform weekly indirect calorimetry measurements to avoid both gross over- or underfeeding.

It is difficult to match nutrient supply to the needs of acutely ill patients for several reasons:

- The energy requirement is difficult to predict, variability between patients is high, variability in a given patient along the stay is high and the energy expended for activity is difficult to predict;
- The route of feeding may alter energy delivery (enteral nutrition). Precise determination of energy requirement is possible at the bedside using indirect calorimetry. This measurement is usually made over a short period (about 20-30 min) and 24 h energy expenditure is extrapolated. This leads to a significant error, reaching 20-30%. A precise determination of the 24 h metabolic rate would require a 24 h measurement, which is not possible in clinical condition.

Calculation of the daily energy deficit, defined as the difference between the 24 h energy expenditure and energy delivery, allows to estimate how appropriate is the caloric supply.

Recent studies suggest that prolonged energy deficit is associated with clinical complications, particularly septic complications in critically ill patients (Fig. 19, Fig. 20, Fig. 21).

---

Table 1  Methods of assessment of energy expenditure

<table>
<thead>
<tr>
<th>Method</th>
<th>Principle</th>
<th>Conditions for use</th>
</tr>
</thead>
<tbody>
<tr>
<td>Calorimetric methods</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Direct calorimetry</td>
<td>Determination of heat produced</td>
<td>Closed environment (entire body in a closed chamber)</td>
</tr>
<tr>
<td>Indirect calorimetry</td>
<td>O₂ consumption, CO₂ production, nitrogen excretion</td>
<td>Ventilation, fraction of inspired oxygen (FiO₂) &lt;0.6</td>
</tr>
<tr>
<td>Non-calorimetric methods</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Isotopic (doubly-labelled water)</td>
<td>CO₂ production estimated from the difference between labelled hydrogen and labelled oxygen</td>
<td></td>
</tr>
<tr>
<td>Fick method</td>
<td>Cardiac output ' Difference in oxygen content between arterial and mixed venous blood</td>
<td>Pulmonary artery catheter</td>
</tr>
<tr>
<td>Physical activity</td>
<td>Pedometer, accelerometer</td>
<td>Not suitable for ICU patients</td>
</tr>
<tr>
<td>Muscular activity</td>
<td>Electromyography</td>
<td>Not assessed in ICU</td>
</tr>
</tbody>
</table>

Table 2  Estimates of energy requirements

<table>
<thead>
<tr>
<th>Name</th>
<th>Formula</th>
</tr>
</thead>
<tbody>
<tr>
<td>Harris-Benedict</td>
<td>Males: 66.5 + (13.8 x weight) + (5 x height) - (6.8 x age)</td>
</tr>
<tr>
<td></td>
<td>Females: 655.1 + (9.6 x weight) + (1.9 x height) - (4.7 x age)</td>
</tr>
<tr>
<td></td>
<td>Correction factors *:</td>
</tr>
<tr>
<td></td>
<td>• Postoperative: Estimated REE x 1.1</td>
</tr>
<tr>
<td></td>
<td>• Multiple fractures: Estimated REE x 1.1 to 1.3</td>
</tr>
<tr>
<td></td>
<td>• Severe infection: Estimated REE x 1.3 to 1.6</td>
</tr>
<tr>
<td></td>
<td>• Burns: Estimated REE x 1.5 to 0.1</td>
</tr>
<tr>
<td></td>
<td>• Fever: Estimated REE x 1.1/°C above 37°C</td>
</tr>
<tr>
<td>Frankenfield</td>
<td>-1000 + 100 (minute ventilation) + 1.3 (haemoglobin) + 300 (sepsis)</td>
</tr>
<tr>
<td>Swinamer</td>
<td>945 (body surface area) - 6.4 (age) + 108 (temperature) + 24.2 (respiratory rate) + 817 (minute ventilation) - 4349</td>
</tr>
<tr>
<td>Fusco</td>
<td>-983 - 4(age) + 32 (height in inches) - 11 (weight)</td>
</tr>
<tr>
<td>Ireton-Jones*</td>
<td>1925 - 10 (age) + 5 (weight) + 281 (sex) + 292 (trauma) + 851 (burn)</td>
</tr>
</tbody>
</table>

 Unless otherwise specified, weight is expressed in kilograms, height is expressed in centimetres, body surface area is expressed in square meters and age is expressed in years. * If required, several correction factors can be used simultaneously.

* Sex: 0 for females, 1 for males
It underestimates resting energy expenditure in most surgical patients. Correction factors for stress have been proposed, but they have been found to be inappropriate for clinical practice, fostering excessive feeding (Fig. 18).

In clinical practice, simple rules are used to estimate REE in critically ill patients:
- 20-25 kcal/kg per day in patients with low or moderate stress;
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A precise determination of the 24 h metabolic rate would require a 24 h measurement, which is not possible in clinical condition.

Calculation of the daily energy deficit, defined as the difference between the 24 h energy expenditure and energy delivery, allows to estimate how appropriate is the caloric supply.

Recent studies suggest that prolonged energy deficit is associated with clinical complications, particularly septic complications in critically ill patients (Fig. 19, Fig. 20, Fig. 21).
4. Adaptation to fasting

Healthy subjects have the ability to adapt to starvation, allowing survival in case of prolonged starvation. The mechanisms of adaptation include a progressive decrease in resting metabolism, stimulation of production and utilization of ketone bodies as fuel and a progressive reduction of protein catabolism.

![Graph showing energy delivery comparison over 4 weeks](image1)

**Fig. 19**

**Negative impact of hypocaloric feeding and energy balance on clinical outcome in ICU patients**

Stéphane Villet, René L. Chioléro, Marc D. Bollmann,

Clin Nutr 2005;

![Graph showing relationship between complications and energy deficits](image2)

**Fig. 20**

<table>
<thead>
<tr>
<th>Variables</th>
<th>F</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Length of stay</td>
<td>25.18</td>
<td>0.0001</td>
</tr>
<tr>
<td>Complications</td>
<td>15.15</td>
<td>0.0003</td>
</tr>
<tr>
<td>Infections</td>
<td>9.14</td>
<td>0.0042</td>
</tr>
<tr>
<td>Days on antibiotics</td>
<td>17.48</td>
<td>0.0003</td>
</tr>
<tr>
<td>Start of nutrition</td>
<td>17.17</td>
<td>0.0002</td>
</tr>
<tr>
<td>Days of mechanical ventilation</td>
<td>17.12</td>
<td>0.0002</td>
</tr>
</tbody>
</table>

**Negative impact of hypocaloric feeding and energy balance on clinical outcome in ICU patients**

Stéphane Villet, René L. Chioléro, Marc D. Bollmann,

Clin Nutr 2005;

![Graph showing relation between progressive negative energy balance and infectious complications](image3)

**Fig. 21**
4. Adaptation to fasting

Healthy subjects have the ability to adapt to starvation, allowing survival in case of prolonged starvation. The mechanisms of adaptation include a progressive decrease in resting metabolism, stimulation of production and utilization of ketone bodies as fuel and a progressive reduction of protein catabolism. Such adaptable mechanisms are blunted by the critical illness (Fig. 22): ketosis is suppressed by stress hormones and cytokines, while protein catabolism stay elevated all over the course of critical illness. Thus starvation should be as short as possible in the most severely ill patients, who should receive adequate energy supply as soon as possible after the initial resuscitation.

References

Learning Objectives
· Understand glucose metabolism in critically ill patients;
· Understand fat metabolism in critically ill patients;
· Understand protein metabolism in critically ill patients;
· Understand the concept of glucose/fat ratio;
· Understand the basis of macro nutrient supply.

Contents
1. Insulin resistance
2. Carbohydrate metabolism
3. Fat metabolism
4. Protein metabolism
5. Use of energetic substrates

Key Messages
· Glucose utilization is increased in non-insulin dependent organs and decreased in insulin dependent organs and tissues;
· Lipolysis is activated by the critical illness, particularly in patients with sepsis and acute inflammatory diseases;
· Fat utilisation is stimulated in fasted and septic patients, reduced in patients with circulatory failure;
· Protein catabolism is increased, and exceeds protein synthesis, promoting an erosion of the fat-free mass. Glucose and insulin decrease protein catabolism;
· Formulas for critically ill patients should include 1.5 - 2.0 g/kg protein per day, carbohydrate and lipids. Lipid supply should be reduced in patients with acute ischemic heart diseases and major burns.

Nutritional Support in Intensive Care Unit (ICU) Patients

Module 18.2

Use of Macronutrients in ICU

Jean-Charles Preiser
René Chioléro
Pierre Singer

Learning Objectives

- Understand glucose metabolism in critically ill patients;
- Understand fat metabolism in critically ill patients;
- Understand protein metabolism in critically ill patients;
- Understand the concept of glucose/fat ratio;
- Understand the basis of macro nutrient supply.

Contents

1. Insulin resistance
2. Carbohydrate metabolism
3. Fat metabolism
4. Protein metabolism
5. Use of energetic substrates

Key Messages

- Glucose utilization is increased in non-insulin dependent organs and decreased in insulin dependent organs and tissues;
- Lipolysis is activated by the critical illness, particularly in patients with sepsis and acute inflammatory diseases;
- Fat utilisation is stimulated in fasted and septic patients, reduced in patients with circulatory failure;
- Protein catabolism is increased, and exceeds protein synthesis, promoting an erosion of the fat-free mass. Glucose and insulin decrease protein catabolism;
- Formulas for critically ill patients should include 1.5 - 2.0 g/kg protein per day, carbohydrate and lipids. Lipid supply should be reduced in patients with acute ischemic heart diseases and major burns.
1. Insulin resistance

Insulin resistance is a hallmark of the critical illness (Fig. 1), leading to hyperglycemia and major changes in glucose, fat and protein metabolism (see module 17.2 for further details).

This has important nutritional consequences, since it may be associated with a decreased efficacy of nutritional support. Insulin resistance influences glucose plasma level, glucose uptake in skeletal muscle and adipose tissue, as well as the endogenous glucose production in the liver and kidney.

In healthy subjects, insulin is a major regulator of endogenous glucose production, to achieve a constant level of blood glucose: glucose production is suppressed by carbohydrate-rich meals and stimulated in the post-absorptive state (Fig. 2).

This is not the case in surgical and critically ill patients, in whom the endogenous production of glucose stays high despite carbohydrate administration, as a consequence of insulin resistance (Fig. 3).

### Table: Prevalence of hyperglycemia in critically ill patients at intensive care unit admission

<table>
<thead>
<tr>
<th>Patients</th>
<th>Control group</th>
<th>Intensive TT</th>
</tr>
</thead>
<tbody>
<tr>
<td>History of diabetes (%)</td>
<td>103 (13)</td>
<td>101 (13)</td>
</tr>
<tr>
<td>Admission glycemia</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 6.1 mmol/l</td>
<td>24 %</td>
<td>27 %</td>
</tr>
<tr>
<td>&gt; 6.1 mmol/l</td>
<td>76 %</td>
<td>73 %</td>
</tr>
<tr>
<td>&gt; 11.1 mmol/l</td>
<td>13%</td>
<td>11 %</td>
</tr>
</tbody>
</table>

Fig. 1 Van den Berghe G et al, N Engl J Med 2001; 345 1359

### Graph: Effects of intravenous glucose on endogenous glucose production in healthy subjects

![Graph showing effects of intravenous glucose on endogenous glucose production in healthy subjects.](Graph)

Wolfe RR et al, Metabolism 1979; 28: 210

### Graph: Glucose endogenous production is not suppressed by glucose infusion in critically ill patients

![Graph showing glucose endogenous production in healthy and ICU patients.](Graph)

Studies performed in critically ill patients receiving isocaloric nutrition with various proportions of glucose and fat, show that the endogenous production of glucose stays constant for glucose supply ranging from 28 to 75% of total energy (Fig. 4). Such mechanism allows a large supply of glucose to the glucose-dependent tissues like the immune, inflammatory cells and the wounds.

2. Carbohydrate metabolism

Glucose is efficiently utilised as a substrate in critically ill patients despite insulin resistance. It should be underlined that insulin resistance is associated with a decreased insulin-mediated glucose uptake, mainly in the skeletal muscle and adipose tissue associated with an increased non insulin-mediated glucose uptake (Fig. 5). The overall glucose oxidation is normal in most patients (trauma, postoperative, circulatory failure) or increased (major burns or trauma) (Fig. 6).
Fat metabolism is altered in critically ill patients. Lipolysis is activated in most patients with major stress, consequent to the release of stress hormones. Plasma free fatty acid levels are usually normal or elevated (Fig. 10). As in healthy subjects, fat uptake by the tissue is not directly influenced by insulin in ICU patients. Fat metabolism is influenced by plasma concentration of free fatty acids, and by the relative importance of oxidation and recycling of fatty acids. The rate of utilisation of free fatty acids is directly dependent on their plasma concentration: the higher the level, the higher the utilisation (Fig. 11). Plasma glucose and insulin levels also influence fat metabolism: when plasma glucose and insulin levels are high, hormone-sensitive lipase and lipolysis are suppressed, while the reverse is true during starvation (Fig. 12). Thus, glucose is a preferential substrate during high supply, while fat is preferentially oxidized during starvation or when glucose supply is low.

3. Fat metabolism

In subjects with normal body composition, fat stores amount to 15-30% of body weight and constitute the main energy reserve. Fat is a preferential substrate for energy metabolism in most critically ill starving patients or with hypocaloric feeding: in fasting condition, fat oxidation fuels 60-70% of the energy expended (Fig. 9).

### Energy metabolism in critically ill cardiac and septic patients: RMR & substrate oxidation

- 6 postoperative cardiac surgery patients with acute heart failure (inotropes)
- 6 patients with severe sepsis

<table>
<thead>
<tr>
<th></th>
<th>Cardiac</th>
<th>Sepsis</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Resting MR (kcal/d)</td>
<td>1390</td>
<td>1610</td>
<td>NS</td>
</tr>
<tr>
<td>Glucose net oxidation (μmol/kg/min)</td>
<td>4.3</td>
<td>1.75</td>
<td>&lt; 0.05</td>
</tr>
<tr>
<td>Lipid net oxidation (mg/kg/min)</td>
<td>0.60</td>
<td>1.26</td>
<td>&lt; 0.05</td>
</tr>
</tbody>
</table>

**Fig. 7** Martínez A et al, Clin Physiol Funct Imaging 2002; 23: 286

### Effects of enteral CHO on fractional hepatic DN lipogenesis in healthy ill & critically ill subjects

Minoheira K et al, Clin Nutr 2002; 21: 345


**Fig. 8**

### Substrate oxidation in critically ill patients after 3 day starvation

- Resting metabolic rate: 1824 kcal/day
- Glycemia: 7.3 mmol/L
- Endogenous glucose production: 360 g/day (1360 kcal/day)
- Net glucose oxidation: 28% (512 kcal/day)
- Net fat oxidation: 46% (840 kcal/day)
- Net protein oxidation: 26% (470 kcal/day)
- Net protein balance: -117 g/day
Fat metabolism is altered in critically ill patients. Lipolysis is activated in most patients with major stress, consecutive to the release of stress hormones. Plasma free fatty acid levels are usually normal or elevated (Fig. 10).

As in healthy subjects, fat uptake by the tissue is not directly influenced by insulin in ICU patients. Fat metabolism is influenced by plasma concentration of free fatty acids, and by the relative importance of oxidation and recycling of fatty acids. The rate of utilisation of free fatty acids is directly dependent on their plasma concentration: the higher the level, the higher the utilisation (Fig. 11).

Plasma glucose and insulin levels also influence fat metabolism: when plasma glucose and insulin levels are high, hormone-sensitive lipase and lipolysis are suppressed, while the reverse is true during starvation (Fig. 12). Thus, glucose is a preferential substrate during high supply, while fat is preferentially oxidized during starvation or when glucose supply is low.
4. Protein metabolism

The critical illness induces protein wasting, particularly in patients with septic or traumatic injury: protein catabolism exceeds protein synthesis despite full nutritional support (Fig. 13, Fig. 14).

This is an adaptative phenomenon allowing an increased delivery of amino acids to immune and inflammatory cells. Activation is the main mechanism of protein of the ubiquitin proteasome pathway by TNF-α catabolism in acute illness (Fig. 15).
Prolonged protein catabolism leads to a progressive erosion of fatfree mass, in trauma and septic patients with complicated evolution (Fig. 16). Increasing protein supply is unable to abolish such protein catabolism (Fig. 17).

---

**Fig. 16**

Body composition (proteins) in patients with abdominal sepsis receiving full enteral support

![Graph showing body composition changes over time](image)

*P < 0.05

*Plank, LD et al, Ann. Surg. 1998; 228: 146*

---

**Fig. 17**

Body composition in septic ICU patients receiving full nutritional support

![Bar chart showing body composition changes](image)

8 ICU septic patients
TPN: 31 kcal nonprotein energy + 2.3 g N /kg FFM
Body composition: neutron activation analysis

*Streat SJ, J. Trauma 1987;27:262*
In patients with burns, protein catabolism has been shown to be improved by intensive glucose and insulin supply although the clinical benefits are yet largely unknown (Fig. 18). Androgen steroids and exercise also stimulate protein anabolism. Growth hormone therapy has been associated with increased mortality and should be avoided.

5. Use of energetic substrates

Both fat and glucose are efficiently utilized in critically ill patients receiving artificial feeding, although the most appropriate proportion remains controversial. In isocaloric feeding, glucose and fat oxidation is directly related to their proportion in the feeding solution (Fig. 19). Fat oxidation is decreased during high glucose supply and insulin therapy. Comparison between high glucose-insulin and glucose fat regimens suggests that the former has a better nitrogen sparing effect (19).
Glucose is the only substrate oxidized by the ischemic tissues. Glucose and insulin have been shown to be an effective metabolic support in patients with severe ischemic cardiac failure (Fig. 20). In septic and inflammatory diseases, there is a preferential oxidation of fat, while glucose oxidation is slightly reduced or normal (6).

Whatever the composition of the diet, a good control of plasma glucose levels is important, particularly in patients with acute cardiac diseases (21).

In addition as being a substrate for energy metabolism, fatty acids exert important regulatory and signalling actions, which may favourably affect the regulation of metabolism and modulate inflammatory and immune responses.

**References**

Learning Objectives
· Key criteria to start nutrition support;
· Assessment of nutritional status;
· Situations where early enteral nutrition was shown beneficial;
· Optimal timing and amount of nutrition support;
· Prevention and management of the common complications of nutrition support.

Contents
1. Criteria for implementation of nutritional support
1.1 Nutritional status
2. Timing
3. Amount
4. Composition of nutrition support formulas
4.1 Basic components
4.2 Additional components

Key Messages
· Increased requirements during critical illness must be matched by appropriate infusion of calories and nitrogen, especially when severe malnutrition is present, in case of insufficient oral intake or expected delay before recovery of eating;
· Early enteral nutrition can be systematically considered in patients unlikely to recover their ability to eat within 48 hours after injury;
· Nutritional status can be assessed from physical and biological variables combined in scores;
· Inappropriately high amounts of energetic substrates can lead to detrimental effects, especially after a long period of fasting;
· The use of local algorithms and protocols is recommended to optimise nutrition support.

Nutritional Support in Intensive Care Unit (ICU)
Patients

Module 18.3

General Principles of Prescription and Management

Jean-Charles Preiser
René Chioléro
Pierre Singer

Learning Objectives

- Key criteria to start nutrition support;
- Assessment of nutritional status;
- Situations where early enteral nutrition was shown beneficial;
- Optimal timing and amount of nutrition support;
- Prevention and management of the common complications of nutrition support.

Contents

1. Criteria for implementation of nutritional support
    1.1 Nutritional status
2. Timing
3. Amount
4. Composition of nutrition support formulas
    4.1 Basic components
    4.2 Additional components

Key Messages

- Increased requirements during critical illness must be matched by appropriate infusion of calories and nitrogen, especially when severe malnutrition is present, in case of insufficient oral intake or expected delay before recovery of eating;
- Early enteral nutrition can be systematically considered in patients unlikely to recover their ability to eat within 48 hours after injury;
- Nutritional status can be assessed from physical and biological variables combined in scores;
- Inappropriately high amounts of energetic substrates can lead to detrimental effects, especially after a long period of fasting;
- The use of local algorithms and protocols is recommended to optimise nutrition support.
1. Criteria for implementation of nutritional support

In general terms, the increased energetic and protein requirements during critical illness must be matched by appropriate infusion of calories and nitrogen. Therefore, the implementation of nutritional support in a critically ill patient is obviously indicated when at least one of the three following criteria is present:

- Pre-existing severe malnutrition
- Oral intake matches < 50% of the energy and nitrogen needs
- Expected delay before recovery of eating > 5-7 days

In addition to this approach, surgical, trauma (including burns) benefit from enteral nutrition started within 48 hours following injury, as confirmed by several studies who demonstrated consistent benefits in terms of decrease in septic morbidity, hospital and ICU length of stay and mortality (1, 2).

The absence of gut feeding, or gut starvation, may represent an important trigger for systemic infections due to typically gastrointestinal micro-organisms. Numerous disturbances found at different levels of the gastrointestinal tract have been advocated and summarized in Fig. 2.

Accordingly, early enteral nutrition is a common practice in intensive care units and is recommended in several circumstances where it has been proven useful (see the algorithm shown on Fig. 1). This algorithm is consistent with others recently updated recommendations (3, 4, 5).
1.1 Nutritional status

Although the assessment of the current nutritional status is an important issue in ICU patients, it may be difficult to estimate precisely with methods validated in other settings, using anthropometric or biological variables and functional tests (muscle and immune function) to generate a risk score (for instance Subjective global assessment SGA (6), MUST (7), Nutritional Risk Index (NRI) (8), MNA (9)), PINI (10).

Importantly, these scores have been designed and validated in patients with chronic illnesses, but not in acutely ill patients, in whom several features will influence the assessment. The PINI score is the only one in whom the inflammatory status (C-reactive protein and orosomucoid) was included.

