Learning objectives:

- Learning about indications for HPN in adult patients;
- Learning about the outcomes of patients on HPN for both benign and malignant diseases;

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   1.5. What are the prognostic factors for HPN weaning?
   1.6. What are the outcomes?
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   1.8. Summary

2. Indications for and outcome of HPN in patients with cancer
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   2.3. What are the crucial issues to consider before starting HPN in a patient with an incurable cancer?
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Key messages:

- HPN is used worldwide in industrialized countries;
- HPN should be used in patients who cannot meet their nutritional requirements by oral and or enteral intake;
- For patients with benign diseases, the main indication is short bowel (80%);
- Incurable cancer patients may enter a HPN program but this is not recommended for those with a short life-expectancy;
- The overall 5-year survival for patients with benign diseases on HPN is about 75% depending on the underlying disease, age of the patient and gut anatomy;
- The survival of cancer patients on HPN depends on the severity of the malignant disease, staging and type. The median survival time is around 3 months.

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1. HPN in patients with benign diseases:

1.1. What is the global indication?

Long-term PN is indicated for patients with prolonged gastrointestinal tract failure that prevents the absorption of adequate nutrients to sustain life. As it is a life-saving therapy for patients with irreversible intestinal failure, it does not require evaluation of efficacy by randomized controlled trial. Its ability to maintain quality of life and promote rehabilitation supports the use of home treatment (1). Intestinal failure is defined as a condition with reduced intestinal absorption to the extent that macronutrient and/or water and electrolyte supplements are needed to maintain health and/or growth. Intestinal failure is severe when parenteral nutrition and/or additional parenteral electrolytes and water are required. The condition may be transient if gut function can be restored.

1.2. What are the most common underlying diseases?

The most common underlying diseases are inflammatory bowel disease, complications following surgery, mesenteric vascular disease, radiation enteritis, and chronic small bowel disease with severe malabsorption and dysmotility syndromes. As described 10 years ago, the underlying diseases of patients receiving HPN in 2011 remain varied across European countries (2) (Fig. 1). The number of patients with Crohn’s disease requiring HPN is decreasing due to better medical control of the inflammatory process (3).

<table>
<thead>
<tr>
<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>
</tr>
<tr>
<td>United Kingdom</td>
<td>72</td>
<td>44%</td>
<td>14%</td>
<td>5%</td>
<td>2%</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>
</tr>
<tr>
<td>Denmark</td>
<td>15</td>
<td>20%</td>
<td>13%</td>
<td>8%</td>
<td>26%</td>
<td>-</td>
</tr>
<tr>
<td>The Netherlands</td>
<td>45</td>
<td>13%</td>
<td>11%</td>
<td>60%</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Spain</td>
<td>31</td>
<td>16%</td>
<td>13%</td>
<td>39%</td>
<td>-</td>
<td>6%</td>
</tr>
<tr>
<td>Poland</td>
<td>14</td>
<td>14%</td>
<td>50%</td>
<td>-</td>
<td>14%</td>
<td>-</td>
</tr>
</tbody>
</table>

**Figure 1:** Underlying diseases of HPN patients in different European countries

1.3. What are the most common indications?

The indication for HPN in patients with chronic intestinal failure will typically be short bowel syndrome, fistula, bowel dysmotility or radiation enteropathy (Fig. 2).
1.4. What are the incidence and prevalence?

The incidence and prevalence of HPN varies across Europe, reflecting different organizational structures and treatment strategies. Reported data include HPN provided to patients with active cancer. The annual incidence for benign disease can be estimated to be about 4-6 per million; the prevalence ranges from 2 to 40 per million (4) (Table 1). Except in Poland, the use of HPN is still limited in the previous so-called Eastern European countries; this is mainly due to restricted financial backing.