---

### Anthropometry

<table>
<thead>
<tr>
<th>Body mass index</th>
<th>18.5-25 kg/m²</th>
</tr>
</thead>
<tbody>
<tr>
<td>17.0-18.5 (grade II)</td>
<td>16.0-18.0 (grade I)</td>
</tr>
<tr>
<td>13.0-15.9 (grade III)</td>
<td>10.0-12.9 (grade IV)</td>
</tr>
<tr>
<td>&lt;10.0 (very severe grade V)</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Waist: Hip ratio</th>
<th>&lt;0.8</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tricipital skin fold thickness</td>
<td>Male: 12 mm</td>
</tr>
<tr>
<td></td>
<td>Female: 25 mm</td>
</tr>
<tr>
<td></td>
<td>&lt;5 mm</td>
</tr>
<tr>
<td></td>
<td>&lt;12 mm</td>
</tr>
</tbody>
</table>

| Mid-arm muscle area | Male: 55 cm² |
|                    | Female: 31 cm² |
|                    | <38.5 cm² |
|                    | <20 cm² |

Lean body mass = \[
\frac{1}{4} \times \left\{ \text{mid-arm circumference (cm)} \times 0.314 \times \frac{\text{triceps skinfold thickness (mm)}}{\text{10 [male]} \text{ or } 6.5 \text{ [female]}} \right\}
\]

### Biochemistry

<table>
<thead>
<tr>
<th></th>
<th>Normal range</th>
<th>Malnutrition value</th>
<th>Half-life (days)</th>
<th>Molecular weight (Da)</th>
<th>Influence of inflammatory status</th>
</tr>
</thead>
<tbody>
<tr>
<td>Albumin</td>
<td>35-50 g/l</td>
<td>&lt;30 g/l</td>
<td>20</td>
<td>66 000</td>
<td>++</td>
</tr>
<tr>
<td>Transthyretin</td>
<td>45-70 mg/l</td>
<td>NA</td>
<td>2</td>
<td>55 000</td>
<td>+++</td>
</tr>
<tr>
<td>Transferrin</td>
<td>2.0-3.5 g/l</td>
<td>NA</td>
<td>8.8</td>
<td>80 000</td>
<td>++</td>
</tr>
</tbody>
</table>

### Muscular / immune testing

<table>
<thead>
<tr>
<th>Variable</th>
<th>Normal value</th>
<th>Malnutrition value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Muscular mass</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mid-arm muscle area</td>
<td>Male: 55 cm²</td>
<td>&lt;38.5 cm²</td>
</tr>
<tr>
<td></td>
<td>Female: 31 cm²</td>
<td>&lt;20 cm²</td>
</tr>
<tr>
<td>24-hour creatinine</td>
<td>Male: Ideal body weight x 23</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Female: Ideal body weight x 18</td>
<td>&lt;80% normal value</td>
</tr>
<tr>
<td><strong>Immune function tests</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cutaneous tests of delayed hypersensitivity</td>
<td>Present</td>
<td>Abolished or severely impaired</td>
</tr>
<tr>
<td>Lymphocyte count</td>
<td>&lt;3000/mm²</td>
<td>&lt;1200 mm²</td>
</tr>
</tbody>
</table>
2. Timing

This issue requires the assessment of possible benefits from early (< 48 h) enteral nutrition. If the patient is not likely to benefit from early enteral nutrition, delayed artificial nutrition (preferentially enteral) or parenteral should be instituted when the patient did not recover the ability to cover his caloric and protein requirement for 5-7 days (see discussion in the “choice of route” module 18.4).

In contrast, no benefit has been associated with an early implementation of parenteral nutrition in critically ill patients (11, 12).

The parenteral route should be reserved only when the gastro-intestinal function does not allow the administration of enteral nutrition, or when the tolerated amount of enteral meets less than 50% energy requirements over a prolonged period.

3. Amount

The amount of artificial nutrition to be supplied is based on the requirements of energy, nitrogen and micro-nutrients.

In general terms, the caloric expenditure and the loss of nitrogen are increased during critical illness.

The actual values of the resting energy expenditure can be estimated by direct measurements or predictive equations (see module 18.1).

Comparative studies indicate that the equations can be used as a reliable estimate even though they do not allow an accurate evaluation of the energy expenditure. The nitrogen losses can be estimated by direct measurements of nitrogen metabolism (Fig. 7).

Although the direct measurements and if not available the predictive equation allow an individual estimation of the patients’ needs, the resting energy expenditure and nitrogen requirements of most critically ill patients fall within the following range:
2. Timing

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Although the direct measurements and if not available the predictive equation allow an individual estimation of the patients' needs, the resting energy expenditure and nitrogen requirements of most critically ill patients fall within the following range:

Table 1 Scoring system

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Functional classes + ranges</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>SGA</td>
<td></td>
<td></td>
</tr>
<tr>
<td>History</td>
<td>A: well nourished</td>
<td></td>
</tr>
<tr>
<td></td>
<td>B: moderately malnourished</td>
<td>JAMA 1994; 271: 54-58</td>
</tr>
<tr>
<td></td>
<td>C: severely malnourished</td>
<td></td>
</tr>
<tr>
<td>Physical examination</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MNA</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Screening</td>
<td>Screening score</td>
<td></td>
</tr>
<tr>
<td></td>
<td>≥12: not at risk for malnutrition;</td>
<td></td>
</tr>
<tr>
<td></td>
<td>≤11: possible malnutrition; continue assessment</td>
<td><a href="http://www.mna-elderly.com">www.mna-elderly.com</a></td>
</tr>
<tr>
<td>Assessment</td>
<td>Assessment score</td>
<td></td>
</tr>
<tr>
<td></td>
<td>≥24: well-nourished</td>
<td></td>
</tr>
<tr>
<td></td>
<td>≤17: at risk of malnutrition</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Total assessment score=</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Screening score</td>
<td></td>
</tr>
<tr>
<td></td>
<td>+ Assessment score:</td>
<td></td>
</tr>
<tr>
<td></td>
<td>17.0-23.5: at risk of malnutrition</td>
<td></td>
</tr>
<tr>
<td></td>
<td>&lt;17: malnourished</td>
<td></td>
</tr>
<tr>
<td>NRI</td>
<td>1.519 x [albumin] + 0.417 x (percentage of weight change)</td>
<td>97.5%: no malnutrition 98.5-97.5%: moderate malnutrition &lt;83.5%: severe malnutrition Am J Clin Nutr 1988 47:366-381</td>
</tr>
<tr>
<td>PINI</td>
<td>{CRP (mg/L) x oroscomucoid (mg/L)/[albumin (g/L) x TT (mg/L)] }</td>
<td>1-10: low risk of malnutrition 11-20: moderate risk of malnutrition 21-30: high risk of malnutrition &gt;30: very high risk of malnutrition Int J Vitam Nutr Res 1985;55: 91-101</td>
</tr>
<tr>
<td>MUST</td>
<td>Height</td>
<td>0: low risk</td>
</tr>
<tr>
<td></td>
<td>Weight</td>
<td>1: medium risk</td>
</tr>
<tr>
<td></td>
<td>BMI</td>
<td>≥2: high risk</td>
</tr>
<tr>
<td></td>
<td>% unplanned weight loss</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Acute disease effect</td>
<td></td>
</tr>
<tr>
<td>NRS</td>
<td>Nutritional status</td>
<td>0-3 for nutritional status 0-3 for severity of disease Score 1 if ≥70 years If sum ≥3, at risk for malnutrition Clin Nutr 2003;22: 321-336</td>
</tr>
<tr>
<td></td>
<td>Weight loss</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Food intake</td>
<td></td>
</tr>
<tr>
<td></td>
<td>BMI</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Severity of disease Age</td>
<td></td>
</tr>
</tbody>
</table>

74
The provision of a too large amount of calories can lead to deleterious effects, related to hyperglycemia, inflammatory response, to increased carbon dioxide production and to liver dysfunction (13).

Remarkably, the provision of an amount of calories calculated to match exactly the resting energy expenditure in severely malnourished patients can also lead to a similar situation, known as “refeeding syndrome”.

This syndrome, reported in hunger-strikers and in war prisoners, is associated with disturbances of body-fluid distribution, abnormal glucose and lipid metabolisms and severe electrolyte abnormalities (mainly hypophosphatemia, hypokaliemia and hypomagnesemia).

The pathogenesis of this potentially life-threatening syndrome involves the sudden shift from fat to carbohydrate metabolism, leading to sudden intracellular glucose loads and increased insulin release (14).

### 4. Composition of nutrition support formulas.

During isocaloric nutrition, glucose is a preferential substrate in most critically ill patients: it should cover 70-100% of non-protein energy supply (15).

The rate of glucose supply should not exceed 4 mg/kg per min, to avoid the activation of de novo lipogenesis pathway and the associated increased pulmonary CO₂ excretion.

It is recommended to provide 15-30% of non protein energy as lipids, except in patients with acute ischemic heart diseases, major burns and severe infection, in whom fat supply should be reduced.

Protein supply should cover 15-20% of total energy supply, or 1.5 - 2.0 g/kg per day.
The provision of a too large amount of calories can lead to deleterious effects, related to hyperglycemia, inflammatory response, to increased carbon dioxide production and to liver dysfunction (13).

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### Table 2 Current recommendation of daily intake

<table>
<thead>
<tr>
<th>Macronutrients</th>
<th>Enteral</th>
<th>Parenteral</th>
<th>PRI</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Carbohydrates</strong></td>
<td>120-185 g</td>
<td>120-160 g</td>
<td>55% of energy</td>
</tr>
<tr>
<td><strong>Lipids</strong></td>
<td>15-68 g</td>
<td>30-45 g</td>
<td>30% of energy</td>
</tr>
<tr>
<td><strong>Proteins</strong></td>
<td>37-94 g</td>
<td>31-44 g</td>
<td>40-100 g</td>
</tr>
</tbody>
</table>

### Minerals

<table>
<thead>
<tr>
<th>Mineral</th>
<th>Enteral</th>
<th>Parenteral</th>
<th>PRI</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Sodium</strong></td>
<td>560-1380 mg (13-32 mEq)</td>
<td>0-6500 mg (0-150 mEq)</td>
<td>575-3500 mg</td>
</tr>
<tr>
<td><strong>Potassium</strong></td>
<td>1000-2630 mg (26-68 mEq)</td>
<td>0-5800 mg (0-150 mEq)</td>
<td>2000-4000 mg</td>
</tr>
<tr>
<td><strong>Chloride</strong></td>
<td>850-1740 mg (24-49 mEq)</td>
<td>0-4250 mg (0-120 mEq)</td>
<td>750-4600 mg</td>
</tr>
<tr>
<td><strong>Calcium</strong></td>
<td>530-1200 mg</td>
<td>0-10 mEq</td>
<td>1000 mg</td>
</tr>
<tr>
<td><strong>Phosphorus</strong></td>
<td>535-1700 mg</td>
<td>0-45 mEq</td>
<td>1000 mg</td>
</tr>
<tr>
<td><strong>Magnesium</strong></td>
<td>200-425 mg</td>
<td>0-20 mEq</td>
<td>400 mg</td>
</tr>
</tbody>
</table>

### Trace elements

- **Iron**: 8.9-24 mg
- **Zinc**: 10-36 mg
- **Copper**: 1.1-3.4 mg
- **Manganese**: 1.7-6.3 mg
- **Fluorine**: 0.1-1.5 mg
- **Molybdenum**: 0.2-20 µg
- **Selenium**: 0.1-1.4 mg
- **Chromium**: 0.1-1.4 mg
- **Iodine**: 75-200 µg

### Vitamins

- **A**: 2331-12000 IU
- **β-carotene**: 10,000(F)-2666(M) IU
- **B1 (thiamine)**: 1.3-3.2 mg
- **B2 (riboflavin)**: 1.5-3.6 mg
- **B5 (panthothenic acid)**: 4.7-22 mg
- **B6**: 1.5-4.3 mg
- **B8 (biotin)**: 40-635 µg
- **B9 (folic acid)**: 200-850 µg
- **B12**: 2.1-13 µg
- **C**: 67-1000 mg
- **D**: 200-520 IU
- **E**: 19-317 IU
- **K**: 43-127 µg
- **PP**: 16-43 mg
4.1 Basic components

The basic composition of the solutions used for nutritional support is similar whatever the route of administration: the caloric supply is shared between carbohydrates, lipids and proteins (Fig.10). The non-protein caloric/nitrogen ratio is an index of the efficiency of the solution, with the highest rate (ideally < 150 kcal/gN) associated with a maximal use of energy for protein anabolism. However, there are several fundamental dissimilarities between the two types of solutions, as shown by the comparison of the usual ranges of the components in ready-for-use solutions.

The initial choice of a nutritional support formula is easy when basic questions are answered. For most patients, at the present time, standard iso-energetic fiber-free enteral solutions, or basic ternary parenteral solutions are reasonable choices although the recommendation of some specialized formulas as a first-line support is possible in the near future.

4.2 Additional components

In contrast to enteral feeding formulas, parenteral nutrition do not contain trace elements nor vitamins. Therefore, these components must be added daily when the patient is only nourished parenterally. Several available solutions of trace elements and vitamins comply with current recommendations of daily intake (Table 2).
4.1 Basic components

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Nutritional Support in Intensive Care Unit (ICU) Patients

Module 18.4

Routes of Nutrition in ICU

Jean-Charles Preiser
René Chioléro
Pierre Singer

Learning Objectives

· To describe the techniques, the indications and contraindications of enteral and parenteral nutrition therapy;
· To describe the access routes for enteral and parenteral infusion, to describe their advantages and disadvantages.

Contents

1. Enteral nutrition
1.1 Contraindications
1.2 Advantages and disadvantages
1.3 Types of enteral feeding techniques
1.3.1 Naso-gastric tubing and placement
1.3.2 Gastrostomy
1.3.3 Postpyloric feeding
1.4 Initiation of enteral feeding
1.5 Prevention and handling of current problems of enteral feeding
1.6 Administration technique
1.7 Complications
1.7.1 Gastroduodenal dysfunction
1.7.2 Diarrhoea
1.7.3 Constipation

2. Parenteral nutrition
2.1 Complications

Key Messages

· Enteral support is always preferable to parenteral nutrition;
· Enteral access is available via nasogastric, gastrostomy or post-pyloric tube;
· Significant risks of enteral feeding include aspiration, pneumonia and motility disorders;
· Parenteral nutrition is associated with catheter-related and metabolic complications.

References

7. www.bapen.org.uk
9. www.mna-elderly.com
Learning Objectives

- To describe the techniques, the indications and contraindications of enteral and parenteral nutrition therapy;
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Contents

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      1.3.2 Gastrostomy
      1.3.3 Postpyloric feeding
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   1.5 Prevention and handling of current problems of enteral feeding
   1.6 Administration technique
   1.7 Complications
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      1.7.2 Diarrhoea
      1.7.3 Constipation
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   2.1 Complications

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- Enteral access is available via nasogastric, gastrostomy or post-pyloric tube;
- Significant risks of enteral feeding include aspiration, pneumonia and motility disorders;
- Parenteral nutrition is associated with catheter-related and metabolic complications.
1. Enteral nutrition

As a general rule, administration of nutritional support is required to critically ill patients (1-12) to limit the negative energy and protein balance observed in these patients (Fig. 1).

**Enteral nutrition is always preferable to parenteral nutrition, for a variety of reasons outlined previously (Module 18.3, Fig. 2).**

Briefly, the absence of nutrients in the gastrointestinal tract has 3 consequences (Fig. 2)(13,14):

- lack of fuel source for enterocytes
- lack of mechanical stimulation
- abnormal hormonal pattern.

Therefore, the absence of nutrients has been proposed as a trigger for the translocation process of endotoxins, bacteria and fungi from the gastrointestinal tract (GIT) (15) lumen into the blood stream despite liver filter, inducing metabolic response, and a body response to a second "hit" that may induce systemic inflammatory response to stress and multi organ failure (16).

Early enteral feeding (17) and even a small amount of nutrients in the gastrointestinal tract may prevent this translocation process, even though others discuss this evidence (18).

Enteral nutrition is often feasible, as the gastrointestinal tract function is usually normal, but some precautions, however, must be taken before initiating enteral feeding.

### 1.1 Contraindications

Absolute contraindications (Fig. 3) for enteral access include:

- complete bowel obstruction
- severe malabsorption
- severe diarrhea.

### 1.2 Advantages and Disadvantages

The gastric access (Fig. 4) has many advantages:

- easy access;
- early access;
- access performed by nurses.

Therefore this access should always been proposed in any case where GIT is functioning and available.

The disadvantages are not negligible and include the risk of inhalation of gastric content, because of supine position, gastroesophageal reflux and impaired gastrointestinal peristaltism (19).

The aspiration complication can induce pneumonia, one of the leading causes of respirator related pneumonias observed in the ICU patient (20) and nasopharyngeal trauma that induces profuse bleeding can be encountered in ICU patients and should be prevented by gentle introduction through the nose of small bored nasogastric tube (21).

Accidental tube displacement should be continuously diagnosed since fixation may be removed and re-fixed and new positioning not reconfirmed by X-ray.

### 1.3 Types of Enteral Feeding Techniques

**Gastric Feeding (Fig. 5)**

- nasogastric tubes available for short time feeding process (less than 3-6 weeks), and achievable using an manual bedside placement that could be confirmed radiologically (not mandatory);
- gastrostomy available for long term feeding through the GIT tract, and achievable using the endoscopic, radiologic and a surgical placement (21, 23, 24).

**Postpyloric feeding**

- nasojejunal feeding tubes;
- jejunostomy.

---

**ICU patients are**

- Normo or Hypermetabolic (elevated REE)
- Hypercatabolic (increased N2 excretion)
- Malnourished (low prealbumin, low lymphocyte count)
- Unable to eat
- Usually with a (almost) normal GIT absorptive capability

**INTESTINAL MUCOSAL ATROPHY IS FAVORED BY:**

- The absence of luminal nutrients and enterocytes fuel sources
- The lack of mechanical stimulation
- An abnormal hormonal pattern

> INDUCING: Translocation, SIRS, MODS

**Enteral access:**

**Contraindications**

- Complete bowel obstruction
- Severe mal absorption
- Severe diarrhea

**Gastric route contraindicated:**
- Delayed gastric emptying (gastric paresis)
1.2 Advantages and Disadvantages

The gastric access (Fig. 4) has many advantages:
- Easy access;
- Early access;
- Can be placed by nurses.

Therefore this access should always be proposed in any case where GIT is functioning and available.

The disadvantages are not negligible and include the risk of inhalation of gastric content, because of supine position, gastroesophageal reflux and impaired gastrointestinal peristalsim (19).

The aspiration complication can induce pneumonia, one of the leading causes of respirator related pneumonias observed in the ICU patient (20) and nasopharyngeal trauma that induces profuse bleeding can be encountered in ICU patients and should be prevented by gentle introduction through the nose of small bored nasogastric tube (21).

Accidental tube displacement should be continuously diagnosed since fixation may be removed and re-fixed and new positioning not reconfirmed by X-ray.

1.3 Types of Enteral Feeding Techniques

Enteral feeding techniques include:

**Gastric Feeding (Fig. 5)**
- Nasogastric tubes available for short time feeding process (less than 3-6 weeks), and achievable using an manual bedside placement that could be confirmed radiologically (not mandatory);
- Gastrostomy available for long term feeding through the GIT tract, and achievable using the endoscopic, radiologic and a surgical placement (21, 23, 24).

Postpyloric feeding
- nasojejunal feeding tubes;
- jejunostomy.
1.3.1 Naso-gastric tubing and placement

Tubes used (Fig. 6, Fig. 7) could be of polyvinyl (more rigid), silicone (more flexible) or of polyurethane (less traumatic). Their diameter varies from 6 to 14. Their length can vary from 95, 105 up to 120 cm, according to the anatomy size of the patients and the extremity could be weighted, although a confirmation of the advantage of this technique is still awaited. Recently, some techniques have developed to improve the rate of success of introducing a nasogastric tube (Fig. 8).

If the purpose is to introduce the tube in the duodenal tube, a 10-10-10 technique has been proposed. This technique proposes to administer metoclopramide (10 mg), to wait 10 min and then to introduce an 10 Fr duodenal tube, achieving around 70% of success. Other techniques have reached similar results and bedside introduction of gastric or duodenal tube have been widely proposed, even in pregnant women suffering from hyperemesis gravidarum (26-28).

The right placement of the tube must always be checked before starting enteral feeding (Fig. 9). Coughing, vomiting or nasotracheal suctioning, as well as extubation of the endotracheal tube can induce dislodgement of the nasogastric or the naso-duodenal tube. Therefore, position of the tube should be checked regularly by nurses during their shift. In case of undetermined position, X-ray should be ordered (29).

Routes of administration

- Enteral route: through naso gastric or jejunal tubes
- Polyvinyl (rigid), silicone (Ch 6 to 14), or polyurethane (less traumatic)
- Length 90, 105 or 120 cm, can be with weight.

Nasogastric Tubes

Precautions in introducing the tube

- Insufflate air, aspirate, Xray control in doubt of intra alveolar placement
- Intraduodenal tube can be placed using the 10 10 10 rule: 10 mg metoclopramide -10 min wait - 10 Ch tube. About 70% success
- Wait for 24 hours for help of peristalsism.
- Prevent obstruction by flushing and using low viscosity formulas
According to (30), 15% of small-bore nasogastric tubes, 27% of weighted tubes and 50% of unweighted nasointestinal tubes were not located at their intended position.

An easy test of position may be the pH analysis of aspirated juice, remembering that gastric juice pH is more close to 2-3, and duodenal pH is closer to 6-7, although biliary reflux may represent a confounding factor. Auscultation of insufflated air is frequently used but of low accuracy.

1.3.2 Gastrostomy

Percutaneous Endoscopic Gastrostomy (32) has many advantages: no need for surgery, performed at bedside, minimal sedations, short procedure and low costs (Fig. 10).

Versus a nasogastric tube, PEG should be suggested if enteral feeding is planned for more than 8 to 12 weeks. Aspiration is not decreased by PEG. But if the patient is agitated, pulling out his tube many times and is in vegetative state, PEG should be recommended (Fig. 11).

The procedure is simple and the complication rate is even lower than the surgical gastrostomy. It is even cost effective. Immediate feeding has been tested in comparison with feeding the next day and in none of the parameters, any difference has been found.

Some patients require surgical procedures because of the abdominal condition and an expected prolonged stay in the hospital and in rehabilitation centres.

Verifying placement of small-bore feeding tubes

- Danger of silent dislocation during coughing, vomiting or nasotracheal suctioning, extubation of NTT
- Radiography?
- 15% of small-bore NGT, 27% of weighted and 50% of unweighted NI tubes were not located at their intended position
- Aspiration of Gastric content
- pH testing, auscultation of insufflated air

Fig. 9

Percutaneous Endoscopic Gastrostomy: Advantages

Rigid

Flexible

- No surgery
- Bedside
- Minimal sedation
- Short procedure
- Low costs

Fig. 10


PEG versus NGT in ICU

Angus et al, Am J Gastro 2003;98:272-7

- PEG vs small-bore feeding tubes: NGT can provide adequate nutritional support, are cost-effective and safe for 8 weeks
- Major complication: aspiration is not decreased by PEG
- PEG is not beneficial in comparison with NGT in patients with anticipated need less than 6-8 weeks
- PEG should be considered in the agitated patient requiring enteral feeding for more than 2 weeks, and in severe head trauma, Persistent vegetative state, long term ICU stay
1.3.3 Postpyloric feeding

The surgical techniques recommended in case the patient is undergoing laparotomy should be performed according to the surgeon experience, the abdominal status and the related risks of the procedure. Complications of the operative gastrostomy tube placement are hemorrhagic in rare cases (less than 1%). Improper lodgement of the tube, or dislodgement in the anterior part of the stomach can be found. The site leak is more frequent. Wound infection can occur in 2-8% of the cases (Fig. 12, Fig. 13, Fig. 14).

Feasibility, Efficacy, Safety
Akkersdijk et al: Injury 1998; 29:11-4

- 129 PEGs from 16,417 trauma admissions: in closed head trauma and agitated patients
- Complication rate: 1.5% vs jejunostomy 18%
- 2 leaks from the gastrostomy (1 MOF)
- Efficient: 24 trauma patients ISS 44 with mean hospital stay of 71 days. Eight patients were discharged with PEG, 1 aspirated and died, 2 had leak, 12 were weaned from PEG

Complications of operative gastrostomy tube placement

- Hemorrhage: fewer than 1%
- Improper placement of the tube
- Dislodgment of the stomach from the anterior abdominal wall
- Site leakage is frequent
- Wound infection (2-8% of the cases)

Complications PEG vs SG in trauma
Dwyer et al: J Trauma 2002; 52:26

- 95 PEG vs 63 SG in 4 years
- Charges for PEG: 1271 $
- Charges for SG: 2761 $(P<0.001)
1.3.3 Postpyloric feeding

**Surgical techniques**

- Witzel jejunostomy
- Needle catheter jejunostomy
- Transgastric jejunostomy
- Roux en Y jejunostomy
- Operatively placed nasojejunal feeding tube
- Gastrostomy surgical or PEG

**Complications of postpyloric feeding**

- 1-2% have serious complications
- Mechanical complications: dislodgement, intraperitoneal migration, occlusion, volvulus
- Diarrhea: 22 to 50% of the patients
- Cramping, abdominal distension
- 13% never tolerate and convert to TPN
- Bowel necrosis
1.4 Initiation of enteral feeding

A list of potential concerns and queries have to be solved before the initiation of enteral feeding, in order to prevent and avoid complications. The systematic use of a checklist and of standard settings, as shown in the (Fig. 19), can be useful to start and to optimise enteral feeding.

<table>
<thead>
<tr>
<th>Figure 18</th>
<th>Initiation of enteral feeding</th>
</tr>
</thead>
<tbody>
<tr>
<td>Question</td>
<td>Suggested solution</td>
</tr>
<tr>
<td>Is the gastric residual volume &gt; 250 ml?</td>
<td></td>
</tr>
<tr>
<td>Suspicion of ileus?</td>
<td>Infuse enteral feeding (30 ml/h) and check gastric residual volume 4-6 h later</td>
</tr>
<tr>
<td>Initial settings?</td>
<td>Pump-driven, continuous, 30-60 ml/h</td>
</tr>
<tr>
<td>Position of the feeding tube?</td>
<td>Naso- or oro-gastric. Distal end in fundus or antrum.</td>
</tr>
<tr>
<td>Catheter type?</td>
<td>PVC</td>
</tr>
<tr>
<td>Patient position?</td>
<td>&gt; 45°</td>
</tr>
<tr>
<td>Which formula?</td>
<td>Polymeric, isoenergetic in most cases (see Module 18.5)</td>
</tr>
</tbody>
</table>

1.5 Prevention and management of current problems of enteral feeding

Once enteral nutrition has been initiated, several adverse events commonly occur, sometimes discouraging or impeding adequate delivery of enteral feeds. Some of the frequently asked questions are shown below. Suggested solutions are also shown (Table 1), although standardization is lacking in this area. Although the guidelines listed in this chapter are not evidence-based and are open to debate, they reflect current practice in several ICUs in Europe and, with minor alterations, could realistically be adopted by most ICUs worldwide (33, 34).

Table 1 Management of current problems of enteral feeding

<table>
<thead>
<tr>
<th>Problem</th>
<th>Suggested solution</th>
</tr>
</thead>
<tbody>
<tr>
<td>High gastric residual volume</td>
<td>Decrease infusion rate by half and give prokinetics</td>
</tr>
<tr>
<td>Prevention of inhalation pneumonia</td>
<td>Constant infusion</td>
</tr>
<tr>
<td></td>
<td>Flush the catheter after administration of drugs, to prevent occlusion</td>
</tr>
<tr>
<td></td>
<td>Elevate: keep the patient in semi-recumbent position</td>
</tr>
<tr>
<td>Prevention of sinusitis/nasal erosions</td>
<td>Frequent mouth washing</td>
</tr>
<tr>
<td></td>
<td>Use small tubes, preferentially in silicon</td>
</tr>
<tr>
<td>Diarrhoea</td>
<td>Exclude infectious diarrhoea</td>
</tr>
<tr>
<td></td>
<td>Decrease infusion rate by half and give loperamide</td>
</tr>
<tr>
<td></td>
<td>Replace by a fibre-enriched solution and add Saccharomyces boulardii</td>
</tr>
<tr>
<td>Constipation</td>
<td>Replace by a fibre-enriched solution</td>
</tr>
<tr>
<td>Oral drug administration</td>
<td>Avoid long-acting medications, use liquid formulas in preference</td>
</tr>
<tr>
<td></td>
<td>Crunch and mix pills, rinse the tube with water after administration</td>
</tr>
<tr>
<td>Keeping a naso-gastric catheter in place when oesophageal erosions have been seen by an endoscopist</td>
<td>Unless responsible for significant bleeding, a small-calibre feeding catheter can be left in place.</td>
</tr>
<tr>
<td>Is stress ulcer prophylaxis useful during enteral nutrition?</td>
<td>Although intragastric administration of enteral nutrition partially prevents the occurrence of mucosal erosions and gastrointestinal bleeding, the efficacy of enteral nutrition alone as stress ulcer prophylaxis is not proven. At present, pharmacological stress ulcer prophylaxis should be independent of enteral nutrition</td>
</tr>
</tbody>
</table>
1.6 Administration technique

Drip feeding is preferred to bolus feeding (no more than 500 mL per bolus or 30 mL/min). This technique requires nurse intensive observation and gastric residue analysis every 4 to 8 hours (Fig. 20).

Continuous enteral feeding decreases the GIT secretion and is achieved using volumetric pumps. Not all the planned volume should be placed in the bag at the room air, but fractioned volumes should be taken from the refrigerated storage.

Practical recommendations include positioning the head in an elevated position of 30 degrees, introduction of nasogastric tube to start with, check residue and start with rates of 40-50 mL/h and a concentration rate of 1 kCal/cc. Increase to 75-100 mL/h after a few hours if the solution is isotonic (Fig. 21).

In case of failure in achieving gastric emptying, try prokinetic agents and in case of failure after hours of try, introduce a nasoduodenal tube. The administration rate of enteral feeding is slower, starting from 25 mL/h (Fig.22). In case of low viscosity of the formula, or in case of obstruction risk, flushing should be a technique to prevent obstruction.

1.7 Complications

The complications most encountered (35) are clogging, aspiration pneumonia, vomiting and esophagitis. Abdominal pain and diarrhea are also encountered. In case of use of hypertonic enteral solutions, hyperosmolality and dehydration can occur. Increase in glucose load can induce glucose intolerance and hepatic steatosis with an increase in alkaline phosphatase, Gamma-glutaryl transferase and sometimes total and direct bilirubin.

<table>
<thead>
<tr>
<th>How to increase administration</th>
<th>GASTRICAL</th>
<th>JEJUNAL</th>
</tr>
</thead>
<tbody>
<tr>
<td>START flow concentration</td>
<td>50 mL/h</td>
<td>25 mL/h and 0.25 kcal/mL</td>
</tr>
<tr>
<td>Daily Progress</td>
<td>Increase concentration by 25% and then the flow by 25 mL/h</td>
<td>Increase the flow by 25 mL/h and then the concentration by 25%</td>
</tr>
<tr>
<td>If polymeric</td>
<td>50 mL/h at 1 kcal/cc &amp; increase to 100 ml/h</td>
<td></td>
</tr>
</tbody>
</table>
In ventilated patients, the gastric motility is decreased. This is even more decreased when morphine or norepinephrine are used. The duodenal activity fronts persist and therefore, duodenal tube should be inserted very early.

1.7.1 Gastroduodenal dysfunction

A common concern during enteral feeding is delayed gastric emptying. This condition is defined by an increased gastric residue more than 150 mL/h or more than the double of the previous administration in the last hour (20) or more than 600 mL for the last 24 hours. Studies have shown that this gastric residue was not enough reliable for gastric emptying evaluation. Other tests as the sophisticated isotope technique (21) or the paracetamol test have been proposed to evaluate bedside gastric evaluation. However, if gastric paresis is observed, it should be inducing evaluation of the gastric emptying function (22).

Although there is no clear consensus on the management of gastro-duodenal dysfunction, one should remember that the infusion of enteral feeding is beneficial for the gut mucosa, even at a low rate. Therefore, enteral infusion should not be discontinued, and pro-kinetic drugs should be used when the patient cannot tolerate “a low delivery rate” of enteral feeding. Importantly, once the gastric residual volume is below the cut-off value, the administration rate should be restored to a higher value. An example of algorithm is shown.

Check gastric residual volume

Head trauma patients are suffering from impaired gastric emptying. Ott et al (Fig. 22) developed a diagram for patients suffering from head injury and requiring nutritional support. According to this diagram, if the Glasgow coma Scale is above 12, a nasogastric tube will be recommended. If the GCS is below 12, nasogastric tube, duodenal tube, PEG, PEJ or parenteral nutrition will be recommended in function of the clinical status and the expected stay of the patient.

Many studies have tested the use of metoclopramide 10 to 20 mg, or erythromycin previous to tube placement in medical, surgical or mixed populations. The rate of success was significantly better in 3 out of the 6 studies included (rates of success of 61% up to 96%).

High gastric residue is not always a sign of poor gastric peristalsism. Cohen et al (36) demonstrated that half of the patients with gastric residue larger than 200 mL had normal gastric emptying demonstrated by paracetamol test. This easy to achieve bedside test can be proposed to decide of continuing enteral feeding administration, to propose nasojejunal tube, or to think about endoscopic or radiologic positioning.

If the patient is receiving enteral feeding for more than 3-6 weeks and will require longer enteral support, percutaneous endoscopic gastrostomy should be considered. If the patient is undergoing abdominal surgery, indication for jejunostomy should be weighted.
In case of high gastric residue

- Nasojejunal tube using the 10-10-10 method or gastroscopy
- Long term: PEG
- If surgery is planned: jejunostomy

Fig. 23

Synthesis of findings on Prokinetics

- A one time dose of erythromycin may facilitate tube insertion
- 8/10 studies on prokinetic agents showed positive effects on GI transit and feeding
- No positive effect on clinical outcome
- Metoclopramide is the safest, increasing GI transit and feeding tolerance

Fig. 24

Additional help can be reached using prokinetic agents that increase gastric peristaltism and gastric emptying.

Heyland's team (34) summarized the different studies in this field. In case of difficult insertion of a nasoduodenal tube, erythromycin as a one time dose may be proposed and facilitate the tube insertion (Fig. 24, Fig. 25).

Prokinetic agents have shown positive effects on the gastrointestinal transit and feeding in most of the studies, but without showing positive effect on clinical outcome.

When comparing between erythromycin, metoclopramide and cisapride, metoclopramide has been found to be the safest, increasing the gastrointestinal transit and the feeding tolerance. Erythromycin arises the question of bacterial resistance and cisapride was reported to increase QT and induce cardiac toxicity in children.

1.7.2 Diarrhoea

Diarrhoea is another common complication of enteral feeding and is actually the most current cause of interruption of enteral feeding.

When diarrhoea is defined as the emission of three or more liquid stools per day, its incidence in critically ill patients ranges from 20% to 50%. In most cases, the continuation of enteral nutrition can often be achieved by using a systematic and standardized approach. The causes of diarrhoea during enteral feeding can be divided into two broad categories: infectious and non-infectious. Standard treatments for infectious diarrhoea associated with Clostridium difficile include oral metronidazole and vancomycin.

1.7.3 Constipation

Although frequent in patients fed enterally, constipation is not a typical feeding-related complication, but is probably related to a prolonged period in the supine position. However, if untreated, constipation can cause ileus, increase abdominal pressure and ultimately impair respiratory function and weaning from the ventilator. Fibre-enriched solutions are usually recommended in cases of constipation.
2. Parenteral nutrition

Parenteral nutrition (Fig. 26, Fig. 27, Fig. 28, Fig. 29) is recommended if enteral nutrition is contraindicated or if enteral nutrition does not reach energy requirements. Access is described in the figures and subclavian access is preferred because it is associated with lowest rates of complications.

Fig. 25 Catheter with Cuff

Fig. 26 Peripheral Central Venous Catheter  Fig. 27 Parenteral Access

Fig. 28 Central Venous Access

Subclavian Vein  Internal Jugular  Cephalic Vein  External Jugular  Central Venous Catheter  Axillary Vein  Superior Vena Cava  Brachial Vein  Basilic Vein

2.1 Complications

Complications (Fig. 29) are related to:

- **Insertion**: (pneumothorax, arterial puncture)
- **Mechanical**: Rupture, occlusion, embolus, thrombosis, poor placement
- **Infection**: Catheter site, subcutaneous tunnel, colonization, bacteremia, sepsis
- **Metabolic**: Hyperglycemia, electrolyte imbalance, refeeding syndrome
- **Liver function disorder**

**Fig. 29**

Complications (Fig. 29) are related to:

- **Insertion** (pneumothorax, arterial, venous or nerve puncture)
- **Infection**: The infection can be located at the catheter site, the subcutaneous tunnel, the catheter extremity, or in the blood. CRS (catheter-related sepsis) is frequent cause of sepsis in critically ill patients and requires blood and hub cultures and replacement of the catheter in case of fever and high suspicion of CRS. New catheters impregnated with antiseptic products have been proposed to reduce the prevalence of catheter related sepsis (Fig. 31).
- **Metabolic complications**: Hyper or hypoglycemia are the most frequent metabolic disturbances encountered. Tight glucose control has become a recommended therapy in critically ill patients. Electrolyte disturbance is diagnosed easily by regular laboratory tests. Hepatic function test disturbances can be found in up to 55% of the patients receiving TPN. A reduction in lipid emulsion load is an usually enough step to improve the liver blood tests.
- **Thrombosis**: mostly encountered in PVC catheters, the venous thrombosis or the catheter occlusion are also associated with catheter misplacement and hyperosmolar solutions use. The diagnosis is suspected when no reflux is obtained and confirmed by Pulsed doppler. Catheter fibrinolysis, catheter removal and/or systemic anticoagulant therapy are usually indicated. The use of polyurethan or silicon catheters can prevent these complications.

The appropriate management of TPN should aim to detect and treat all of the complications associated with this type of feeding. The frequent complications (catheter-related or metabolic/hepato-biliary) and the specific managements are listed in the following tables. When enteral feeding cannot meet > 50% of the energy and nitrogen requirements for more than 5 days, TPN used as a complement calculated to match the difference between the amount on enteral feeds and the actual requirements.

**Table 2 Complications**

<table>
<thead>
<tr>
<th>Catheter-related</th>
<th>Metabolic and hepato-biliary</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pneumothorax/hemothorax Catheter misplacement or torsion Thrombosis or occlusion Infection</td>
<td>Hyper-/hypoglycaemia Hypertriglyceridaemia/macrophage activation syndrome Electrolytic disturbances Steatosis Cholestasis Acalculous cholecystitis</td>
</tr>
</tbody>
</table>
### Table 3 Catheter-related complications

<table>
<thead>
<tr>
<th>Type</th>
<th>Risk factors</th>
<th>Diagnosis</th>
<th>Prevention</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pneumothorax</td>
<td>Sub-clavian puncture</td>
<td>Chest X-ray</td>
<td></td>
<td>Insert thoracic drain</td>
</tr>
<tr>
<td>Hemothorax</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Catheter misplacement or torsion</td>
<td>Internal jugular puncture</td>
<td>Chest X-ray</td>
<td></td>
<td>Remove the catheter</td>
</tr>
<tr>
<td>Venous thrombosis</td>
<td>PVC catheters</td>
<td>Inflammation and/or swelling</td>
<td>Use polyurethane or silicon catheters</td>
<td>Remove the catheter systemic anticoagulant therapy or catheter fibrinolysis</td>
</tr>
<tr>
<td>Catheter occlusion</td>
<td>Catheter misplacement Hyperosmolar solutions</td>
<td>(local/homolateral arm) No reflux</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Pulsed Doppler</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Catheter infection</td>
<td>Femoral access</td>
<td>Local inflammation</td>
<td>Surgical preparation</td>
<td>Remove the catheter</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Fever Systemic inflammation</td>
<td>Line solely dedicated to TPN</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Positive culture of the catheter</td>
<td>Aseptic manipulations</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Sterile handling of the solutions</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Removal of unnecessary lines</td>
<td></td>
</tr>
</tbody>
</table>

### Table 4 Metabolic and hepato-biliary complications

<table>
<thead>
<tr>
<th>Type</th>
<th>Risk factors</th>
<th>Prevention</th>
<th>Treatment</th>
<th>Complication</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hyperglycaemia</td>
<td>Rate of glucose infusion &gt; 4 mg/kg.min</td>
<td>Provide calories as a dextrose + lipids mixture</td>
<td>Reduce glucose supply (2-4 mg/kg.min)</td>
<td>Coma</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Check glycaemia every 4 hours</td>
<td>Intensive insulin therapy</td>
<td></td>
</tr>
<tr>
<td>Hypoglycaemia</td>
<td>Abrupt withdrawal of dextrose administration Excessive insulin therapy</td>
<td>Check glycaemia every 4 hours</td>
<td>Re-infuse dextrose solution</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Coma</td>
</tr>
<tr>
<td>Hyper triglyceridaemia</td>
<td>Excessive lipid supply (&gt;4-6 g/kg.day)</td>
<td>Check plasma triglycerides 1-2 times /week</td>
<td></td>
<td>Macrophage activation syndrome</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cholestasis</td>
<td>Absence of oral alimentation Sepsis</td>
<td>Check liver tests 2-3 times/week</td>
<td>Interrupt TPN</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Re-start oral nutrition as soon as possible</td>
<td></td>
</tr>
<tr>
<td>Steatosis</td>
<td>High caloric supply</td>
<td>Avoid excessive caloric supply. Check liver tests 2-3 times/week</td>
<td>Interrupt TPN</td>
<td>Hepatic failure</td>
</tr>
<tr>
<td>Acalculous cholecystitis</td>
<td>Fasting Intraluminal microbial overgrowth</td>
<td>Check liver tests 2-3 times/week</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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References

Nutritional Support in Intensive Care Unit (ICU) Patients
Module 18.5
Use of special substrates in ICU

Jean-Charles Preiser
René Chioléro
Pierre Singer

Learning Objectives
· To understand the rationale for the increased requirements of glutamine and antioxidants;
· To highlight the physiological importance of glutamine and antioxidant defense mechanisms.

Contents
1. Glutamine
2. Antioxidants
   2.1 Introduction
   2.2 Sources of reactive oxygen species
   2.3 Mechanisms of neutralization of ROS
   2.4 Presence of increased oxidative stress in critically ill patients
   2.5 Current recommendations
   2.6 Antioxidant vitamins
   2.7 Trace elements
3. Conclusions

Key Messages
· Addition of glutamine and antioxidants improves outcome in critically ill patients;
· Glutamine is involved in several pathways and systems involved and active during critical illness;
· The systematic increase in oxidative stress is associated with the rapid exhaustion of endogenous antioxidant defence mechanisms;
· Trace elements and antioxidant vitamins were found efficient in decreasing infectious morbidity and mortality in critically ill patients.

32. Loser C. Et al PEG Clin Nutr (in press)
Nutritional Support in Intensive Care Unit (ICU) Patients

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3. Conclusions

Key Messages
- Addition of glutamine and antioxidants improves outcome in critically ill patients;
- Glutamine is involved in several pathways and systems involved and active during critical illness;
- The systematic increase in oxidative stress is associated with the rapid exhaustion of endogenous antioxidant defence mechanisms;
- Trace elements and antioxidant vitamins were found efficient in decreasing infectious morbidity and mortality in critically ill patients.
Glutamine is actually the most abundant free amino acid in the human body and is found in higher quantities and concentrations than any other free amino acid. Although it can be manufactured from α-ketoglutarate and glutamate via glutamate aminotransferase and glutamine synthetase in all cells. The majority is built in skeletal muscle and transported to intestinal cells, kidney, and lymphocytes. Therefore, it is likely that, during critical illness, the status of glutamine moves from “conditionally essential” to essential. Importantly, the standard nutrition support solutions contain very few (polymeric casein-derived enteral formulas) or no glutamine (standard parenteral formulas).

Several studies of different sizes consistently reported that supplemental glutamine is efficient when a daily dose higher than 0.20 g/kg is administered for at least 5 days (4-10).

The particular alterations found in ICU patients are associated with increased demands for some otherwise unessential nutrients, or with specific mechanisms of tissue injuries. These findings led to the development of special solutions designed to fill the stores, or to blunt pathogenetic mechanisms. Among the numerous so-called “pharmaconutrients” investigated so far, the clinical efficacy was confirmed for some of them, including glutamine, antioxidants and modified lipids.

1. Glutamine

There is a considerable and continuous interest for glutamine as an adjunct in the treatment of critical care patients for several decades. Shortage of glutamine, mirrored by a low plasma concentration of glutamine in ICU patients on the day of admission is associated with an unfavourable outcome. Actually, a low plasma glutamine concentration (below 0.42 mmol/l) can serve as a predictive factor independent of the APACHE II scoring, and the mortality rate is double in the low plasma glutamine group as compared to the normal plasma glutamine group, despite only a marginal difference in the APACHE II score (1).

The rapid depletion of the glutamine stores during critical illness has been reported (2, 3). Indeed, during the catabolic phase of critical illness states, a substantial part of the amino acid release from peripheral tissues is from branched-chain amino acids converted and released into the circulation as glutamine and alanine, in contrast with the normal gut and portal origin of amino acids in the physiological conditions.

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**Nutrition in ICU**

**Glutamine-supplemented - PRO**

- Glutamine is the most abundant amino-acid in the body
- Muscle represents the major body protein pool
- Semi-essential amino-acid during stress
- Primary fuel for all rapid proliferating cells (enterocytes, lymphocytes, etc.)
- Helps to maintain gut integrity
- Reduces muscle degradation

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**Fig. 1**

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**Fig. 2**

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*Bisti et al Intensive Care Med. 2002 28:1512*
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Several studies of different sizes very consistently reported that supplemental glutamine is efficient when a daily dose higher than 0.20 g/kg is administered for at least 5 days (4-10).
2. Antioxidants

2.1 Introduction

An increase in the oxidative stress is typically present in critically ill patients (Fig. 9), as a consequence of the overproduction of reactive oxygen species (ROS) and of the rapid depletion of the endogenous stores of anti-oxidants (14). Importantly, oxidative stress has been incriminated in the pathogenesis of the systemic inflammatory response and the dysfunction of organs, via cellular energetic failure and via an interaction with several pathways following lipid peroxidation, and oxidative damage to proteins, DNA and RNA (Fig. 10).

Therefore, the incorporation of exogenous antioxidants in the treatment of various models of experimental shock, inflammation and ischemia/reperfusion injury (15) and in different categories of critically ill patients have been considered from several years (16). However, the efficacy of this strategy was confirmed in some studies, while others failed to demonstrate any benefit. Several reasons may be advocated to explain the failures:

· First, in physiological conditions, an increased oxidative stress is desirable for some cell functions (proliferation, gene expression, apoptosis). The role and importance of the ROS and RNS in the regulation of these functions is only partially understood during critical illness.