**Table 1:** Registry of HPN patients in Spain

<table>
<thead>
<tr>
<th>Year</th>
<th>Number of registered patients</th>
<th>% age of patients with cancer</th>
<th>% age of patients with short bowel</th>
<th>% age of patients on HPN for more than 2 years</th>
</tr>
</thead>
<tbody>
<tr>
<td>2007</td>
<td>133</td>
<td>24%</td>
<td>43%</td>
<td>50%</td>
</tr>
<tr>
<td>2008</td>
<td>143</td>
<td>20%</td>
<td>44%</td>
<td>67%</td>
</tr>
<tr>
<td>2009</td>
<td>158</td>
<td>25%</td>
<td>42%</td>
<td>58%</td>
</tr>
</tbody>
</table>

Puiggros C et al, Nutr Hosp 2011, 26, 220-227

1.5. What are the prognostic factors for HPN weaning?

The gut anatomy, as well as its function, is important in determining the likelihood of weaning from HPN. Patients with short bowel may be considered in three main anatomical types: end-jejunostomy (type I, no colon in continuity), jejuno-colonic (type II, some part of the colon in continuity), and jejun-ileal (type III, the full colon in continuity). The minimal length of remnant small bowel required to wean patients off parenteral nutrition is around 100, 60, and 35 cm, respectively, but many patients with poorly functioning longer lengths are also dependent.
Patients with a preserved colon, as well as being less dependent on parenteral supply, generally have a better prognosis (5) (Fig. 3). Measuring the wet weight and energy absorption by balance studies provides objective measurements of intestinal function. The results will help to identify patients with irreversible intestinal failure, in contrast to those in whom dietary measures in combination with pharmacological manipulation may render the patients autonomous.

Plasma levels of post-absorptive citrulline, a non-essential amino acid not incorporated into peptides or proteins can be used as a biomarker of remaining functional enterocyte mass, a level of 20 being the approximate minimal concentration compatible with PN-free existence (6).

<table>
<thead>
<tr>
<th>Cut-off values of SB</th>
</tr>
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<tbody>
<tr>
<td><strong>lengths</strong></td>
</tr>
<tr>
<td>• End-enterostomy (I)</td>
</tr>
<tr>
<td>• Jejunocolonic (II)</td>
</tr>
<tr>
<td>• Jejunoileocolonic (III)</td>
</tr>
</tbody>
</table>

Figure 3. Short bowel syndrome. Parenteral nutrition-dependency

**1.6. What is the global outcome?**

Chronic intestinal failure may be associated with life-threatening complications, and the condition itself is highly disabling and impairs the quality of life. The basic goals of medical treatment are to maintain fluid, electrolyte, and nutrient balance and to minimize the risk of side effects. The overall 5 year survival for patients with benign disease on HPN is about 75% depending on the underlying disease, age of the patient and gut anatomy (7) (Fig. 4, 5). Patients usually succumb to their underlying disease rather than to complications of HPN (Fig. 6).

A 5-year survey of a cohort of patients on HPN recently confirmed that the survival rate for patients who were not candidates for intestinal transplantation reached 86% (8). For patients with chronic intestinal dysmotility disorders, the survival rate at 5 years is 78% (9).

In patients with benign diseases, the overall percentage of weaning from HPN is around 50% at 2 years (7); even if not so frequent we may expect recovery of intestinal autonomy after 2 years in some patients; this may be due to intestinal adaptation, colonic hyperfermentation with production of short chain fatty acids, hyperphagia and in some cases reconstructive surgery.

Besides survival and weaning the goals of HPN are to provide the best possible quality of life as well as social and professional rehabilitation (10-11).
Figure 4. Probability of survival for the 217 patients included in the HPN programs in France and Belgium between 1980 and 1989 (Messing et al, Gastroenterology 1995)