Enzyme Inactivation (e.g. MnSOD)

Several possible mechanisms can be advocated to explain the beneficial effects of glutamine (11, 12), including metabolic, immunologic, anti-oxidant and gut protective effects listed in Fig 1. These effects can be exerted directly by glutamine, or via one of its byproducts (glutamic acid or nucleotides). When intravenous glutamine is given to ICU patients there is a dose response situation. A dose of 20 g / 24 h normalizes plasma glutamine concentration in the majority of ICU patients. This indicates that plasma glutamine concentration may be a good surrogate parameter to titrate the dosage of glutamine necessary to put all ICU patients in a more favourable position in terms of glutamine supply.

It is recommended to give long-stayers in the ICU, which are only possible to feed by the parenteral route extra glutamine. This recommendation is not controversial, but perhaps one should rather try to prevent the state of glutamine depletion than wait to see it actually occur. Therefore one might consider giving intravenous glutamine in parallel to the combination of enteral and parenteral nutrition but separately. This will guarantee the patient the prescribed dose of glutamine regardless of how enteral and parenteral nutrition is combined on the individual day.

### Nutritional Considerations

**Glutamine dose**

**Total AA:**

\[
1.2 + 0.3 \text{ à } 1.6 + 0.4 \text{ g / kg / j}
\]

**Glutamine-supplemented PN**

The committee noted that in patients receiving PN, there was a modest reduction in mortality associated with parenteral glutamine. The high cost and lack of availability of parenteral nutrition limit the application of this intervention.

Recommendations... when PN is prescribed to critically ill patients, parenteral supplementation with glutamine, where available, is recommended.
2. Antioxidants

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- First, in physiological conditions, an increased oxidative stress is desirable for some cell functions (proliferation, gene expression, apoptosis). The role and importance of the ROS and RNS in the regulation of these functions is only partially understood during critical illness.
The major non-enzymatic defence mechanisms include endogenous molecules (glutathione, urate, ubiquinones/ubiquinol, albumin and bilirubin) and vitamins (ascorbic acid, \(a\)-tocopherol, \(b\)-caroten). Importantly, the reduction of oxidised \(a\)-tocopherol, which is necessary for the perpetuation of its antioxidant effect requires the presence of glutathione or ascorbic acid. Therefore, an efficient antioxidant effect would be obtained by the simultaneous administration of vitamins C and E.

In addition to the generation of ROS, oxidative injury can be amplified or inhibited by reactive nitrogen species (RNS) (18, 19). RNS include nitric oxide (NO), peroxynitrite (ONOO\(^-\)), nitrosonium (NO\(^+\)), nytrosyl (NO\(^+\)) and can induce per se nitrosative injuries, or combine to ROS to enhance or attenuate the oxidative injury. At present, the exact physiological role of RNS is only partially understood, and there are very few clinical data on the manipulation of nitrosative injury.

### 2.2 Sources of reactive oxygen species.

Stricto sensu, a free radical or reactive species is an unstable atom with an unpaired electron. ROS include superoxide (\(O_2^-\)), hydrogen peroxide (\(H_2O_2\)) and the hydroxyl radical (\(OH^-\)).

In critically ill patients, ROS can be produced from 4 different pathways:

- The mitochondrial respiratory chain produces \(O_2^-\) as a byproduct of the reaction of molecular oxygen with semi-ubiquinone. In case of severe mitochondrial dysfunction, as observed during septic shock (17), this pathway could be up-regulated and massive amounts of \(O_2^-\) could be released.
- The NADPH oxidase enzyme of neutrophils and macrophages is activated in case of cell stimulation and can produce massive amounts of \(O_2^-\) as a microbiocidal mechanism. This pathway is probably predominant in the overproduction of ROS during severe sepsis.
- The xanthine oxidase enzyme is an ubiquitous enzyme activated during ischemia, which produced massive amounts of \(O_2^-\) during the reperfusion phase. This pathway is probably activated during major cardiac and vascular surgery, and during solid organs transplantations.
- Some metallic ions (iron, copper) are released in case of cell lysis and can amplify the oxidative stress, as they are co-factors of the conversion of hydrogen peroxide into hydroxyl.

### 2.3 Mechanisms of neutralisation of ROS

If unopposed, the free electron of the ROS will bind to lipids, proteins, DNA, RNA, thereby triggering cell injury and tissue dysfunction. In physiological conditions, the free electron of ROS are scavenged by enzymatic or non-enzymatic anti-oxidant defence mechanisms. The mechanisms of inactivation of ROS include successive steps: the dismutation of superoxide into hydrogen peroxide under the influence of SOD and the conversion of hydrogen peroxide into water under the influence of catalase and glutathione peroxidase. Importantly, trace elements (copper/manganese/zinc, iron and selenium) are respectively required for the activity of SOD, catalase and glutathione peroxidase.
The major non-enzymatic defence mechanisms include endogenous molecules (glutathione, urate, ubiquinones/ubiquinol, albumin and bilirubin) and vitamins (ascorbic acid, \(\alpha\)-tocopherol, \(\beta\)-caroten).

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### 2.4 Presence of increased oxidative stress in critically ill patients

Due to the very short half-life of ROS, the proof of increased oxidative stress in patients implies the demonstration of a presence of byproducts of oxidative damage of lipids (thiobarbituric-acid reacting substances (TBARS measured by the malonyldialdehyde (MDA) assay, 4-hydroxynonenal, lipoperoxides), DNA or proteins) or a decrease in the stores of endogenous antioxidants (e.g. Total radical-trapping antioxidant parameter, TRAP) (for a detailed and comprehensive review see 20).

Numerous studies published until 2001 already demonstrated an increased oxidative stress, mainly in patients with acute respiratory failure, ARDS, sepsis or septic shock. More recent studies confirmed the presence of increased TBARS in patients with systemic inflammatory response syndrome and multiple organ failure (MOF) (21).
2.6 Antioxidant vitamins

All nutritional support formulas contain antioxidant vitamins, already incorporated in the solution (enteral support) or added prior to infusion (parenteral support). We recently compared the effects of an enteral solution enriched with vitamin A (133 mg/dl including 66.7 mg/dl of \(\beta\)-carotene), vitamin C (13.3 mg/dl) and vitamin E (4.94 mg/dl) with an iso-nitrogenous, iso-caloric control solution in 37 critically ill patients with neurological impairment (27). This study demonstrated that \(\alpha\)-tocopherol (total dose 350 mg over 7 days) and \(\beta\)-carotene (total dose 5000 mg over 7 days) were absorbed, as the plasma and lipoprotein-bound fractions of these vitamins increased in the supplemented, but not in the control group. Importantly, these antioxidants were biologically active, as the resistance of low-density lipoproteins to experimental oxidative stress induced by copper sulphate increased. However, there was no difference in plasma TBARS level nor in the resistance of erythrocytes to oxidative stress. Similarly, Nelson et al (28) demonstrated in 98 patients with ARDS that \(\alpha\)-tocopherol and \(\beta\)-carotene incorporated into a nutrition support formula were absorbed, but that the TRAP and the plasma lipid peroxide levels were unchanged, as compared with the control group. Importantly, clinical outcome variables including pulmonary function parameters (PaO\textsubscript{2}/FiO\textsubscript{2} ratio, duration of mechanical ventilation) were found improved in patients receiving this solution (29).

2.5 Current recommendations

The currently used recommendations for the daily requirements in vitamins and trace elements are known as the Dietary Reference Intakes (DRI) (Table 1) and have been adapted for the enteral and parenteral support (26). However, higher doses could be necessary to meet the specific requirements of critically ill patients. The most recent clinical studies reported the effects of antioxidants given prophylactically to patients “at risk” of oxidant-related complications, either as a component of nutritional support or as an individual medication. Other recent clinical trials assessed the effects of specific prophylaxis in patients before a scheduled procedure associated with intense oxidative stress.
2.6 Antioxidant vitamins

All nutritional support formulas contain antioxidant vitamins, already incorporated in the solution (enteral support) or added prior to infusion (parenteral support). We recently compared the effects of an enteral solution enriched with vitamin A (133 µg/dl including 66.7 µg/dl of β-carotene), vitamin C (13.3 mg/dl) and vitamin E (4.94 mg/dl) with an iso-nitrogenous, iso-caloric control solution in 37 critically ill patients with neurological impairment (27). This study demonstrated that α-tocopherol (total dose 350 mg over 7 days) and β-carotene (total dose 5000 µg over 7 days) were absorbed, as the plasma and lipoprotein-bound fractions of these vitamins increased in the supplemented, but not in the control group. Importantly, these antioxidants were biologically active, as the resistance of low-density lipoproteins to experimental oxidative stress induced by copper sulphate increased. However, there was no difference in plasma TBARS level nor in the resistance of erythrocytes to oxidative stress. Similarly, Nelson et al (28) demonstrated in 98 patients with ARDS that α-tocopherol and β-carotene incorporated into a nutrition support formula were absorbed, but that the TRAP and the plasma lipid peroxide levels were unchanged, as compared with the control group. Importantly, clinical outcome variables including pulmonary function parameters (PaO₂/FiO₂ ratio, duration of mechanical ventilation) were found improved in patients receiving this solution (29).

Nathens et al (30) analysed the effects of prophylactic
administration of vitamin C (1000 mg i.v.) and \( \alpha \)-tocopherol (3,000 IU/day enterally) in 301 critically ill trauma patients. The plasma levels of both vitamins were increased. When compared to a matched group of 294 patients not receiving antioxidant supplementation, there was a significant reduction in the risk of developing multiple organ failure (relative risk 0.43, 95% confidence interval 0.19-0.96), and shorter durations of mechanical ventilation and length of stay in the intensive care unit. The incidences of pneumonia and ARDS tended to decrease in the group supplemented with antioxidants. In contrast, in a multi-center recent study on 220 critically ill patients (31) designed to compare the effects of a diet supplemented with antioxidant vitamins and arginine with an isonitrogenous isocaloric control formula on the incidence of nosocomial infections, there was a decrease in the rate of catheter-related infections, but not in the rate of other infections nor mortality.

2.7 Trace elements

The effects of supplementations with large doses of selenium, zinc, copper and manganese, the four trace elements involved in the enzymatic antioxidant defence mechanisms were the focus of intense clinical research in the last decade (see 32 for review). However, during the last two years, there were few investigations specifically designed to document their effects on oxidative stress in critically ill patients.

**Fig. 20**

Kaplan-Meier estimates of the risk of pulmonary morbidity (ARDS or pneumonia) among 301 patients receiving antioxidant supplementation and 294 patients receiving standard care. There is a suggestion that antioxidant supplementation might be associated with a lower likelihood of pulmonary morbidity (\( P = 2 \) by the log-rank test). Solid line: no antioxidant supplementation; dashed line: antioxidant supplementation.

**Fig. 21**

**EFFECTS OF TRACE ELEMENTS SUPPLEMENTATION** Berger et AJCN 1998
3. Conclusions

The importance of the implication of oxidative stress in the development of multiple organ failures is consistently demonstrated in critically ill patients. Therefore, the administration of antioxidants as a prophylaxis in patients at risk seems to represent an efficient approach, in view of the results of recent clinical trials. Optimal doses and combinations of antioxidants are still to be defined.

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Chapter 3

Topic 19

Nutritional Support outside the Hospital: Home Parenteral Nutrition (HPN)
Nutritional Support outside the Hospital: Home Parenteral Nutrition (HPN)

Module 19.1

Indications and Epidemiology

André Van Gossum

Learning Objectives

- Learn about epidemiology and the extent of the use of HPN in adult patients;
- Learn about indications for HPN in adult patients and clinical features (including prognosis) of these patients.

Contents

1. Incidence and prevalence
2. Indications
3. Demographic data of long-term HPN patients
4. Perfusion regimen
5. HPN-related complications
6. Rehabilitation status
7. Prognosis
8. Conclusions

Key Messages

- HPN is worldwide used in industrialized countries;
- For patients with benign diseases, the main indications is short bowel (80%);
- In many European countries as well as in US, cancer has become the main indication for HPN;
- The point prevalence of HPN in US is expected to be 5 to 10 times higher than in Europe (from 2 to 12/10^6 inhabitants);
- HPN-related complications are quite rare.
1. Incidence and prevalence

The use of parenteral nutrition administration started in the early 1960s. Schils et al (1) tried to maintain a patient at home on parenteral nutrition (HPN). Although this patient only survived during a few months, several teams in North America and in Europe initiated a program of HPN during the 1970s. Subsequently, many groups reported their initial experience with HPN, mentioning a low incidence of complications and a good survival rate (2-5).

According to the data collected by the North America Registry on HPN patients, the estimated number of HPN patients in the US was approximately 18,000 in 1986 and reached 40,000 in 1992 (6).

A multicentre survey performed in nine European countries in 1997 showed a mean incidence of three newly enrolled patients on HPN per million inhabitants (7) and a mean prevalence of four per million (Fig. 1). The increased use of HPN in Europe is obvious when comparing data obtained in 1986 and in 1993 (7, 8). However, use of HPN is still ten times higher in the US than in Europe. HPN is routinely used in Japan, Israel and Australia. In the European survey, age distribution of the patients at the onset of HPN was as follow: 28% aged 16-40, 44% aged 41-60, 18% aged 61-70 and 10% over 70 years (7).

Since 1997, data about HPN incidence are only available in a few European countries. In the UK, a national register was started by BANS since 1996 (9). The number of adult HPN registered with BANS has grown progressively since 1996 (Fig. 2).

An increase in the number of centres reporting was seen in 2002, but despite it is felt that HPN is underreported. A total of 103 new adult patients were registered in 2002, making the total number of registered patients receiving HPN at the end of 2002 to 465. It is noteworthy that there are significant national but also regional variations in the reporting HPN. In Scotland, all patients receiving HPN have been identified with the development of the Managed Clinical network (MCN) and data from 2001 found the point prevalence to be 12 patients per million of the population (10). The figure exceeds the overall UK rate of approximately 8 patients per million of the population. Within the UK, further regional variation has also been identified.

In Spain, data are annually collected throughout a designed questionnaire (11). In 1997, the registration rate of HPN in Spain was about 0.7 patients/10^5 inhabitants/year. In 2000, fourteen hospitals participated and 67 patients adults and children were newly enrolled. The registration of patients that was expected to reflect the incidence was 1.9/10^5 inhabitants/year. In 2001, seventeen hospitals participated enrolling 66 patients (1.65 patients 10^5 inhabitants/year).
In France, a national HPN registry was open in 2001 (12). Between June 2001 and June 2004, 413 adults were included in the registry; the estimated incidence was 3 newly enrolled patients/1.10^6 inhabitants/year.

2. Indications

Overall, the distribution of underlying diseases requiring HPN is quite similar in Europe, the US and Japan (6, 7).

### Distribution of underlying diseases for HPN patients in Europe (1997; n = 479)

![Distribution of underlying diseases for HPN patients in Europe (1997; n = 479)](image)

Cancer has become the largest single indication for HPN throughout the world (40%). Crohn's disease, mesenteric vascular diseases, radiation enteritis and disorders of intestinal motility remain the most frequent benign conditions requiring long-term HPN. HPN is also used in AIDS patients with intractable diarrhoea (Fig. 3).

However, the number of AIDS patients receiving HPN recently decreased since the introduction of more efficacious tritherapy. We have to underline that 25% of HPN patients are suffering of "miscellaneous" diseases, including chronic pancreatitis, intestinal mucosa atrophy, anorexia nervosa, cachexia, etc.

However, the distribution of underlying diseases in HPN patients varies among the different European countries (7) (Fig. 4). Cancer has become the largest single indication for HPN throughout the world (40%). Crohn's disease, mesenteric vascular diseases, radiation enteritis and disorders of intestinal motility remain the most frequent benign conditions requiring long-term HPN. HPN is also used in AIDS patients with intractable diarrhoea (Fig. 3).

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However, the distribution of underlying diseases in HPN patients varies among the different European countries (7) (Fig. 4).

### Indications for HPN in 7 different European countries where reporting was assumed to be more than 80% of patients (1997)

<table>
<thead>
<tr>
<th>Country</th>
<th>Number of patients</th>
<th>Crohn's disease</th>
<th>Vascular</th>
<th>Cancer</th>
<th>Radiation</th>
<th>AIDS</th>
<th>Others</th>
</tr>
</thead>
<tbody>
<tr>
<td>France</td>
<td>173</td>
<td>16%</td>
<td>23%</td>
<td>27%</td>
<td>15%</td>
<td>0.5%</td>
<td>16.5%</td>
</tr>
<tr>
<td>United Kingdom</td>
<td>72</td>
<td>44%</td>
<td>14%</td>
<td>5%</td>
<td>2%</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Belgium</td>
<td>26</td>
<td>12%</td>
<td>15%</td>
<td>23%</td>
<td>15%</td>
<td>35%</td>
<td>-</td>
</tr>
<tr>
<td>Denmark</td>
<td>15</td>
<td>20%</td>
<td>13%</td>
<td>8%</td>
<td>26%</td>
<td>-</td>
<td>33%</td>
</tr>
<tr>
<td>The Netherlands</td>
<td>45</td>
<td>13%</td>
<td>11%</td>
<td>60%</td>
<td>-</td>
<td>-</td>
<td>16%</td>
</tr>
<tr>
<td>Spain</td>
<td>31</td>
<td>16%</td>
<td>13%</td>
<td>38%</td>
<td>-</td>
<td>6%</td>
<td>25%</td>
</tr>
<tr>
<td>Poland</td>
<td>14</td>
<td>14%</td>
<td>50%</td>
<td>-</td>
<td>14%</td>
<td>-</td>
<td>22%</td>
</tr>
</tbody>
</table>

![Indications for HPN in 7 different European countries where reporting was assumed to be more than 80% of patients (1997)](image)

is intestinal obstruction which is common in cases of peritoneal carcinomatosis. Intractable diarrhoea associated with severe malnutrition is the major indication in AIDS patients.

3. Demographic data of long-term HPN patients

A survey that was performed by the ESPEN-HAN group - included 228 adult patients, including 141 females and 87 males, with a median age of 49 years (range 19-92) (13). The underlying diseases were Crohn's disease (33%), mesenteric vascular diseases (25%), post-surgical (19%), intestinal pseudo-obstruction (8%), radiation enteritis (4%), abdominal trauma (2%) and miscellaneous (8%).
Intestinal anatomy was defined in 222 patients. The remaining small bowel was less than 50 cm in 84 patients, less than 100 cm in 67 patients, less than 200 cm in 44 patients and less than 300 cm in six patients. Twenty-one patients had no small bowel resection (12%).

In patients with short bowel, the intestinal anatomy was a terminal jejunostomy (I) in 41% (Fig. 5), jejunocolic (II) (Fig. 6) in 46% and jejuno-ileocolic (III) in 13%.

The distribution of underlying diseases is typical and similar to other reported HPN series.

As was also expected, 80% of the patients had a short bowel.

The fact that 65% of these patients had less than 1 m of remaining small bowel and that 88% had a type I or II anastomosis confirms previous observations that showed the importance of the length of the residual small bowel and the type of intestinal anastomosis for predicting the HPN-dependency (14).

4. Perfusion regimen

In the majority of the cases (69%), administration of nutritional solutions is performed through a subcutaneous tunnelized catheter and is positioned in the vena cava via the internal jugular vein or a subclavian vein, preferentially on the right side (7).

Based on the reports of the North America Registry on HPN and the European surveys, the use of subcutaneous reservoirs (port-a-cath) is growing (6). This trend is due, on one hand, to its wide use in cancer patients who receive chemotherapy and, on the other hand, to the willingness of some patients who prefer implantable catheters for functional and esthetic reasons, for instance for practicing aquatic sports or for taking a shower.

The number of perfusions that are administered per week may vary along in time in function of intestinal adaptation capacities. The European survey has shown that the percentage of bags/week was as follows: 7 (67%), 6 (9%), 5 (12%), 4 (8%), or less (4%) (7).

Oral feeding is not only allowed but also encouraged in patients without bowel obstruction or need for bowel rest. It has been shown that patients with short bowel are in fact hyperphagic. In the 1997 European survey, 50% of patients had free oral intakes, 27% had limited oral intakes, while 23% ingested nothing (7).

5. HPN-related complications

HPN-related complications are detailed in another chapter. However, the following data were obtained by the ESPEN-HAN group (13).

Within the 12-months period prior to evaluation, the mean number of hospitalisation was 2.7 (0-12), corresponding to a mean period of 23 days (range 0 to 270 days). Reasons for hospitalisation were related either to the underlying diseases in 27% of days admitted to hospital, to HPN complications in 48% or to other medical reasons in 25%. Of the HPN complications catheter
related sepsis accounted for 61%, metabolic disorders for 27%, venous access thrombosis for 12%. One of the main goals of HPN is by definition to avoid prolonged or recurrent hospitalisations. When we consider the 12-month period before the evaluation, the mean time of hospitalisation corresponds to 8% of the year. This seems acceptable for patients with life threatening intestinal failure. However we have to accept that a few patients stayed much longer in hospital (up to 270 days).

The mean number of central venous catheters used during the total HPN period was 3 (range 1 to 17), with a mean survival time per catheter of 34 months (range 4-245 months). During the 12-month-period before evaluation, an episode of catheter related sepsis occurred in 31% of the patients. Central venous thrombosis was reported in 9% and vascular access problems in 13% of the patients.

**6. Rehabilitation status**

When comparing the rehabilitation score before HPN and at the time of evaluation, it appears that the percentage of HPN patients who are capable of coping with a job is about 65% (Fig. 7) (13). Nevertheless, there is a sharp decrease in this percentage in favor of part-time work when on HPN. This can be easily explained by limitations due to the time spent on taking parenteral nutrition.

On the other hand, it clearly appears that the percentage of grade IV (bedridden at home) patients significantly decreased meaning that HPN may improve the status of patients who had a very low rehabilitation score before starting HPN.

**7. Prognosis**

Several studies have shown that survival (prognosis) is linked to the underlying disease (14). In a European survey performed in 1997, mortality rate after a 6 to 12 month follow-up period was 4% in Crohn’s disease, 21% in radiation enteritis, 13% in vascular diseases, 16% in miscellaneous but 74% in cancer and 34% in AIDS (Fig. 8).

The North America HPN Registry reported similar results (6). B. Messing et al. performed a study on 217 HPN patients with benign diseases and that have been enrolled in a HPN program between 1980 and 1989 in Belgian - French specialized centres (15).

Seventy three patients died during the follow-up period. Mortality rate due to HPN was 11%. This work showed a survival probability at 1, 3 and 5 years of 91%, 70% and 62%, respectively. Multifactorial analysis of prognostic factors showed that independent factors associated with a good survival rate were: an age below 40 years at the start of HPN, initiation of HPN after 1987, that was reflecting the experience of the center, and the absence of chronic intestinal obstruction.
8. Conclusions

- HPN is worldwide used in industrialized countries;
- In many European countries as well as in US, cancer has become the main indication for HPN;
- For patients with benign diseases, the main indications are short bowel and chronic intestinal motility disorders;
- The number of HPN centres increased with a variable degree of expertise;
- The prevalence in US is expected to be 10 times higher than in Europe (from 2 to 12/10^6 inhabitants);
- HPN related complications are quite rare and rehabilitation status is good in the majority of the patients.

References

Conclusions

HPN is worldwide used in industrialized countries; in many European countries as well as in US, cancer has become the main indication for HPN. For patients with benign diseases, the main indications are short bowel and chronic intestinal motility disorders. The number of HPN centres increased with a variable degree of expertise.

The prevalence in US is expected to be 10 times higher than in Europe (from 2 to 12/1000 inhabitants). HPN related complications are quite rare and rehabilitation status is good in the majority of the patients.

References

1. Training for HPN

1.1 Introduction

The provision of parenteral nutrition in the home requires the collaboration between more players including the patient, relatives, the discharging hospital, the community nurse and general practitioner and in some cases also a home care agency. Before being able to cope with parenteral nutrition patients or family members must be trained to manage necessary procedures. Although only few studies are available, the best approach is to launch the process using a multi-disciplinary care team with expertise in intestinal failure. Collaboration with the family of the patient and with community nurses is very important. No official guidelines on training for HPN are available.

1.2 Patient suitability

Teaching patients about HPN and training them to administer it at home takes a lot of nursing time and commitment from those involved including the patient. Before starting it is important to assess the suitability of the individual in a multidisciplinary team approach, in which also the gastroenterologist or nutrition expert is involved. Important factors that should be taken into consideration:

- Physical ability;
- Mental status, intellect, social status, family support;
- Age;
- Underlying disease;
- The patients home, facilities for preparing and storing nutrition bags.

1.3 Training objectives

The aim of the training programme is to teach the patient procedures so that provision of parenteral nutrition can be carried out safely by the patient, a family member or a caregiver. Also patients must be educated in all relevant complications that may occur and learn how to handle. Overall the teaching programme also should focus on the patients return to as normal lifestyle as practically possible. A training program aims at the best possible quality of life and the lowest rate of complications with HPN.

Training for HPN may include the following:

- Teaching patients essential anatomy, physiology, basics of nutrition;
- The complications occurring during treatment with HPN;
- Practical issues, initially by demonstration, followed by hands on exercises;
- The use of hand-out material is recommended and used by many centres;
- Patients previously trained may support education;
- Testing the patients capabilities before sending the patient home is essential;
- Periodic or on demand surveys of the patients capabilities should be considered.

1.4 The teaching practice in Europe

To gather information about how patients are taught the necessary procedures to undertake HPN a questionnaire about HPN teaching practice was circulated to centres in 7 European countries via representatives on the ESPEN-HAN working group in 2001 (1).

Responses were obtained from 51 centres in 7 countries. Centres ranged in size from 18 to 203 beds and had between 0-95 patients on HPN, 63% of centres having less than 10 patients. Not all patients with intestinal failure will be able to cope with HPN and in the survey one or more criteria, was used by 62% centres to exclude patients from their HPN programme. These included intellect (33%), physical disability (24%), social situation (25%), underlying disease (18 %) and age (16%).

All centres had a nutrition support team and 96% followed guidelines, usually locally developed. Generally training was carried in an inpatient setting over 1-2 weeks with one or more patients simultaneously. The personnel involved were hospital nurses/clinical nurse specialists (84%) and/or doctors (39%).
The centres reported that teaching included catheter care (100%), preventing and recognising complications (98%), most common mistakes (92%), pump care (92%), managing complications (90%), adding vitamins (55%), bag preparation (51%), iv-medication (50%), compounding (18%). Quality of care was assured by periodic surveys (47%) and re-checking the teaching process (33%) following the occurrence of complications. There was no significant variation between the large and small centres for either exclusion criteria or teaching methods. This survey highlighted common teaching practice across seven European countries. Local or national guidelines underpinning practice in the majority of centres.

1.5 Training methods

From the European survey we know that centres use different methods for training, including instruction manuals with illustrations of the procedures, some centres use video tapes. Training sessions usually involves more patients, team members and the patient's family, if required. It is important that only key designated members of the nursing staff provide the training. Training should start when the central venous access has been obtained, if the patient's condition allows. No time limits for training should be set allowing patients to make progress at individual pace. The literature on training regimens is scarce and there are no studies showing which training regimen is the best in terms of complications or quality of life.

1.6 Training for home parenteral nutrition and catheter related infection

This has been investigated prospectively in one study (2). 221 patients on HPN were consecutively followed and patients were divided into two groups that received either standard or detailed instructions with regard to handling and prophylactic measures regarding line infections. The overall catheter infection rate was 14% corresponding to 1.7 episodes yearly. Conventionally tunnelled lines had fewer infections compared to implanted ports. The rate of infections was reduced with 50% in those who had the detailed instruction supporting that training is an important factor.

1.7 Conclusions for training in HPN

- Training patients for HPN make take place in hospital or in the home of the patient;
- Careful selection of the patient before starting training;
- Nutritional support teams and instruction manuals are essential elements in the process;
- Nearly no studies on the effect of different training regimens or the impact of training on complication rate are at hand;
- Many centres adhere to guidelines, developed locally and not underpinned by quality assurance studies.
2. Monitoring HPN

2.1 Introduction

The purpose of monitoring is to secure and improve the quality of life of patients managed in the home with parenteral nutrition. Although well trained, patients must cope with complications, infections, and mechanical problems with the catheter, venous thrombosis as well as metabolic disturbances. Being complex and an every day task, dealing with HPN also may impact the mood of the patient.

2.2 How is the monitoring of HPN patients carried out in Europe?

This has been investigated in 2002 using a questionnaire about HPN monitoring practice, that was circulated to HPN centres in 8 European countries through the representative of the ESPEN HAN-working group (1). Centres were asked about guidelines, home visits and how monitoring and handling of complications were managed. 42 centres in the following 8 European countries completed the questionnaire: UK n=14, France n=9, Belgium n=4, Italy n=4, Poland n=4, Denmark n=4, Spain n=2, Germany n=1. The HPN-experience of the centres was in the range 2-30 years and ranged in size from 0-125 HPN-patients representing a total number of 934 of whom 54 % had received HPN for more than 2 years. The primary disease was non-malignant in 90 % whilst 10 % had been diagnosed with active cancer.

2.3 Guidelines

Of the centres 92% had a HPN team and 66% had written guidelines for monitoring HPN. The guidelines generally were locally developed, to some extent based on national guidelines.

2.4 Who monitored the patients and at what intervals?

Home visits after discharge for monitoring purposes were carried out by 31 of the centres involving the HPN team, general practitioner, community nurse or home care agency. Stable patients on HPN for more than 12 month were monitored at the discharging hospital (73%), at a local hospital (12%), by the General Practitioner (11%) or by a home care agency (4%). Of the centres 90% reported that the main responsibility for monitoring was assigned to a specific person (Fig. 1 and Fig. 2). Fig.1 shows at which location the HPN-patients were monitored after discharge from the hospital with HPN.

Fig. 2 shows which personnel are involved in monitoring the HPN-out-patient after discharge from hospital.
The intervals between monitoring visits for the stable HPN patient (Fig. 3) was in the range 1-6 months, 52% of the centres reported intervals of 2-3 months.

Fig. 3 shows the distribution of intervals for monitoring of the stable HPN patient.

2.5 Which parameters were monitored?

Fig. 4 and Fig. 5 present the main results regarding which parameters HPN patients had evaluated at monitoring visits in this European study.

Fig. 4 shows which parameters that were evaluated at monitoring visits for HPN-patients.

Fig. 5 shows the pattern of blood tests and BMD measurements at monitoring visits.

Bodyweight or anthropometry was measured at every visit in all centres and 20 (48%) centres assessed blood pressure and pulse at every visit, but 14 (98%) centres only did this in case of problems.

At every visit 37 (88%) of the centres evaluated the state of hydration and 31 (74%) of the centres asked patients about oral intake. The mood of the HPN-patient was considered at 36 (86%) centres at every monitoring-visit.

Regarding blood tests the following results were obtained: at every monitoring visit 39 (93%) centres measured haematology, in 36 (86%) centres biochemical tests for liver-function, in 40 (95%) centres s-creatinine and electrolytes, in 39 (93%) centres s-Ca, s-Mg, s-Phosphate, in 34 (81%) centres s-glucose, in 20 (48%) centres s-cholesterol / triglyceride, in 20 (48%) centres s-albumin, 8 (19%) centres measured trace-elements, 6 (14%) centres analyzed vitamins AED, B-12 and folic acid. The rest of the centres did this regularly, but not at every visit or only in case of problems.

One centre evaluated the bone mineral density (BMD) of the patient at every visit and 27 (64%) centres did this 1-2 times per year. Seven centres measured the BMD only in case of problems and from 1 centre there was no information available.
2.6 HPN and handling complications

In case of complications 76% of centres reported that patients got in touch with the HPN-team, 2% the local hospital, 5% the home care agency, and 17% other. Re-admission to hospital was usually to the HPN-centre and only occasionally to a local hospital.

2.7 Conclusions for monitoring HPN

- Monitoring usually takes place at the discharging hospital with access to the specialised team; Monitoring can also be carried out by a home care agency involving the hospital or the general practitioner;
- Intervals between visits vary, being on average 3 months. Do not forget that the unstable patient may need more attention;
- Assignment of responsibility for monitoring is probably very important for the quality of the process. The questionnaire based study indicated that in general responsibility is assigned to a specific person most often associated with the specialised team in hospital;
- Biochemistry, anthropometry should be measured at all visits, trace elements, vitamins and BMD only occasionally, yearly intervals are recommended;
- Official guidelines for monitoring are not available and prospective studies on the impact of different monitoring regimens on outcome including the quality of life of HPN patients are warranted.

References

Module 19.3

Venous Access for Home Parenteral Nutrition

Michael Staun

Learning Objectives

- Learn about different central venous access devices (CVAD);
- Catheter related complications of infectious and mechanical origin;
- Strategy to prevent problems and treatment of complications.

Contents

1. Introduction
2. Choice of central venous access
3. PICC lines an option for HPN?
4. Tunnelled catheters
5. Implantable ports
6. Conclusions: which type of venous access for HPN
7. Choice of central vein
8. Position of the distal tip of the catheter
9. Loss of vascular access
10. Conclusions: Catheter insertion and position
11. Catheter related blood stream infection or sepsis, risk factors
12. Prevention of infection - dressing
13. Antimicrobial impregnated catheters
14. Nutrition support team and patient education
15. Treatment of catheter related blood stream infection
16. Repeated line infection
17. Catheter related thrombosis
18. Conclusions: Catheter related infection and thrombosis

Key Messages

- Chose access for central venous access device in accordance with the need of the patient;
- General use of aseptic techniques are of paramount importance;
- Support patients educationally to minimise line related complications;
- In case of complications use protocols to treat patients;
- Support clinical studies of venous access for HPN patients.
1. Introduction

Parenteral nutrition is required when patients are unable to maintain an adequate nutritional status, fluid or electrolyte balance due to insufficient function of the gastrointestinal tract. The most common causes of intestinal failure are resection of the small bowel due to a catastrophic event such as mesenteric thrombosis, small intestinal disorders that cause malabsorption and conditions with pseudo-obstruction as well as malignant disease with ensuing intestinal complications or a general need for nutritional support.

Home parenteral nutrition (HPN) is an option for patients with chronic intestinal failure, a condition with a prevalence in the range 1-20/10,000 in the European countries (1, 2, 3). For the patient with benign disease, the prognosis of chronic intestinal failure is fairly good with a 5 year survival about 75%; in contrast the prognosis of patients with malignant disease is poor (3, 4). Considering that the number of patients is low the aim should ideally be management in specialist centres, but this may not always be possible.

2. Choice of central venous access

HPN requires a well functioning central venous line. When considering which is the best type of central venous device a number of issues must be taken into consideration; these include the number of weekly infusions, for how long the therapy is going to continue (temporarily or life long), the diagnosis of the underlying disease (benign or not), any previous history in relation to obtaining central venous access and the available expertise.

In relation to quality of life, the age and hence the daily activities of the patient should be taken into account as well as the patients own wishes regarding type of catheter.

3. PICC lines an option for HPN?

For short-term treatment, mostly for in-patients, a peripherally inserted central catheter (PICC) can be used for intravenous nutrition. PICC lines have limitations; insertion may be difficult since many patients with a need of parenteral therapy will have damaged peripheral veins and short bowel patients may need infusion of a high volume of parenteral nutrition with a high osmolality thus exceeding the capacity of the line.

Considerations when selecting a venous access device (VAD)

- The number of infusions to be given
- Type and length of therapy
- Available resources and expertise
- The age and diagnosis
- Specific vascular problems
- The VAD history
- Patients preference if long term treatment

Fig. 1

Peripherally inserted central catheter (PICC)

- Inserted in the cubital or upper arm region
- Intravenous nutrition and other infusion therapies
- No risk of trauma to neck structures, low risk of thrombosis
- For short term (3-4 weeks) use only
- Mostly for in patients

Horattas MC et al. 2004; 10:2419-22

Fig. 2
1. Introduction
Parenteral nutrition is required when patients are unable to maintain an adequate nutritional status, fluid or electrolyte balance due to insufficient function of the gastrointestinal tract. The most common causes of intestinal failure are resection of the small bowel due to a catastrophic event such as mesenteric thrombosis, small intestinal disorders that cause malabsorption and conditions with pseudo-obstruction as well as malignant disease with ensuing intestinal complications or a general need for nutritional support.

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Lower rates of infections have been reported with PICC lines and the cost is definitely lower, compared to conventional central lines or ports (5, 6). Altogether, based on the available evidence, PICC cannot be recommended for HPN.

4. Tunnelled catheters
Catherisation of the superior vena cava with a tunnelled silicone rubber catheter has been the most commonly used for long-term parenteral nutrition for more than 25 years. The types used in most centres are Hickman or Broviac catheters.

The catheter has a felt cuff and fixation is achieved as the subcutaneous tissue adheres to the cuff, which is placed in the subcutaneous tunnel about 1 inch from the exit site. The tip of the catheter should be located in the caval vein or right atrium. Multi-lumen catheters are available, but cannot be recommended, as an increased number of access points theoretically will increase the risk of infection. In a single study however no increase in infection rate was reported with multi-lumen catheters supporting that if strict infection control measures are used the increase in risk is not clinical significant (7).

Groshong® catheters have a rounded tip with a pressure sensitive two-way valve at the intravascular end. The valve is closed when the catheter is not used and opens outwards during fluid infusion or bolus injection. The valve can open inwards if blood is drawn and is closed after the procedure. The risk of catheter occlusion and air embolism is reduced, and heparin can be replaced by saline to flush the catheter between infusions since blood reflux is avoided. Long-term experience with this type of catheter has not been published.
The advantages of tunnelled catheters in general are that they may remain in place for many years and connecting does not require puncture of the skin as with implantable ports. If the external part of the catheter is damaged, it can be replaced using a repair kit. In case of infection it is not always required to remove the catheter; antibiotic treatment may salvage catheters in about 30% of cases with line infection (3). The disadvantage relates to the change in body image because of the external part and the transparent dressing that many centres advocate the use of to cover the exit site.

5. Implantable ports

Another option is totally implantable ports for administration of parenteral nutrition. A stainless steel chamber with a membrane is implanted in a subcutaneous pocket in the chest wall and the catheter part is placed in the subclavian vein with the tip in the superior caval vein or right atrium. The advantage is that the skin covers the port, which is practically invisible, no dressing is needed and the body image is unchanged. Among the disadvantages is the need for perforating skin for infusions; compared to catheters with an external segment the port generally requires more frequent replacement. When infected, antibiotic treatment will very rarely salvage the port, which has to be removed surgically (8).
6. Conclusions: which type of venous access for HPN

- PICC are generally not recommended;
- Broviac or Hickman are durable and the most commonly used tunnelled catheters;
- Implantable ports can be used, advantages regarding the body image;
- Avoid multi-lumen catheters for HPN due to increased risk of infection.

7. Choice of central vein

There are no data on this subject for catheters for long-term use. Studies mainly in the intensive care setting have shown that subclavian puncture is associated with a lower frequency of catheter related infections compared to jugular insertion (9). A further advantage of subclavian cannulation is that the exit site of the tunnelled catheter can be placed readily available allowing the patient self-management of parenteral nutrition and this is obviously important for patients on HPN. Complications in relation to insertion, among which are arterial puncture and damage to neck structures, can be reduced using imaging techniques such as ultrasound for jugular insertion, but this does not apply to the preferred subclavian site (10).

In case of previous complications and suspicion of thrombosis venography can provide essential information to guide insertion at the subclavian site. Generally, femoral vein catheterisation should be avoided due to a much higher risk of mechanical complications and thrombosis, which is about 10 times the rate for subclavian access (9).

8. Position of the distal tip of the catheter

Position of the distal tip of the central venous catheter is important for increasing longevity and minimizing adverse events in patients on HPN. Thus after insertion it recommended to verify the position of the tip using x-ray or fluoroscopy.

In a retrospective study of 141 central venous lines catheter tip location was the only factor that was statistically predictive of malfunctions (11). A significant increase in malfunctions was observed in cases where the catheter tip was located more than 4 cm superior to the junction of right atrium and caval vein. Malfunctions were minimized in those cases where the catheter tip was located in the right atrium.
9. Loss of vascular access

Patients maintained on HPN for many years may encounter repeated line complications with thrombosis and loss of vascular access may eventually be the result. Case reports of access by direct puncture of the right atrium or by cannulation of the hepatic veins have been reported (12). The use of an external arterio-venous graft for intravenous nutritional support may also be an unconventional option (13). It is important to consider the possibility of intestinal transplantation and this should be done at the latest when one vascular access route remains open since this is required for the nutritional and intensive care support if a transplant is performed.

10. Conclusions: Catheter insertion and position

- Sterile conditions when inserting catheters to reduce infectious complications;
- Lower rate of complication at subclavian < jugular < femoral veins;
- Ultrasound my help to guide when inserting at jugular veins;
- Avoid using femoral veins due to high risk of complications;
- Catheter tip at junction of caval vein and atrium results in fewer malfunctions;
- If only a single venous access is left consider referring for intestinal transplant.

11. Catheter related blood stream infection or sepsis, risk factors

Catheter related sepsis remains one of the most frequent complications in this group of patients and requires that patients be admitted to hospital for treatment. The ESPEN-HAN group performed a survey reporting the experience of 12 centres, a total 447 patients and an impressive total number of catheter days of 110 869. Complications occurred in about 25% of patients and in about half the cases it was an infection and this required removal of the catheter in about 12 % of patients. Implantable ports and a daily need for nutrition could be identified as risk factors. Interestingly, the use of catheters for other than nutritional purposes reduced the risk of infection, probably reflecting that thorough care of the line as well as careful administration of parenteral nutrition is very important (14). In a study from this center (3) the presence of a stoma and high age were associated with a higher risk of catheter related bloodstream infection.

ESPEN-HAN survey sepsis 2002

- 12 centres, 447 patients, a total of 110869 catheter days
- About 25 % had problems, about 50 % of infectious origin and removal of catheter in half the cases
- Risk factors port-a-cath and daily use of catheter

12. Prevention of infection dressing

Generally patients to cover the exit site of the catheter use a transparent dressing. This prevents friction with clothing, which may present a problem. About 25 controlled and uncontrolled studies have been carried out testing different types of dressings and in a review 15 studies were included in a meta-analysis (15). The conclusion was that no specific type of dressing or gauze is superior regarding the prophylactic effect on infections, but studies are hampered by inclusion of small number of patients.

Central venous catheter dressings

- Different types of dressings available
- 25 studies, controlled/uncontrolled
- 15 studies included in meta-analysis
  - Comparison of gauze with dressings
  - Comparison of different dressings

Conclusion
- No difference in infectious complications rate between any dressing type
- Small patient samples – lack of power


13. Antimicrobial impregnated catheters

May lower risk of infection, but the effect is relatively short and this approach is not at this stage relevant for the HPN patients in whom the number of catheter day generally exceeds months (16).

14. Nutrition support team and patient education

Educational intervention generally reduces complications if patients use the information they have been taught, and in particular if the education is interactive. This has also been applied in HPN patients in a randomized controlled trial to test interactive video based intervention. Patients in the active group had a significantly lower frequency of line infection at 6 and 18 months (and of admissions for this) (17). Patients in the active group also proved better at defined problem solving, had less depression, and scored better on quality of life measures. Many centres will use some kind of instruction, handout material, and hands on exercises and in some case video based programs or other teaching methods, but very few have been validated.

Patient support and education

Patient affiliation to ongoing HPN education interactive video-based for 18 months (randomised controlled), 39 patients
- Significantly fewer hospitalisations for line infection at 6 and 18 months
- Better quality of life score
- Lower rate of depression
- Patients better at defined problem solving

15. Treatment of catheter related blood stream infection

If a line infection is suspected initiation of antibiotic treatment is the response of the clinician. Longevity of lines should be as high as possible since repeated insertion of new line carries a risk of complications and loss of vascular access.

It may not always be easy for the clinician to distinguish between colonization of the catheter and blood stream infection. In a study to investigate the difference in bacteriology between colonized catheters and blood stream infection in 354 HPN patients 249 catheter tips of a total of 600 catheters were cultured. Sixty tips were culture positive. There were significant differences between microbiology of those who were judged to have catheter related sepsis and those who only had a colonized catheter. The presence of fungi indicated true catheter infection, in contrast to the finding of Gram positive cultures, which rather indicated colonization (18). This confirms the clinical experience from our centre that if patients present with fungal infections it is always required to remove the line, in case of bacterial infection the line can generally be saved in about 30% of cases with blood stream infection.

<table>
<thead>
<tr>
<th>Catheter associated infection</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Colonisation</td>
</tr>
<tr>
<td>– The presence of organisms in the catheter by culture</td>
</tr>
<tr>
<td>• Blood stream infection</td>
</tr>
<tr>
<td>– Culture of the same organism in the catheter and blood stream and no other source of infection</td>
</tr>
<tr>
<td>• Exit site infection</td>
</tr>
<tr>
<td>– Erythema and tenderness or pusulence within 2 cm of the exit site</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Suspected catheter related infection</th>
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<tbody>
<tr>
<td>• Blood cultures drawn from catheter and a peripheral site</td>
</tr>
<tr>
<td>• Culture from the hub</td>
</tr>
<tr>
<td>• Inspect catheter site for signs of infection – if erythema or pus consider removal</td>
</tr>
<tr>
<td>• Antibiotic treatment</td>
</tr>
</tbody>
</table>

Fig. 15

16. Repeated line infection

If patients on long term HPN encounter repeated line infections, intervention apart from changing the line may be appropriate. Re-education in all necessary procedures should be carried out in all patients with line sepsis. Other measures that have been applied are the use of line lock with antibiotics, urokinase to lyse a thrombus and possibly alcohol to dissolve debris (19), but no controlled studies of this are available. In a recent study, Jurewitsch et al (20) applied daily antimicrobial chemotherapeutic treatment with taurolidine, an antibiotic, as a catheter lock in seven HPN patients. The pre-treatment infection rate of 10.8 line infections pr 1000 catheter days dropped to 0.8. More studies are warranted.