Figure 5. Five-year survival rates (Kaplan-Maier analysis) and causes of death on home paranteral nutrition (HPN) and after intestinal transplantation (ITx) in patients with irreversible intestinal failure. (A) Survival rate in non-candidates (■■■■), candidates with HPN-failure(···), candidates with high-risk underlying disease (---), candidates with high morbidity IF/low acceptance of HPN (−), ITx recipients (·−·). Non-candidates versus HPN-failure p<0.003, versus high-risk underlying disease p=0.631, versus high morbidity IF/low acceptance of HPN p=0.168, versus ITx recipients p<0.001); ITx recipients versus HPN-failure p=0.036, versus high-risk underlying disease p=0.003, versus high morbidity intestinal failure/low acceptance of HPN (p<0.001). (B) Causes of death. Non-candidates on HPN (total deaths 38): HPN-related(7), underlying disease-related(12), other causes related(17), unknown(2). Candidates on HPN (total deaths 25): HPN-related (13), underlying disease-related(6), other causes related(5), unknown(1). ITx recipients (total deaths 8): ITx recipients (8).

Pironi Le tal, Gut 2011
1.7. What are the mechanisms of adaptation?

With surgical reconstruction when feasible, from intestinal adaptation, from the future development of medical therapies (such as growth hormone and glucagon-like peptide-2-analogues) and with improvements in the outcome of small bowel transplantation, some HPN patients can eventually become nutritionally autonomous.

In case of short bowel, there are 3 mechanisms of adaptation:

1. Small intestinal adaptation
   Positive adaptive absorptive functions of nutrients such as amino acids, glucose, Na, Ca, cholesterol and vitamin B12 have been described in SBS. This adaptation develops over a period of 2-4 years.
   To date, morphological adaptation has not been clearly demonstrated in humans. The physiological adaptive process however must not be impaired either by the privation of intra-luminal nutrition or through protein malnutrition (1,12).

2. Colonic adaptation
   Modification in the gut flora composition and production of short chain fatty acids (butyrate, propionate, acetate) by the colonic bacteria may increase hydroelectrolyte absorption and increase colonic hyperfermentation of carbohydrates that allows an important increase in energy absorption (up to 1000 kcal/day) (13).

3. Hyperphagia
   More than 50% of the patients with a short gut are expected to become hyperphagic; that means that their oral intake is superior to 1.5 times their needs. Hyperphagia may occur within one year after the bowel resection (14). Patients with a residual colon are encouraged to eat carbohydrates to increase the production of short chain fatty acids. The mechanism of adaptive hyperphagia is unknown but probably related to digestive hormones (such as gastrin, leptin and ghrelin) (3).

1.8. Summary

Long-term PN is indicated for patients with prolonged gastrointestinal tract failure that prevents the absorption of adequate nutrients to sustain life. The most common underlying diseases are inflammatory bowel disease, complications following surgery, mesenteric vascular disease, radiation enteritis, and chronic small bowel disease with severe malabsorption and dysmotility syndromes. Short bowel syndrome is the indication in 80% of the patients.
The incidence and prevalence of HPN varies across Europe reflecting different organizational structures and treatment strategies. The gut anatomy as well as its function is important in determining the likelihood of subsequent weaning. The overall 5 year survival for patients with benign disease on HPN is about 75% depending on the underlying disease, age of the patient and gut anatomy. In the case of short bowel, there are 3 mechanisms of adaptation:
1. Small intestinal adaptation
2. Colonic adaptation
3. Hyperphagia

2. HPN in patients with cancer

2.1. What is the global indication?

Nutritional support (including HPN as necessary) for cancer patients is generally accepted in relation to malnutrition while the patient is receiving oncologic therapy, or if the patient suffers severe complications following chemotherapy, radiation therapy or surgery. In the incurable patient with cancer, the decision to embark on HPN is more a source of debate. While some clinicians will consider that medical care including nutritional support is justified through an increase in length of survival and quality of life, data to support this are often absent. Other caregivers may argue that patients will still die despite nutritional support even if small increments in life-expectancy can be obtained, and that measures such as HPN are inappropriately invasive (1,15).