<table>
<thead>
<tr>
<th>Catheter related infection</th>
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</thead>
<tbody>
<tr>
<td>• Antibiotic treatment according to microbiology</td>
</tr>
<tr>
<td>• *Catheter lock ?</td>
</tr>
<tr>
<td>– Antibiotics to disinfect</td>
</tr>
<tr>
<td>– Alcohol to dissolve organic debris</td>
</tr>
<tr>
<td>– Urokinase to lyse fresh thrombus</td>
</tr>
<tr>
<td>• Save catheter when possible</td>
</tr>
<tr>
<td>• Remove immediately in case of septic shock</td>
</tr>
</tbody>
</table>

*Case reports and small studies in support

Fig. 16
17. Catheter related thrombosis

Catheter related venous thrombosis

- In 33% of ICU patients by Doppler
- Risk higher with insertion at femoral > jugular > subclavian site
- If diagnosed in the HPN patient population
  - Removal of catheter, anticoagulant treatment
  - Thrombolytic medication?
  - Loss of venous access
  - Probably under diagnosed
  - Clinical studies warranted

Fig. 17

18. Conclusions: Catheter related infection and thrombosis

- General barrier precautions and education of patients is of paramount importance;
- Save lines for HPN on average possible in about 25% of cases with infection;
- Infections with fungi requires line shift;
- Repeated line infections may be reduced by antibiotic lock (case reports);
- Thrombosis related to catheter is relatively rare complication.

References
Nutritional Support outside the Hospital: Home Parenteral Nutrition (HPN)

Module 19.4

HPN in Cancer Patients

Federico Bozzetti

Learning Objectives

- To learn about the feeding of the incurable cancer patient (why, which and how);
- To understand the impact of HPN on survival and quality of life;
- Withdrawing HPN.

Contents

1. Introduction
2. Why feed the incurable cancer patient?
3. Which patients should be fed?
4. How to feed?
5. What is the impact of HPN on survival and quality of life?
6. Ethical and spiritual issues: the will-to-live and the “good death”
7. Withdrawing HPN

Key Messages

- Why feed the incurable cancer patient?
- Which patients should be fed?
- How to feed?
- What is the impact of HPN on survival and quality of life?
- Ethical and spiritual issues: the will-to-live and the “good death”;
- Withdrawing HPN.
1. Introduction

There is some controversy in the indication of home parenteral nutrition in cancer patients. The high cost of HPN coupled with the limited life expectancy of these patients, has led some countries and institutions to consider cancer as a contraindication in providing such support. In particular, knowing that cancer patients die “despite” HPN whereas patients with benign intestinal failure survive “thanks” to HPN, argues against the use of parenteral nutrition in patients with malignancy, at least on the basis of a cost/efficacy evaluation.

In addition there are other reasons behind this discrimination:

- the concept of medicine as a cure more than as a form of care;
- the fear of embarking on a futile treatment or of prolonging agony;
- the uncertainty of the quality of life, the “will-to-live” of the patients, and the poor ability of caregivers to predict the life expectancy of the patients;
- the lack of randomized investigations comparing TPN with no-TPN;
- the misunderstood principle to rationalize the resources more on the basis of indicators of a favorable outcome than on the needs and expectations of patients and their family;
- finally the lack of a proper reference (the surgeon? the oncologist? the palliativist? the nutritionist? a combination of different specialists?).

Despite this fact, cancer patients account for a high percentage (sometimes even the majority) of subjects receiving HPN and the proportion of patients with cancer reported on registers of home parenteral nutrition in various countries ranges from over 50% in Italy and Japan to less than 10% in Denmark and the UK.

2. Why to feed the incurable cancer patient?

We prefer to speak of “incurable” and not of “terminal” cancer patients because a patient can have an incurable tumor without being in terminal conditions and, sometimes can be in terminal conditions after the cure of a tumor which is no longer present in the body.

Furthermore, the word “terminal” suggests the presence of an irreversible state of agony or pre-agony where the nutritional support does not have any obvious role.

However, as it usually occurs in modern medicine, malignant diseases that cannot be cured sometimes become chronic and patients continue to live without really being cured, and they survive thanks to a variety of support treatments.
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• the misunderstood principle to rationalize the resources more on the basis of indicators of a favorable outcome than on the needs and expectations of patients and their family;
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Despite this fact, cancer patients account for a high percentage (sometimes even the majority) of subjects receiving HPN and the proportion of patients with cancer reported on registers of home parenteral nutrition in various countries ranges from over 50% in Italy and Japan to less than 10% in Denmark and the UK.

2. Why to feed the incurable cancer patient?

We prefer to speak of "incurable" and not of "terminal" cancer patients because a patient can have an incurable tumor without being in terminal conditions and, sometimes can be in terminal conditions after the cure of a tumor which is no longer present in the body. Furthermore, the word "terminal" suggests the presence of an irreversible state of agony or pre-agony where the nutritional support does not have any obvious role. However, as it usually occurs in modern medicine, malignant diseases that cannot be cured sometimes become chronic and patients continue to live without really being cured, and they survive thanks to a variety of support treatments.

In some of these patients a prolongation of survival becomes dependent on their nutritional status and on the availability of an artificial nutritional support. This is the case of some cancer patients who are severely hypophagic because of chronic intestinal obstruction/ subobstruction, usually due to a peritoneal carcinomatosis without metastatic involvement of vital organs (liver, lung, brain) and who are condemned to die more from starvation than from actual tumor progression.

We know from the literature, that a proportion ranging from 4 to 23% of patients with an incurable cancer will die from cachexia and even if cachexia cannot be equated to simple starvation, nevertheless anorexia and hypophagia play an important role in progressive deterioration of the nutritional status.

We know from the tragic experiences of the Warsaw Ghetto, the Leningrad siege and more recently from the hunger strikes in Ireland and Turkey, that the mean survival during a total macro-nutrient deprivation is about two and a half months. After this, the weight loss is about 35% and the consumption of lean body mass becomes incompatible with survival.

Should you consider a weight-losing and ill subject (as is a patient with an advanced cancer), who is unable to adapt to a condition of starvation, you could expect a much shorter survival and total protein-calorie starvation.

This information provides us with an interesting speculation: if an aphagic cancer patient is surviving on HPN longer than 3 months it is quite likely this was made possible by the artificial nutritional support.

3. Which patients to feed?

There are no randomized studies that indicate which patients have to be treated with HPN. All the RCTs as well as a recent meta-analysis investigating the role of the TPN in cancer patients have considered TPN vs no-TPN in well-nourished (or mildly malnourished patients) who were not aphagic. Aphagic malnourished patients were excluded for obvious ethical reasons and TPN was not considered a true feeding, rather as an adjunctive therapy to be administered to people who were still able to eat, with all the consequent risks of overfeeding them.
In our experience, HPN may be proposed to patients who fulfill the usual general and logistic criteria for admitting subjects to a HPN program and who meet the following specific requirements for cancer patients:

- unable to eat mainly because GI obstruction/subobstruction;
- life expectancy due to their disease longer than 3 months;
- no or minimal involvement of vital organs and no functional deterioration;
- performance status equal or higher than 50;
- absence of important and/or poorly-controlled symptoms;
- absence of pleural and/or peritoneal effusion which may reduce the tolerance to parenteral fluids infusion;
- previous consent of the patient and relatives to modify and substantially reduce the nutritional regimen should a functional deterioration occur.

Experience has shown that cancer patients entering in these programs of HPN are those affected by peritoneal carcinomatosis from GI cancer (mainly colon-rectum, stomach), ovary, by slow-growing retroperitoneal tumors, neuroendocrine tumors, and desmoids. Some of these criteria can easily be applied to potential candidates: performance status, stage of tumor, symptoms (type and treatment), main organ function, and presence of pleural or peritoneal effusions can easily be assessed; the remaining ones may represent critical issues.

### INCLUSION CRITERIA FOR A HPN PROGRAM

- Unable to eat mainly for obstruction / subobstruction
- Life expectancy due to the cancer > 3 mos (?)
- No or minimal involvement of vital organs and no functional deterioration
- No pleural or peritoneal effusion
- PS higher than 40
- Absence of important and/or poorly-controlled symptoms
- Previous consent of the patient & relatives to modify and substantially reduce the nutritional regimen should a functional deterioration occur (?)

The guidelines of the European Association of Palliative Care help distinguish patients with malignant obstruction that need to be surgically explored (usually patients at their first obstructive episode), patients with an advanced intra- and extra-abdominal disease who mainly require some hydration and antisecretive therapy, and finally patients in an intermediate condition which may be suitable for a program of HPN.

A major problem is the prediction of life expectancy. A vast literature as well as a meta-analysis has shown the poor accuracy of predictive indices; it is easier to estimate a short survival (few days/weeks) than a longer one and senior components of the staff are usually more able than junior ones.

The informed consent requires that both diagnosis and prognosis be fully disclosed. This may be really difficult, at least in Southern European countries where the patient is more considered a subject to protect in some way than a client who has signed a contract with a physician. Moreover, quite often the patients themselves do not ask for the diagnosis and prognosis and there is some doubt they are really able to fully understand the condition of their disease and all the implications of a program of HPN and/or potential alternatives. Relatives too, may ask to filter truth and raise a barrier between patient and physician.
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### METABOLIC & NUTRITIONAL FEATURES OF INCURABLE CANCER PATIENTS

- TEE is reduced due to limited physical activity even if RME may be increased or relatively high for poor adaptation to a state of (semi)starvation
- Expansion of EF further exacerbated by insulin and saline administration
- Host utilizes fat better than glucose, whereas the preferred fuel of cancer cells is glucose

### Specificity of the nutritional regimen for incurable cancer patients

<table>
<thead>
<tr>
<th>Component</th>
<th>Requirement</th>
</tr>
</thead>
<tbody>
<tr>
<td>Water</td>
<td>≤ 30mL/kg</td>
</tr>
<tr>
<td>Non Protein Energy</td>
<td>~ 30 kcal/kg</td>
</tr>
<tr>
<td>glucose</td>
<td>≤ 50%</td>
</tr>
<tr>
<td>fat (MCT, olive oil)</td>
<td>≥ 50%</td>
</tr>
<tr>
<td>Amino acid</td>
<td>1-1.5 g/kg</td>
</tr>
<tr>
<td>Sodium</td>
<td>≤ 1mEq/kg</td>
</tr>
</tbody>
</table>

### Survival of cancer patients on HTPN

<table>
<thead>
<tr>
<th>Author</th>
<th>N° Patients</th>
<th>Survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>Howard 1993</td>
<td>1672</td>
<td>28% at 1 yr; median 6/4 mos</td>
</tr>
<tr>
<td>Howard 1995</td>
<td>2122</td>
<td>37% at 1 yr</td>
</tr>
<tr>
<td>Messing 1998</td>
<td>524</td>
<td>19.5% at 6 mos</td>
</tr>
<tr>
<td>Van Gossum 1997</td>
<td>200</td>
<td>26% at 6-12 mos</td>
</tr>
<tr>
<td>Howard 2000</td>
<td>1073</td>
<td>25% at 1 yr; median 6 mos</td>
</tr>
<tr>
<td>SINPE Register 2004</td>
<td>1103</td>
<td>20% at 1 yr; median 6 mos</td>
</tr>
</tbody>
</table>

4. **How to feed?**

There are some peculiar aspects of parenteral nutrition of cancer patients which rely both on some metabolic features of these patients and of the cancer cells themselves. Cancer patients candidate for HPN are typically malnourished, have experienced weight loss, have reduced total energy expenditure due to their limited physical activity even if their resting energy expenditure may be increased, or at least relatively high, because of a poor adaptation to a state of (semi)starvation. They have an expansion of the extracellular fluid which can be exacerbated by the frequent administration of insulin and saline solutions. Furthermore, patients utilize glucose more than fat, whereas the preferred fuel of cancer cells is glucose and not lipid.

Consequently we should plan a daily nutritional regimen as follows:

- **Total fluid volume:** about 30 mL/kg
- **Nonprotein energy:** about 25-30 kcal/kg
- **Glucose/fat ratio:** 60/40 or 50/50 (prefer MCT or olive oil lipids)
- **Amino acid:** 1.5g/kg
- **Na:** about 1 mEq/kg
5. What is the impact of HPN on survival and quality of life?

In literature mean survival of cancer patients on HPN is about 3-4 months, with a range of a few weeks to several months. This means that at least 50% of these patients have survived longer than time allowed by a state of macronutrient deprivation and less than 50% of them have no apparent benefit from HPN.

Therefore the controversy whether “to feed or not to feed” is moving towards the question “how can we select the patients who will benefit from HPN?”

The evaluation of the Quality of Life of cancer patients deserves further investigation due to the extreme complexity of the issue. Quality of Life is obviously relevant to each of us, but in this medical context, where no cure is possible but only a prolongation of survival, Quality of Life is of the utmost importance.

Besides the basic uncertainty of the meaning and definition of Quality of Life, it is extremely difficult to untangle what are the effects of underlying disease and what are the additional problems attributed to HPN. Problems arising from underlying disease will remain but it should be possible to remove or minimize those arising from HPN, once they are identified as a real problem rather than as a patient’s perception.

There are dozens of instruments, questionnaires, scales and scores about the Quality of Life: no one is perfect, and broadly speaking, they are more suitable for longitudinal studies than for comparison with a no-HPN population.

Box and whisker plot of actual survival for various prediction categories. The black boxes indicate the interquartile range of actual survival, and the white bar is the median survival for that prognostic category. The whiskers are drawn to 1.5 times the interquartile range, which would represent the 99.65 centile if the data were normally distributed, although they are not. Points beyond that range are drawn individually.

Fig. 9

Survival of patients with an advanced incurable cancer on HPN.

Fig. 10
What is the impact of HPN on survival and quality of life?

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There are dozens of instruments, questionnaires, scales and scores about the quality of Life: no one is perfect, and broadly speaking, they are more suitable for longitudinal studies than for comparison with a no-HPN population.

The prospective investigation by the Italian Society for Parenteral and Enteral Nutrition on the quality of Life of cancer patients on HPN using the Rotterdam Symptom Checklist has shown that patients with an "acceptable" quality of Life at the start of HPN were able to maintain unchanged these parameters for 2-3 months before death.

Our main conclusion was that we should make every effort to try and identify the single patients with an expected cancer-dependent survival of over 3 months. In such a case not only should we be reasonably sure that we are prolonging survival with HPN in subjects who are otherwise condemned to succumb from starvation, but they could also have a window of acceptable life before final deterioration and death.

6. The will-to-live and the "good death"

A recently published self report measure of the desire for death of terminally ill cancer patients with a life expectancy of less than six months demonstrated substantial fluctuations in will-to-live score within various intervals of time (12-24 hours, 7 days, 1 month). Another recent study examined the perception of dying patients, family members and care providers and revealed six major components of a "good death": 1) effective pain and symptoms control; 2) the ability to engage in clear decision making; 3) preparation for death; 4) a sense of completion; 5) continued ability to contribute to others; and 6) affirmation of the whole person. However, it is disturbing that although these items were recognized important by all members of this focus group, there were several issues that were extremely important for the dying...
patients, but were not so important to their physicians. These included: 1) being mentally aware; 2) being at peace with God; 3) not being a burden to one's family; 4) being able to help others; 5) being able to pray; 6) having funeral arrangements made; 7) not being a burden to society, and 8) feeling that one's life is complete. These experiences show that caregivers should pay close attention to the desires of their patients, and avoid the presumption that they know in advance what is good for them. They also must accept suggestions about the will to live when statements and answers are consistent. This is only possible if a climate of true empathy is created between clinicians and their patients.

7. Withdrawing HPN

Although most ethicists have concluded that distinction between withholding and withdrawing treatment is morally incoherent, many physicians feel ethically justified in withholding treatments that they never started, but not in withholding treatments that already were initiated. Physicians also find it easier to limit resuscitative efforts or forms of therapy that support organ that failed for natural reasons and not for iatrogenic factors or interventions that were recently instituted rather than long-standing treatments. The problem arises because the cultural and symbolic value of the nourishment, which is traditionally viewed as an expression of love and care for both living and the dying. While physicians tend to see “nourishment as a medical treatment” aimed at achieving

---

**Major components of a “good death”**

* (Steinhauser 2000)

- Effective pain and symptoms control
- Ability to take part to the decisions
- Preparation for death
- A sense of completion
- Continued ability to contribute to others

Fig. 14

---

**Issues important for the dying patient and not for the physician**

* (Steinhauser 2000)

- Being mentally aware
- Being at peace with God
- Not being burden to one’s family
- Being able to help others
- Being able to pray
- Having funeral arrangements made
- Not being burden to society
- Feeling one’s life is complete

Fig. 15

---

**WITHDRAWING HPN (I)**

- Physicians tend to see “nourishment as a medical treatment” aimed at achieving physiological objectives, while families see “feeding as an expression of love and care” for both living and the dying (Miles 1989)

- HPN usually accepted as a solution for tremendous problems (intractable anorexia, progressive weight loss, deterioration of body image…) of both patients and relatives (Orreval 2004)

Fig. 16
Patients, but were not so important to their physicians. These included:
1) being mentally aware; 2) being at peace with God; 3) not being a burden to one's family; 4) being able to help others; 5) being able to pray; 6) having funeral arrangements made; 7) not being a burden to society, and 8) feeling that one's life is complete.

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**WITHDRAWING HPN (II)**

- Physicians feel ethically justified
  1. in withholding treatments that they never started but not in withdrawing treatments that already were initiated
- Physicians feel easier
  2. to limit a form of therapy that supports organs that failed from natural reasons and not for iatrogenic factors, or
  3. interventions that were recently instituted rather than long-standing treatments

**Fig. 17**

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Nutritional Support outside the Hospital

Module 19.5

Guidelines for Home Parenteral Nutrition in Chronic Intestinal Failure
Bernard Messing
Francisca Joly

Learning Objectives
· How to adapt nutrition support in HPN patients?
· What are the nutritional needs of a patient?
· How to cover the needs for a patient?
· How to evaluate PN dependence?

Contents
1. Introduction
2. General HPN guidelines
3. Nutritional support team
4. Nutritive mixtures
5. CIF in short gut patients and PN dependence
6. PN dependence and HPN management
7. Patient management
8. Conclusion

Key Messages
· Management of HPN must be an integrated part of the management of the disease which has led to chronic intestinal failure;
· A better prognosis is observed in HPN patients having a short but functioning gut than in patients with a longer but non-functioning;
· Along with medical therapy, dietary management of intestinal failure due to very short bowel is a crucial point which may reduce the PN dependence at its lower level, therefore decreasing the risk of technical and metabolic complications associated with long term HPN;
· Indeed, HPN for intestinal failure must not be viewed as "hyperalimentation" but rather a complete nutrition support for each PN cycle with a minimum number of nocturnal cycles per week. This is better observed in patients in which hyperphagia takes place;
· Then, HPN is in most cases, a complementary non-exclusive mode of nutritional support.

Withdrawing HPN
32. Cristakis et al. Lancet 1993;342: 642
35. Mc Clement et al 2003;6:737

Will-to-live and the “good death”
31. Steinhauser et al. JAMA 2000; 284: 2476
Nutritional Support outside the Hospital: Home Parenteral Nutrition (HPN)

Module 19.5

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- Then, HPN is in most cases, a complementary non exclusive mode of nutritional support.
1. Introduction

Home parenteral nutrition (HPN) is the gold standard of treatment which applied to the concept of chronic intestinal failure (1). The recognized definition of chronic intestinal failure is a non functioning small bowel either removed, after severe disease leading to very short bowel syndrome, or present but impossible to use by enteral support even accessed through jejunostomy (e.g. chronic intestinal pseudo obstruction or extensive villous atrophy diseases) (2). HPN should be administrated to patients if nutritional requirements cannot be met by or enteral nutrition feeding (3). This manuscript focuses on nutritional support of adult HPN patients in a tertiary care center in the setting of chronic intestinal failure excluding cancer patients and focusing on short bowel patients (see HPN ESPEN Book) (5).

2. General HPN guidelines

Published guidelines for the use of (H)PN should be looked at by the reader (3). These published guidelines related to this chapter are summarised for HPN adults in Table 1 (3, 4).

3. Nutrition support team

Nutrition support team (NST) is required to safely manage HPN. It includes specialized nurse, dietetician, pharmacist, physician and surgeon ideally trained in both nutrition and gastroenterology, plus social worker, care giver and general practitioner, patient and family being at the center of the medical sphere. The NST has to:

- identify appropriate candidates;
- develop a nutritional plan of care agreeable to the patient and care giver;
- make a prescription appropriate for the home setting;
- properly train the patient / care giver (6).

According to the ASPEN the standard but “minimally required” care for HPN patients is standardized method for “ordering and monitoring HPN support”: this is necessary because physicians with various academic training may order home artificial nutrition support.
It is also highly recommended to use “disease specific pathways” for obtaining laboratories values and patient’s visits and to organize formal communication between home care staff and the involved general practitioner (7).

HPN survey in the eighties in French approved HPN centers, has showed a significant increase in the probability of survival according to the date of inclusion: number of deaths being higher during a 3-year run in period than during the two subsequent 3-years periods (8). Then, NST(s) specialized in chronic intestinal failure are a prerequisite for running HPN programs. The learning curve observation showing long term health outcome improvement in HPN pleads now for intestinal failure units covering and integrating expertises in all medical and surgical aspects of chronic intestinal failure treatment (5).

4. Nutritive mixtures

**HPN : Nutritive Mixtures for adults**

<table>
<thead>
<tr>
<th>Per cycle</th>
<th>60 Kg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cyclic PN :</td>
<td>10-12 h</td>
</tr>
<tr>
<td>Amino acid solution (s) :</td>
<td>1.25 (1 to 1.5) g/Kg</td>
</tr>
<tr>
<td>Energy :</td>
<td>1.0(0.8 to 1.3) x REE (1200±300)</td>
</tr>
<tr>
<td>- Glucose based :</td>
<td>≤ 6mg/Kg/min (up to 9)</td>
</tr>
<tr>
<td>+ EFA : around 5% of total Kcal (1000 Kcal/wk)</td>
<td>20% ω6 rich emulsion :</td>
</tr>
<tr>
<td>- Lipid based (ternary) :</td>
<td>≤ 30% of E load</td>
</tr>
<tr>
<td>or ≤ 1 g/Kg</td>
<td>45g</td>
</tr>
<tr>
<td>Minerals &amp; electrolytes :</td>
<td>“a la carte”</td>
</tr>
<tr>
<td>Vitamins &amp; trace metals: AMA recommendations x 1-2</td>
<td></td>
</tr>
</tbody>
</table>

Nutritive mixtures, apyrogenic and sterile, are compounded under the responsibility of pharmacists in single bags called “all-in-one” - sometimes bipartite (the second compartment for a lipid emulsion is just opened and mixed with other compounds before use). Bags are made of phthalate-free multi-layered ethyl vinyl acetate plastic. The use of all-in-one nutritives mixtures facilitates the practice of cyclic (nocturnal) PN which is the main mode of HPN therapy (9-14).


**Definition of All-In-One Parenteral Nutrition Therapy**

- **All 38 nutrients in a single container**
  - 2 or 3 macronutrients :
    - Dextrose–Aminoacids solution(s)
    - ± Lipid emulsion(s) in mono/bi partite bag
  - 35 micronutrients :
    - electrolytes, minerals, vitamins, trace metals

- **A separate sheet for nutrition prescription should be used to avoid omission**

*BM A–I–O2a*
When nutritive mixtures done by pharmaceutical companies are used in PN, especially at home, there is a risk of deficiencies (vitamins are usually absent from these mixtures) and imbalances (e.g. electrolytes, minerals, excess fat/glucose ratio) if additives are not added according to the patient's requirements.

Doing these necessary IV supplement(s) at home by nurse, care giver or patients themselves (6), instead of doing it under laminar hood flow, brings, despite using aseptic techniques, an additional risk of infection.

Stability of the mixture might be also compromised by inappropriate supplementation. Then, "optimized" HPN care is still sometimes not used after more than 35 years experience in HPN (13,17,18).

Then, the authors advise that, for each HPN patient, “all-in-one” complete nutritive mixtures should be tailored according to the specific type of chronic intestinal failure with a cyclic nocturnal infusion of a variable volume, a variable infusion duration (10 h-16 h) and a variable number of cycles per week.

5. Chronic Intestinal failure in short gut patients and PN dependency

CIF is "reduction in functioning gut mass below the minimal amount necessary for adequate digestion and absorption of nutrients" (1).

Three variables (2 clinical and one biochemical) have been then shown to be able to delineate transient from permanent - or indefinite - CIF in short bowel syndrome (SBS) adult patients (20-24). SBS representing nearly 80% of long term HPN in adult patients (5, 8, 25).

• length of remnant bowel
• duration of HPN use
• citruline levels.

---

**TRACE-METAL NEEDS in HPN**

<table>
<thead>
<tr>
<th>Decan® (40 ml)</th>
<th>Specific for IF**</th>
<th>RDA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Se</td>
<td>70 µg</td>
<td>50-100 µg</td>
</tr>
<tr>
<td>Cr*</td>
<td>15 µg</td>
<td>10 – 20 µg</td>
</tr>
<tr>
<td>Mo</td>
<td>25 µg</td>
<td>300 µg</td>
</tr>
<tr>
<td>Cu°</td>
<td>0,48 mg</td>
<td>up in celiac</td>
</tr>
<tr>
<td>Zn</td>
<td>10 mg</td>
<td>3 mg / L</td>
</tr>
<tr>
<td>I &amp; Co</td>
<td>1.5 µg</td>
<td>- µg</td>
</tr>
<tr>
<td>Mn°</td>
<td>0.2 mg</td>
<td>0.15 - 0.80 mg</td>
</tr>
<tr>
<td>Fe°</td>
<td>1 mg</td>
<td>according losses</td>
</tr>
<tr>
<td>Fluor</td>
<td>1,45 mg</td>
<td>- mg</td>
</tr>
<tr>
<td>Al°°</td>
<td>-</td>
<td>&lt; 30 µg/d</td>
</tr>
</tbody>
</table>

* Better to decrease or stop in chronic cholestasis patients

* contaminant of NP solutions with potential toxicity. **Intestinal failure

---

**Vitamin requirements and supply in TPN**

<table>
<thead>
<tr>
<th>Vitamin</th>
<th>Requirement/Unit</th>
<th>AMA/d</th>
<th>IV/d</th>
</tr>
</thead>
<tbody>
<tr>
<td>B1, Thiamine</td>
<td>mg</td>
<td>1,5</td>
<td>1-5 / CHO</td>
</tr>
<tr>
<td>B2*, Riboflavin</td>
<td>mg</td>
<td>1,7</td>
<td>3,4</td>
</tr>
<tr>
<td>PP, Nicotinamide</td>
<td>mg</td>
<td>20</td>
<td>40</td>
</tr>
<tr>
<td>B6, Pyridoxine</td>
<td>mg</td>
<td>2</td>
<td>4</td>
</tr>
<tr>
<td>B9, Folic acid</td>
<td>µg</td>
<td>200</td>
<td>400</td>
</tr>
<tr>
<td>B12, Cyanocobalamin</td>
<td>µg</td>
<td>2</td>
<td>4</td>
</tr>
<tr>
<td>Pantothenic acid</td>
<td>mg</td>
<td>7</td>
<td>14</td>
</tr>
<tr>
<td>Biotin</td>
<td>µg</td>
<td>100</td>
<td>200</td>
</tr>
<tr>
<td>C, Ascorbic acid</td>
<td>mg</td>
<td>60</td>
<td>200</td>
</tr>
<tr>
<td>A, Retinol (RE)</td>
<td>IU / µg</td>
<td>1000*</td>
<td>3300</td>
</tr>
<tr>
<td>D, Cholecalciferol</td>
<td>IU / (µg)</td>
<td>200 = (5 µg)</td>
<td>200</td>
</tr>
<tr>
<td>E, α-Tocopherol</td>
<td>IU / mg</td>
<td>10</td>
<td>0.6mg/g PUFA</td>
</tr>
<tr>
<td>K+, Phyt/Phenquinone</td>
<td>µg</td>
<td>1/Kg daily or 10mg / wk</td>
<td></td>
</tr>
</tbody>
</table>

*not recognized clinical deficit, * contribution by colonic bacteria

Formulations : Kahl & Baxter around 2 – 2.5 times AMA...

---

**Proposals to delineate transient from permanent intestinal failure in SBS**

- Time limit of weaning or not off HPN:
  - = 2 yr in adult*, = 4 yr in children
  ? time to allow maximum intestinal adaptation
- Citruline blood threshold:
  - transient: 20-30 umol/L
  - permanent: Adult < 20", Kids < 19 umol/l
- Lenght of remnant small bowel threshold*:
  - = 100 cm for abnormal but non-occluded
  - = 100, 60, 35 cm for EE, JC, JIC SBS types

Weaning off HPN can be obtained, according to different remaining lengths of small bowel depending on the three main anatomical types of SBS (20, 21); in end-jejunostomy (type I, no colon in continuity), in jejunocolonic (type II, some part of the colon is in continuity) and in jejunileoal (type III, the full colon is in continuity) type of anastomosis, the minimal lengths of a normal small bowel are respectively 100 cm, 60 cm and 35 cm (20, 22). For types II and III, 100 cm is required to wean off HPN patients if remaining bowel is abnormal but without stenose(s).

- Probability of weaning off HPN, became less than 10%, if the weaning off has not been obtained during the first two years of HPN (21, 22).

- A plasma level of post absorptive citrulline - a non essential amino-acid, not incorporated into peptides or proteins - lower than 20 µmol/l (half the normal value in controls) is significantly associated with permanent intestinal failure, past the adaptive - 2-year - period following the re-establisment of bowel continuity after extensive small bowel resection (24).

This biochemical marker cannot be used in renal insufficiency. It is highly correlated to remnant small bowel length and absorptive capacity; it is more predictive of permanent CIF (negative and positive predictive values of 86% and 95% respectively) than remnant length of small bowel within the 3 anatomical types of SBS. In fact, citrulline seems to reflect the absorptive function of the remaining short gut because its level was significantly higher in 10 hyperphagic patients than in 10 normophagic patients paired with a same length of remnant small bowel (24).
It is interesting to note that in children with SBS, a similar citrulline threshold (19µmol/L) has been recently found for both length of remnant small bowel and development of enteral tolerance with comparable high negative (100%) and positive (87%) predictive values to observe weaning off HPN (26).

Then, length of remnant bowel plus citrulline level offer the advantage to better define appropriate HPN candidates for either complementary (pharmacological trophic gut factors or reconstructive surgery) or alternative treatments for permanent intestinal failure (5).

6. PN dependence and HPN management

Knowing the probability of HPN weaning off (see previous paragraph), it is also important to know the capacity and eating intake of a given patient, plus the absorption of the remnant gut (under optimal therapy including dietary counselling, to set up a minimum level of PN dependence during HPN management.

PN dependence can be viewed as minimal needs through a complementary IV route for:

- Water, Na and mineral (K and especially Mg), at one hand
- Macronutrients on the other hand
- both should be set up at equilibrium for nutritional purpose (27, 28).

In each patient, it is useful to look at the degree of PN dependence (from 0 to 100%) by comparing net absorption (expressed in percentage of oral autonomy (3-day balance study for both energy/protein and water/Na-)) and PN inputs of water, protein and energy delivery (mean of one week IV infusion) expressed in percentage of nutritional needs. This calculation will give data to set the PN delivery closer to the effective PN dependence level.

PN dependence: a complicated matter

- PN dependence depends from 3 parameters:
  1. Energy/protein absorbed (oral autonomy)
  2. Water salt equilibrium (= 0 balance)
  3. Normal magnesium
- Attempt to dissociate Energy/protein absorbed from H2O/Na & Mg balances deserves attention
- Oral autonomy should be crossed against HPN dependence to point out discrepancy

Fig. 10

PN dependence versus oral autonomy

Balance studies are complicated to perform

\[ \text{In - out} = 3 \text{-day absorption} \]

- Energy balance
- Hydro-electrolyte
  \[ \pm \text{Magnesium (hypoK & hypoCa)} \]
- Easier to get: urinary collection/day
  volume of fluid intake/day

Fig. 11

How to adapt nutritional support in HPN adult patients?

- What are the nutritional needs of a patient?
- How to cover the needs for this patient?
  - Partial PN is better than total PN-dependence
  - Management of primary disease has to be optimal
- How to evaluate PN dependence?

Fig. 12
It is interesting to note that in children with SBS, a similar citrulline threshold (19 µmol/L) has been recently found for both length of remnant small bowel and development of enteral tolerance with comparable high negative (100%) and positive (87%) predictive values to observe weaning off HPN (26).

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For example, an important discrepancy may exist in a patient between its potential for achieving oral autonomy with diet alone (i.e., its rate of absorption for energy/protein and/or water/salt indicate positive balance whereas its HPN prescription is still important: i.e., more or equal than 3 infusions per week)(27).

Indeed, initial overuse of PN upon entry into a study of diet, growth hormone and glutamine therapy may explain, in part, the long-term success at weaning from PN over time with modified diet + glutamine alone, long after a short course of growth hormone was completed (29).

Noteworthy, a parallel 3-arm study, comparing PN-dependent short bowel syndrome patients given either an individualized modified diet + oral glutamine (control), individualized modified diet with growth hormone alone or the modified diet with growth hormone + oral glutamine showed that a significant decrease in PN needs occurred in the control group during a one-month treatment period, although it was significantly less than the one achieved in the two other arms (30).

Insufficient oral intake or "oral failure" - not directly dependent on the intestinal condition - is another caveat which compromise oral autonomy and may also induce a higher than needed PN delivery. In that circumstance, apart from psychological evaluation, one may decide having a period of nasogastric tube feeding in order to properly evaluate absorptive capacity of the remnant gut. This management may be justified because a high degree of PN dependence with IV "hyperalimentation" may accelerate, as demonstrated in the past, the occurrence of metabolic complications: i.e., liver failure (31).

---

**How to adapt nutritional support?**

- Therapy of diseases should be optimized:
  - Surgical for: Crohn’s & radiation enteritis
  - Medical for: Crohn’s, CIP0...
  - Endoscopy for Crohn’s: eg, prosthesis for stenoses...
  - Endoscopy for CIP0: eg, double-lumen gastrostomy with gastric aspiration & jejunal perfusion...

  "To access the gut in order to feed the gut and the patient through the gut, i.e., partial, non exclusive mode of PN"

*Fig. 13* In HPN ESPEN Book, F Joly & B Messing, to be published
*M. Murr et al: Am coll Gastro 1995;90:2147*

**How to adapt nutritional support?**

<table>
<thead>
<tr>
<th>Prognosis is worse in Exclusive HPN (nil po) than in Partial HPN (non negligible enteral feeds)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Consequences:</td>
</tr>
<tr>
<td>Total vs Partial HPN regime</td>
</tr>
<tr>
<td>7 vs 2-6 Cyclic infusion / wk</td>
</tr>
<tr>
<td>Lower vs Higher QOL</td>
</tr>
<tr>
<td>Higher vs Lower rate of complications*</td>
</tr>
</tbody>
</table>

*Fig. 14* Higher PN dependence has more frequent line connections & higher IV loading implying greater risk of complications (eg, Stanko RT, Gastro 87. Messing B, Nutrition 92).

**Intestinal Resection**

To decrease PN dependency?

- In chronic radiation enteritis: yes°
- In crohn’s disease: yes°
- in CIPO without systemic fate: ? **

*°It is better to have a short gut than a longer but non functioning gut*
*M Irving et al Gut 1994, F Joly et al ESPEN 2003 (a total of 10 patients)*

*Fig. 15* Messing B et al Gastro 1995

For example, an important discrepancy may exist in a patient between its potential for achieving oral autonomy with diet alone (i.e., its rate of absorption for energy/protein and/or water/salt indicate positive balance whereas its HPN prescription is still important: i.e., more or equal than 3 infusions per week)(27). Indeed, initial overuse of PN upon entry into a study of diet, growth hormone and glutamine therapy may explain, in part, the long-term success at weaning from PN over time with modified diet + glutamine alone, long after a short course of growth hormone was completed (29).

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7. Patient Management

Two principles apply to obtain in a patient the minimum required level of PN dependence:

- Avoid, as much as possible, exclusive or total IV feeding and
- Implement, as much as possible, enteral feeding.

Indeed, prognosis of HPN patients was shown to be significantly better in patients with no bowel obstruction than in patients with chronic obstruction (e.g. Crohn's or radiation enteritis patients). So, the lesson issued from this observation is that it is better to have a functioning and accessed short gut rather than a longer but non functioning gut (8).

In our tertiary care center we therefore discuss every case in order to:

- Re-establish colonic continuity in SBS patients whatever the age of the patient or the percentage of remaining colon (if > to 30% of a full colon (32)) or the recto sigmoid alone provided a normal anatomy and function after treatment with short chain fatty acid enemas (33): in these cases, water mineral and energy balance (34) improve and the numbers of PN cycles per week decrease;
- Perform bowel resection in patients with multifocal obstructive disease (e.g. in radiation enteritis plus a left colostomy if the anorectum is involved by the disease): in these cases, patients may recover normal fluid intake and enjoy again food intake as large as possible, with a benefit of a reduced PN dependence.

SBS treatment: postoperative phase

- Fluid and electrolyte monitoring is needed several times /day until equilibrium status is obtained (Vanderhoof, 1997)
- Gastric hypersecretion gastrique contributes to water and electrolyte losses. Anti H2 receptors antagonists or proton pump inhibitors are needed. Octreotide can be useful for secretory diarrhea (Nightingale, 1993).
- Parenteral nutrition must be initiated early, on a separate venous access.
- Parenteral nutrition is able to attenuate body weight and fat-free mass depletion, and to improve long term survival (Gouttebeil, 1986).

Mr Ba...: SGC type II with Jejunal reverse segment

* Percent of Oral Autonomy : Total Absorption / 1.5 x REE

55 yr old Patient; mesenteric arterial infarction; J(40 cm)-C anastomosis

Management of HPN: examples

- In SBS, attempt to re establish colonic continuity should always be discussed
- In SBS, “solid”oral free hyperalimentation should be encouraged instead of restrictive regimens
- In SBS with secondary anorexia, enteral nutrition through gastrostomy may decrease PN dependence
Promote absorption in IF-SBS patients

<table>
<thead>
<tr>
<th>Discuss to implement</th>
<th>Expected result</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hyperphagia :</td>
<td>no obvious decrease in % absorbed</td>
</tr>
<tr>
<td>Enteral :</td>
<td>+ 30% (750 kcal/d) : 30% of TEE*</td>
</tr>
<tr>
<td>Reverse :</td>
<td>+ 20% (600 Kcal/d) : 25% of TEE</td>
</tr>
<tr>
<td>rh-GH* :</td>
<td>+ 15% (500 kcal/d) : 15% of TEE</td>
</tr>
<tr>
<td>GLP2%** :</td>
<td>+ 5% (100 kcal/d) : 5% of TEE</td>
</tr>
<tr>
<td>rH.GH + GLP2 :</td>
<td>? (Not done)</td>
</tr>
</tbody>
</table>

* 4-Wk treatment (0.05 - 0.10 mg/Kg/d); ** Electrolytes & Prot
* TEE = total energy expenditure

Indeed the macronutrient absorption of a very short remnant bowel is never negligible and the net balance increases with increased intake of free oral solid foods as large as 3-fold the patient's Resting Energy Expenditure (REE) (27, 35).

The behavior of hyperphagia should be encouraged with no futile solid food restriction since it promotes "physiological" adaptive intestinal process (34) and gives some patients with borderline remnant gut a full oral nutritional autonomy.

The latter lesson is derived for our large experience with balance studies on western free solid food feeding to determine net intestinal absorption (In-Out): "In" being measured either with dietary enquiry or with duplicated diets and "Out" by 3-day stool collections (27, 28, 35).

To this regard, our HPN management in a patient with chronic intestinal failure is a two-stage process:

1. first, with a goal of restoring a low normal BMI in under weight patients, we implement a 6-cycle PN regimen per week with a PN-free day - water electrolytes only (23) - each cycle being no more than 1.3 fold the REE (19) together with a free solid oral feeding pertaining a non occluded gut (34);
2. second, with a goal of maintaining a near normal nutrition status, we tried to reach, step by step, a minimum number of cycles per week (22); water-electrolytes needs being dissociated from energy-protein needs, especially in SBS patients type I, where the fluid balance is more difficult to achieve than the energy balance. Indeed, it was showed that 20% of these patients require only a water-electrolyte supply (23).

How to adapt nutritional support?

- What are the nutritional needs of a patient?
  - Each PN cycle must be complete+++:
    - Glucose : minimum 200g/d up to 350g/d
    - Lipids : no more than 1/3 of non protein energy need
    - Proteins : 1.0 g/kg/d up to 1.5 g/kg/d (150-250 mg N)
      2g Prot or 320 mg N/kg in hypocaloric regimen
    - Minerals, micronutrients : increased as needed*
  * i.e., magnesium & vitamins (Cernevit®...) when infusions / wk are reduced,
  - Zn according to intestinal (stoma, fistulae, stool) losses S Woolman gastro 79

Attempt to wean off PN SBS patients

Protocol for the reduction of parenteral supplies:
1/ Reduce daily supply during one week
2/ Cyclic PN 3/week during the second week
3/ Cyclic PN 2/week during the 3rd week.
4/ Return to initial PN if: - weight loss > 1 kg/week
  - water and electrolyte disequilibrium

Gouttebel MC et al. DDS 1986

1/ When « desired weight » is obtained, decrease NP cycles
2/ Implement minimal Home PN to obtain hyperphagia
3/ Be sure of optimal dietary counselling & GI treatments
4/ Implement rh-GH with Gin for 4 weeks and stop PN
5/ Return to PN if necessary

8. Conclusion

Management of HPN must be an integrated part of the management of the disease which has led to chronic intestinal failure. We have new tools which allow to better delineate, in short bowel patients, transient from permanent; i.e., irreversible intestinal failure. A better prognosis is observed in HPN patients having a short but functioning gut than in patients with a longer but non-functioning gut. Along with medical therapy, dietary management (27, 28, 34, 35) of intestinal failure due to very short bowel is a crucial point which may reduce the PN dependence at its lower level, therefore decreasing the risk of technical and metabolic complications associated with long-term HPN. Indeed, HPN for intestinal failure must not be viewed as “hyper-alimentation” but rather a complete nutrition support for each PN cycle with a minimum number of nocturnal cycles per week. This is better observed in patients in which hyperphagia takes place. Then, HPN is in most cases, a complementary non-exclusive mode of nutritional support.

PN dependence: a complicated matter

<table>
<thead>
<tr>
<th>Weaning off PN attempt: parameters to check</th>
</tr>
</thead>
<tbody>
<tr>
<td>- Diuresis and natriuresis</td>
</tr>
<tr>
<td>- Transthyretin</td>
</tr>
<tr>
<td>- no obvious dehydration: weight, Ht, creat</td>
</tr>
<tr>
<td>- K &amp; Mg</td>
</tr>
<tr>
<td>- Albumin</td>
</tr>
<tr>
<td>- micronutiments</td>
</tr>
</tbody>
</table>

Fig. 22  BM.05

Management of HPN

- Should be an integrated part of the management of the primary disease which has led to Intestinal Failure (IF)
- Outcome is better in functioning and accessed short gut than in a longer non-functioning gut
- Absorption of the (very) short remnant functioning bowel is never negligible
- In SBS patients Transient IF can be distinguished from permanent “irreversible” IF

Fig. 23  BM.04

Conclusion: Management of HPN Nutrition Support

- HPN is not Hyper alimentation
- HPN is a full complete IV support per cycle
- A minimum Number of cycles per week should be tried after reaching an “optimal” BMI
- Protein / calorie input should be dissociated from the hydroelectrolytes / minerals needs
- In most cases, HPN is a complementary, non exclusive mode of nutritional support

Fig. 24
Learning Objectives

· Learn about identifying the main metabolic HPN complications in adult patients;
· Learn how to prevent and cure these complications.

Content

1. Introduction
2. Fluid and electrolytes
3. Overall complications and hyperglycemia
4. Intestinal consequences of HPN
5. Micronutrient deficiencies
6. Trace element excess
7. HPN associated liver disease (HPNALD)
8. Gallbladder sludge and lithiasis
9. Renal function impairment
10. Metabolic bone disease
11. Summary

Key Messages

· HPN metabolic complications are still frequent but they can be significantly decreased through present knowledge, expertise and continued attention;
· Most of metabolic complications are multifactoral and interrelated;
· Nutrition support team, education and a "complete", but non exclusive, HPN adapted to the type of CIF is able to lower the rate of metabolic complications;
· Further understanding is needed especially in renal, bone and liver HPN associated complications to ameliorate preventive and curative treatments.

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- Further understanding is needed especially in renal, bone and liver HPN associated complications to ameliorate preventive and curative treatments.
1. Introduction

Long-term HPN metabolic complications will be identified in order to assure prevention and curative treatments. Will be reviewed, liver, gallbladder, bone, renal associated HPN complications as well as vitamin deficiencies and trace metals deficiencies or toxicity (Fig. 1). Psychosocial issues will not be reviewed. Hyperglycemia, fluid and electrolytes disturbances and gastrointestinal HPN effects will be briefly quoted: readers will be informed with these matters on recent reviews (1-5).

Monitoring for complications is indicated on table according to the A.S.P.E.N. (1).