2.2. What are the indications and criteria for patients with incurable cancer?

When considering which patients to include in an HPN programme, incurable patients in the final phases of life should normally be excluded. Incurable patients to whom no more (oncologic) treatment will be offered can logically be included in HPN programmes provided the clinical problem is under-nutrition or starvation rather than direct progression of the underlying malignant disease and that death is not imminent. The incurable cancer patient who is a candidate for HPN will typically have: little or no oral intake due to partial or complete obstruction of the gastrointestinal tract; relatively normal function of other vital organs; no severe, uncontrolled symptoms; and reasonable performance capacity (e.g. Karnofsky–Burchenal index >50) (16). In clinical practice patients characteristically chosen for HPN might be those with peritoneal carcinomatosis, and slow growing tumours such as ovarian carcinoma, retroperitoneal cancers, and some intra-abdominal recurrences (Fig. 7). Some patients with complete intestinal obstruction required the placement of a percutaneous endoscopic gastrostomy (rarely surgical) that is used for discharging the gastric stasis of liquids (17).
2.3. What are the crucial issues to consider before starting HPN in a patient with an incurable cancer?

(i) An estimate of life-expectancy. HPN should not be commenced if it is probable that the patient will soon succumb from the underlying disease rather than from poor nutritional status. However, the negative impact of low nutritional intake must also be taken into consideration.

(ii) Communication with the patient and his/her family to balance their expectations with the realistic outcomes to be expected from HPN.

(iii) Definition of the criteria for withholding and withdrawing the nutritional support if there is no effect (18). The decision to start HPN in a patient with an incurable cancer should be always taken on an individual basis by a multidisciplinary team. Advantages and potential discomfort should be clearly explained to the patient. Moreover the monitoring of the patient must be done integrating nutritional, medical (such as pain control), and psychological aspects. We should also consider the concept of “good death” as well as the issues that are important for the dying patient but which are not always perceived by the caregivers (19). Cultural, religious, social, and economical factors may also influence the decision but basic ethical issues should always be respected.

2.4. What is the global outcome in patients with advanced cancer?

The survival of cancer patients on HPN depends on the severity of the malignant disease, its staging and type. Median survival in several small series ranged from to 53 to 120 days, and is heavily dependent on selection criteria. The median survival of patients with incurable cancer was 140 days (20-783) amongst 68 patients who were treated in Israel (20) and 40 days for 60 patients who were followed in Belgium (17). In patients who survive for more than 3 months there is some evidence that the quality of life remains stable and fairly acceptable. The early addition of parenteral nutrition to patients with advanced cancer may improve survival and quality of life in some cases (21).

2.5. What are the requirements for patients with incurable cancer?

Nutritional requirements are similar to those of other patients on HPN other than those with large stomal losses. Some restriction of the intravenous water supply may be appropriate given an expansion of the extra-cellular fluid volume caused by cachexia.
Combined with sodium (and glucose) a water load can readily precipitate ascites in patients with peritoneal carcinomatosis. Other factors operating in cancer also influence water clearance negatively, and the total amount of fluid and sodium should probably not exceed 30 ml/kg per day and 1 mmol/kg per day, respectively. Thus in general more energy dense preparations with higher proportions of energy from fat emulsions may be considered a favourable choice for this patient group. When treatment continues for longer periods fat emulsions providing n-3 fats may be considered through extrapolation from the successful studies of oral supplements of n-3 fatty acids in cachectic cancer patients. All patients on HPN should received micronutrients.

2.6. Summary

The incurable cancer patient who is a candidate for HPN will typically have: little or no oral intake due to partial or complete obstruction of the gastrointestinal tract; relatively normal function of other vital organs; no severe, uncontrolled symptoms; and reasonable performance capacity (e.g. Karnofsky–Burchenal index >50). The decision to start HPN in a patient with an incurable cancer should be always taken on an individual basis by a multidisciplinary team. The survival of cancer patients on HPN depends on the severity of the malignant disease, its staging and type. The early addition of parenteral nutrition to patients with advanced cancer may improve survival and quality of life in some cases.

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