Table 1 Practice Guidelines (A.S.P.E.N.): Monitoring of Complications

| Malnourished patients at risk for refeeding syndrome should have serum phosphorus, magnesium, potassium and glucose levels monitored closely at initiation of SNS | B  
| In patients with diabetes or risk factors for glucose intolerance, SNS should be initiated with a low dextrose infusion rate and blood and urine glucose monitored closely | C  
| Blood glucose should be monitored frequently upon initiation of SNS, after any change in insulin dose, and until measurements are stable | B  
| Serum electrolytes (sodium, potassium, chloride, and bicarbonate) should be monitored frequently upon initiation of SNS until measurements are stable | B  
| Patients receiving intravenous fat emulsion should have serum triglyceride levels monitored until stable and when changes are made in the amount of fat administered | C  
| Liver function tests should be monitored periodically in patients receiving PN | A  
| Bone densitometry should be performed upon initiation of long-term SNS and periodically thereafter | C  

The authors used the AHRQ criteria to classify the strength of the evidence supporting each guideline statement.

The evidence supporting each statement is classified as follows:
A - There is good research-based evidence to support the guideline (prospective, randomized trials)
B - There is fair research-based evidence to support the guideline (well-designed studies without randomization)
C - The guideline is based on expert opinion and editorial consensus

Nutrition Support Team is required for HPN (see chapter on HPN nutrition support): it is important that patient, family and care giver as well as the general practitioner have had a good understanding of the “disease specific pathways” used in each case (1, 4). Monitoring has also to be adapted in timing for each patient. Using booklets and/or video tapes for educational purposes has the aim to get the patient’s participation to all aspects of care, and obtaining this goal reduces rate of complications (especially but not only catheter related) and improves quality of care, quality of life and economic outcomes (6, 10).
2. Fluid and electrolytes

Digestive balances of water/Na, especially for short bowel patients (SBS) type I with a high output stoma output, had to be carried on to evaluate needs (see corresponding Module 2.1 and Module 12.1).

Hydration should be enough to produce a urine output of more than 1L/d. Input, output records should be look at by patients during establishing initial balance and during attempt of weaning off HPN (3).

Chronic fatigue can be caused by chronic dehydration, hypokalemia, hypomagnesemia, the latter inducing refractory hypokalemia. Hypernatremia can be caused by poor control of oral fluid intake with dehydration, excess loss of hypoosmotic water through post duodenal remnant shorter than 1m (see the ESPEN chapter on SBS (65).

It is also important to measure enterostomy or high output fistulae - to know if there is discrepancy between expected output and observed output because such a gap should prompt to search for causes of excessive enteric losses well described in a recent review (3).

Refeeding syndrome (pseudo hyperthyroidism with hypophosphatemia and cardio pulmonary insufficiency) is beyond the scope of this review (1, 11, 12) mainly because HPN is usually conducted in “stable” patients after adjustment of PN requirements and when cyclic PN is feasible. Indeed cyclic PN is contraindicated in severely malnourished patients as well as in non controlled cardiac patients.

3. Overall complications and hyperglycemia

In a recent meta analysis, it has been shown that infectious complications, in clinical practice, are more frequent during PN than during enteral tube feeding nutrition (EN) (0.66; 95 confidence interval (CI) = 0.56, 0.79) independently of whether catheter sepsis was included in the analysis (13). Interestingly, the non infectious complications were found higher in EN (RR = 1.36; 95CI: 0.96, 1.83) than in PN. The higher risk of infection (Catheter and non catheter related) during PN may be partially explained by a higher incidence of hyperglycemia (4).

Then tight glucose control (14) might be a goal to achieve to decrease overall infectious complications during HPN, as demonstrated in the ICU setting (15). In our experience (personal unpublished data), glycemic control is easier to achieve in our HPN diabetes patients with fast insulin into the nutritive mixture (1 U/ 10 g of dextrose) than with usual SC insulin injections.

In any case, do not forget to use programmable pumps for appropriate down rates at the end of the cyclic nocturnal PN infusion to avoid rebound hypoglycemia. (6) The latter complication can be observed, even with down rates of infusions, when cyclic follows several weeks of continuous PN infusions. To avoid this problem, transition between continuous and cyclic should be made in one week; i.e., minus 2 h infusion per day from 24 h to 10 h of PN infusion.

4. Intestinal consequences of HPN

They are more related to CIF causes than to HPN per se. Changes following SBS had been reviewed elsewhere (see ESPEN Book). Bacterial translocation in humans has not been related to bowel rest only but to either gut occlusion or pseudo obstruction (4, 16). These patients benefit from sequential antibiotic treatment to decrease intestinal bacterial overgrowth. Contrary to most animal models, exclusive TPN, i.e., bowel rest, is associated neither with mucosal atrophy nor with intestinal immune dysfunction assessed through intestinal immunoglobulins (4).
5. Micronutrient deficiencies

They were recognised in the early years of long term HPN. Regular provision through commercial parenteral vitamin and trace metal preparations avoid these deficiencies (Zn, Cu, B1, B6, B12...) (Fig. 2), since these preparations brings 1.5 to 2 fold AMA IV allowances (3). Danger exists if there is a shortage of provision (check list of complete PN) or when patients went off HPN. When less than 5 cycles per week are used it is advisable to double vitamin preparation in each cycle.

Important fat malabsorption is almost constantly associated with ADEK deficiencies (3) (Fig. 3) and then appropriate oral supplements should be used. Fe deficiency developed in 36% of patients due to occult blood loss (18). In specific diseases leading to CIF, oral supplements are insufficient and parenteral supplements should be used, e.g. Vitamin E in chronic pseudo obstruction syndrome, especially with significant fat calorie intake (19).

In our experience, Cu deficiency may follow severe protein loosing enteropathy (extensive villous atrophy diseases or Waldman disease). Vitamins C, PP, B6 and other (Fig. 3, Fig. 4) may not be optimal with current allowances if HPN dependence is at its highest level, i.e., during periods of exclusive HPN. EFA deficiency on the n-6 series is frequently seen even with sufficient intake of usual fat emulsions (19, 20) implying perhaps larger use of fat emulsions enriched in the n-6 series at least in diseases having a propensity to inflammation. Blood testing of micronutrients should be limited to 2 to 3 times / year in stable long term patients (3).

The following rule should be kept in mind: a deficit in micronutrient is rarely single and excess(s) can be present with deficiencies masking each other.

---

### TRACE-METAL DEFICIENCIES during (H)PN

<table>
<thead>
<tr>
<th>Element</th>
<th>Deficiency</th>
<th>Presentation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Se</td>
<td>++</td>
<td>Cardiomyopathy / Heart Failure</td>
</tr>
<tr>
<td>Cr</td>
<td>-</td>
<td>Diabetes</td>
</tr>
<tr>
<td>Mo</td>
<td>?</td>
<td>Coma, ? Met, Uric acid</td>
</tr>
<tr>
<td>Mo</td>
<td>++</td>
<td>Anemia ± mild leucopenia</td>
</tr>
<tr>
<td>Zn</td>
<td>++</td>
<td>Acrodermatitis, diarrhea, hair loss, - NB</td>
</tr>
<tr>
<td>I</td>
<td>+</td>
<td>Goitre (nil po)</td>
</tr>
<tr>
<td>Fe</td>
<td>+</td>
<td>Liver thesaurismosis, Perl's</td>
</tr>
<tr>
<td>Al*</td>
<td>+</td>
<td>Porotic + painful osteopathy, blood, Ur</td>
</tr>
<tr>
<td>Mn*</td>
<td>+</td>
<td>Extrapyramidal syndrome</td>
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### Vitamin deficiencies during (H)PN

<table>
<thead>
<tr>
<th>Deficiency</th>
<th>Presentation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vitamin A</td>
<td>Night blindness, xerophamnna, dark field adaptation, defective bone mineralization</td>
</tr>
<tr>
<td>Vitamin E</td>
<td>In vitro plateled hyper-aggregation and H2O2-induced RBC hemoysis.</td>
</tr>
<tr>
<td>Vitamin D</td>
<td>Osteomalacia</td>
</tr>
<tr>
<td>Vitamin K</td>
<td>Bleeding tendencies, defective II, VII, IX, XII</td>
</tr>
<tr>
<td>Vitamin C</td>
<td>Scurvy, bleeding sore gums, peri joint and bone hemorrhages</td>
</tr>
</tbody>
</table>

---

**Fig. 2** *Excess and toxicity (chronic dehydration, renal insufficiency, cholestasis). (Chronic Zn deficit : altered growth in children with nanism)*

Mo 0.62±0.29 (Clin Chemistry, 1991, 47(2)279)  BM, 0093

**Fig. 3**

**Fig. 4**

**Fig. 6**
6. Trace element excess

Greater than needed micronutrients have a harmful effect, meaning apparent paradoxical propensity to increased peroxidation (21, 22). Thus, large doses of micronutrients should not be used routinely. Zn and Fe had been demonstrated to increase acute phase reaction response and should not be given during period of sepsis or inflammation, having the capability to aggravate both (22, 23). In chronic cholestasis, trace metals (Cu and Mg) may accumulate in the liver due to decreased choleresis: then decreasing or stopping those inputs is recommended (3).

Excess Mn accumulates in basal ganglia and can be responsible for parkinsonian-like symptoms in HPN patients (3, 24, 25). Reduction of Mn supply is followed by lengthy disappearance of abnormal (Hyper signal in weighed T1) magnetic resonance brain imaging (3) (Fig. 5). Al IV load was, in the past, higher than safe IV input (26): quality of glasses and interaction between glasses and trace metals, phosphorus or amino acids solutions to store these IV nutrients had been implicated in this thesaurismose (27). It is rarely seen at present times but patients with renal insufficiency are at risk. Al accumulates in brain, bone and liver where harmful effects had been demonstrated (26) especially in children (28) in which impairment of cognitive function had been reported (29).

7. HPN associated liver disease (HPNALD)

Comprehensive reviews had been recently published (2, 5, 30) including the one in the ESPEN-HPN Book (65). HPNALD led in the past two decades to liver failure in one every 5 adult patients on long-term HPN (31) being then responsible for either death or being put on a waiting list for combined liver-intestine transplantation (32).

Prevention of HPNALD is therefore of crucial importance from the first PN days, and the first PN regimen months have to be managed carefully in order to avoid chronic cholestasis; to 6-month duration. These facts plaid for management of these patients in centres expert in the whole spectrum of Intestinal failure therapy (32). Chronic cholestasis, if not turned off, led to HPNALD and then to severe liver disease: its natural clinical and histological evolution was recently published in 90 long-term HPN patients followed up with a median duration of 5 years (33).
After 2 years of HPN, glucose based-HPN was associated with macrovacuolar steato-hepatitis and severe liver disease in less than 25% of patients (34) whereas lipid based-HPN, i.e., ternary mixtures including standard LCT emulsions of more than 1g/Kg/d, was associated with portal inflammation, ductular abnormalities, microvacuolar steatosis and cholestatic severe liver disease in 50% of patients (33) (Fig. 6).

When liver function tests became abnormal, timing of occurrence of extensive fibrosis and liver failure can be accelerated within several months if high degree of PN dependence is maintained, i.e., poor oral intake and ongoing IV hyperalimentation (35, 36).

In HPN patients, jaundice with increased conjugated and unconjugated bilirubin, splenomegaly and thrombocytopenia, can be significantly associated with noticeable sea-blue histiocytes (activated macrophages CD 68+) infiltration of bone marrow without hemophagocytosis (37). This latter fate traduces accumulation of polyunsatured-fat (PUFA), coming from too high long term standard lipid delivery through ternary mixtures, in the reticulo-endothelial cells (35, 37). Microvacuolar steatosis, phospholipidosis (38), accumulation of phospholipids, polyunsaturated triacyl glycerol within hepatocytes and hyperplasia of macrophages, i.e., Kupffer cells in and around sinusoids or in or around portal areas (38, 39) need special staining to be revealed (Oil red O and Otan Baker+), and are especially seen when ternary nutritive mixtures are used. This fate explained why microsteatosis was not described with the use of IV fat infusions whereas hepatocyte macrosteatosis was easily demonstrated, e.g. with high glucose infusions.

(Long-term) HPN Associated liver disease: Main physiopathological components*

**Chronic Cholestasis**

<table>
<thead>
<tr>
<th>PN-dependent</th>
<th>Patient-dependent</th>
</tr>
</thead>
<tbody>
<tr>
<td>LCT (w6) emulsion: hepatocytes/macrophages</td>
<td>Excluded segment (s), bacterial translocation sepsis</td>
</tr>
<tr>
<td>Macrophages (Kupffer): decreased bacterial clearance</td>
<td>Very short bowel/no ileum</td>
</tr>
<tr>
<td>Deficit in tauro-Conjugates BS</td>
<td></td>
</tr>
</tbody>
</table>

**extensive fibrosis, cirrhosis**

*Hypernutrition per se and through imbalance between pro & antioxidant promoting peroxidation of various substrates, notably IV lipids. * BS = Biliary salts

**PN « TOXICITY » AND HEPATOPATHY**

<table>
<thead>
<tr>
<th>? EXCESS OF</th>
<th>? DEFICIENCY IN</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Vit. A*</td>
<td>• Selenium</td>
</tr>
<tr>
<td>• Cu.</td>
<td>• Vit. E *</td>
</tr>
<tr>
<td>• Fe*</td>
<td>• Sulfur AA (glutathion).</td>
</tr>
<tr>
<td>• Mn.</td>
<td>• Carnitine</td>
</tr>
<tr>
<td>• Alu*</td>
<td>• Choline*</td>
</tr>
<tr>
<td>• Phospholipids*</td>
<td></td>
</tr>
<tr>
<td>• P.U.F.A (soya)*</td>
<td></td>
</tr>
<tr>
<td>• Other micronutrients...</td>
<td></td>
</tr>
</tbody>
</table>

* Strong arguments for implication

(Long-term) HPN Associated liver disease

- **Best treatment : prevention through adapted IV**
  - « no hyperalimentation » with sufficient micronutrients
  - if « nonoromnutrition », no more than 33% of energy as lipids
  - IV soya lipids : Less than 1g / Kg /d (20 or 30%)
    - or 100 g / Wk to avoid EFA deficiency
  - IV Soya lipids = MCT/LCT. Structured : ? Olive oil: =
    - supplement PUFA with α-tocopherol (oral + IV)
- **Treat « contributive » patient’s covariates**
  - encourage enteral feeding as much as possible
  - avoid or treat sepsis
  - treat bacterial overgrowth
  - nourish excluded segments especially colon (SCFA)
  - decrease or stop some of the trace metals if cholestasis
- **Curative :** Ursodeoxycholate; hope with methyl donors / taurine enriched AA
Pathogenesis of HPNALD, yet not fully understood, is intricate and multifactorial (see HPN in ESPEN book, 65). Are involved: (a) patient-dependent factors, especially very short-bowel syndrome and an excluded colon and (b) nutrition factors, especially “intravenous hyperalimentation” or high soya rich PUFA triglycerides emulsion (more than 1 g/Kg/d) even without hyperalimentation (33). New lipids emulsions might be better tolerated (40) (Fig. 7).

Deficiency (Se, Vitamin E and C, choline, taurine…) and or excess (amino acids, Fe, Mn, Al, Vitamin A, phytosterols…) of nutrients may also contribute to liver disease during HPN (Fig. 8).

It is clear from clinical observation that more than one factor is, most of the time, needed to provoke this complication, suggesting a second hit physiopathology notably through sepsis whatever the origin, or intestinal bacterial translocation.

A schematic view of physiopathology is presented on (Fig. 7). Based upon this knowledge, preventive and curative treatments are summarised on (Fig. 9).

8. Gallbladder sludge and lithiasis

A schematic view of physiopathology is presented on. (Fig. 10) Comprehensive reviews had been recently published (3, 41).

Lack of enteral intake during exclusive HPN induces gallbladder stasis which is the main factor inducing gallbladder sludge (calcium bilirubinate and cholesterol crystals). The latter can disappear upon enteral CCK stimulation, or - if the causative factor persists evolve to lithiasis in weeks to months (42) (Fig. 11). Too long bowel rest with surgery is similarly a sludge provocation factor (3, 41).
In large series of long-term HPN patients, biliary lithiasis and/or sludge is observed during HPN in one third of patients and biliary complication rate (acute cholecystitis, angiocholitis, acute pancreatitis) occurred in 50% to 12% of positive patients (43, 44) (Fig. 12).

In early days, because high rate of morbidity / mortality was associated with biliary complications, a prophylactic cholecystectomy was recommended (43). Today, complications and their morbidity implicating that cholecystectomy, at the time of the initial surgery, is not warranted if the gallbladder is healthy (3, 44).

9. Renal function impairment

Serious progressive renal impairment may occur on long years in HPN patients (2, 45). Largely unexplained decline in the creatinine clearance was greater than the one seen in controls (45) (Fig. 13).

Nephrotoxic drugs, bacteremia / fungemia, high load in amino acid solution(s) explained 50% of the yearly 3.5% creatinine clearance decline in 33 adult patients followed up during a median of 8 years (Fig. 14).

Mineral water imbalances, chronic dehydration (diuresis should be more than 1 L/d), trace metal depositions, hyperoxaluria and or nephrolithiasis (up to 25% in type II and III SBS patients; i.e., those with large steatorrhea and presence of at least part of the colon in continuity) may contribute to the problem (3, 46).

It is therefore interesting to note that one experimental study has suggested that arginine deficiency was the cause of focal tubulointerstitial fibrosis in the kidney after massive small bowel resection in rats (47). The same group, reported a single case of a SBS boy, 3 years old on HPN, who received GH supplementation between 11 and 17 years and who had, at 20 years old, hyperuricemia and renal focal tubulointerstitial fibrosis (48). Huge orotic aciduria and significant decreases in uric acid and urea excretion had been described after few days on arginine free diet in four SBS patients (49).

These studies may have opened a window to a new metabolic complication. Indeed hypoargininemia can be seen in HPN SBS patients despite a normal oral diet including more with more than 5 g/d of oral arginine (50).

Serious Renal Impairment Is Associated With Long-Term Parenteral Nutrition

- 33 (13M, 20 W) adult 51 (21-79) y old
- on Long-term HPN: 8.3±4.4 yrs
- Protein load: 1.28± 0.32 g.Kg.d
- Nephrotoxic drug: 3.4±4.0% of all HPN days
- Bacteremia/fungemia: 2.3 (0.5±0.5 / y ) episode
- Cr clearance (CrCl) decline: 3.5±6.3% per year
  - age + 3 above factors: 50% change in CrCl
  - age + infection factor: idem
  - excessive urinary phosphate excretion (? aciduria)
  - but no association with amino acid content of TPN
  - this decline in renal function is largely unexplained

From L-A. Buchman; A. Mokarzel, M.-E. Ament et al. JPEN 1993;17: 438-444

Fig. 13

Fig. 14
10. Metabolic bone disease

Recent reviews have addressed this problem (2, 3). Only recently was studied, in two large cross sectional studies, the prevalence of low bone mineral density, a priori designed to make a diagnosis of osteoporosis (< 2.5 DS in T score, with comparison to sex paired peak bone Ca) (51, 52) (Fig. 15).

Osteoporosis was diagnosed in 41% and 67% of patients, bone pain in one third and fractures in 10% (51, 52). Same authors looked at the evolution of bone mineral density with DEXA during HPN of 1.5 and 5.5 yr duration respectively, in more than 50 patients each, showing, with no specific treatment, a modest but significant increase in lumbar spine (trabecular bone) and no significant change in the femoral neck (cortical bone of lower rate of remodelling than trabecular bone) (52, 53).

Thus, it can be suggested that HPN, in expert centres is not a causative factor for osteoporosis, but that low bone mineral density may either predate HPN in chronic intestinal diseases or be aggravated during the stormy period of acute intestinal failure with associated sepsis, inflammation and immobilisation (5, 52, 55). Bone loss has not been addressed in this latter PN condition.

Another caveat is that osteomalacia, a frequent fate in chronic malabsorptive diseases, is a cofounder of the mere presence of osteoporosis because its low rate of Ca deposit in the increased osteoid.

Establishing a normal vitamin D status is therefore of primary importance and a prerequisite before discussing specific treatment for osteoporosis (56, 57). Indeed, treatment of osteomalacia may enhance abruptly and dramatically the bone mineral content (58), more than modern treatments of osteoporosis with biphosphonates, natural GLP2 or recombinant low doses of PTH (59-62).

In addition, IV biphosphonates bring a higher risk, in CIF malabsorptive patients, of hypophosphatemia and hypocalcemia (61) meaning again optimal minerals and vitamin D status when prescribing such a treatment (Fig. 16).

Low BMI (51, 52) disease requiring corticosteroids (52) were found associated significantly with osteoporosis.
Younger age of CIF occurrence, before acquisition of the bone peak, brings higher risk for osteoporosis (52) (Fig. 17).

High HPN input in amino acids induced negative Ca balance through metabolic acidosis, a fact that can be negated with acetate infusion (2, 57). IV Ca should not be too important, given its negative feed back on PTH, a positive factor on bone remodelling. Hypocalcemia has a negative effect on bone through hyperparathyroidism (56). Many other factors modulate bone remodeling including vitamin K through Gla proteins (63). Finally, low remodeling is a poorly understood multifactorial metabolic disease (64). Based upon present knowledge, preventive and curative treatments are summarised on slide (Fig. 18).

To illustrate the results, we chose 3 ages equally spaced within the age-range of our patients, and we calculated the evolution, using the regression equation. As the duration of treatment decreased linearly with age, we did not extrapolate the evolution above the duration of follow-up. The negative evolution under HPN in young patients became positive with aging, and the change was reversed when the patients reached the age of 21. Similar evolutions were observed among patients with osteoporosis. However their Z-Scores were much lower (all values were reduced by 1.1 SD).

Fig. 17

**Metabolic bone disease & LT-HPN**

- **Osteomalacia**
  - Check vit D metabolites & Ca, P and Mg balance
- **Low remodeling bone**
  - *ibid* & reinforces Ca, Mg, Vit D metabolites orally
  - Avoid too much N & Ca IV (calciumia & lower PTH)
  - Check Al in Blood & in All-in-One (& in renal risk patients++)
  - Check DEXA & BMD at PN start & annually
  - Check bone markers : osteocalcin & cross lapa/deoxyxypyridinoline
- **Specific treatments of osteoporosis**
  - Bisphosnates* : positive moderate results at lumbar site,
  be careful with Ca & vit D status before treatment to avoid deficits
  - Near future : trophic factors (GLP2*) or rH-PTH**

Fig. 18

* Haderstev KV Scand J Gastroenterol 2002;  
** Khosla S. N Eng J Med. 2003 (editorial)

11. Summary

- HPN metabolic complications are still frequent but they can be significantly decreased through present knowledge, expertise and continued attention.
- Most of metabolic complications are multifactorial and interrelated.
- Nutrition support team, education and a complete, but non exclusive HPN adapted to the type of CIF is able to lower the rate of metabolic complications.
- Further understanding is needed especially in renal, bone and liver HPN associated complications to ameliorate preventive and curative treatments.
curative treatments are based upon present knowledge, expertise and continued attention. HPN metabolic complications are still frequent but they can be significantly decreased through present knowledge, expertise and continued attention.


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STUDY MANUAL

Educational Modules

Volume 1

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