



# Nutrition:

## An important part of the treatment plan in surgical oncology

Gastrointestinal (GI) and head and neck cancer have a major impact on patients' nutritional status. Many patients with these cancers will require surgical intervention, which imposes further metabolic demands and compounds pre-existing nutritional disorders. Malnutrition is associated with higher chemotherapy-induced toxicity, poor treatment response, increased risk of postoperative complications, and decreased quality of life (QoL). Clinical studies show that specialized nutritional interventions help to reduce postoperative complications and healthcare costs. During the Nestlé Nutrition Institute satellite symposium, held in conjunction with the 33rd European Society for Clinical Nutrition and Metabolism (ESPEN) Annual Congress, international experts discussed the role of nutritional support and specific nutritional intervention – immunonutrition – in a surgical oncology treatment plan.

### Factors associated with PEG dependence in head and neck cancer



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Over the past decade, advancements in the treatment of head and neck cancer have resulted in maintenance of organ anatomy, increased tumor control, and increased survival; however, the risk of severe oral complications remains. In fact, dysphagia is one of the most serious and persistent complications associated with all treatments for head and neck cancer patients, particularly radiation therapy. Up to 40% of patients experience nutritional deficits or problems with oral intake at presentation, which is typical of late-stage disease, and 100% of patients experience varying degrees of difficulty during treatment.<sup>1</sup>

### Long-term PEG dependency can be debilitating

Percutaneous endoscopic gastrostomy (PEG) tubes are routinely placed in head and neck cancer patients, both prior to, and following, the onset of treatment in order to provide temporary nutritional support until adequate oral intake is achieved. Unfortunately, the resumption of oral intake after treatment does not occur in all patients, and dependence on feeding tubes has been defined as one of the most debilitating late toxicities associated with treatments for head and neck cancers. Emerging evidence indicates that while 77% of patients with head and neck cancer (n=154) will have their PEG tube removed within 1 year, long-term PEG tube dependence occurs in approximately 25% of patients.<sup>2</sup>

**“Dysphagia is a serious and persistent complication in patients with head and neck cancer.”**

In patients with head and neck cancer, the risk of PEG retention is influenced by patient-, tumor- and treatment-related characteristics. Of greatest importance are primary radiation therapy, marital and insurance status. Patients who live alone are four times more likely to retain their PEG tube.<sup>2</sup> However, to date, no study has investigated the important role that social support may play in long-term dependence on PEG tubes in head and neck cancer survivors.

The cancer-cachexia syndrome (eg, loss of appetite, reduced GI absorption, hormone-induced metabolic changes), anatomic location (larynx/hypopharynx primary site and pharyngeal tumors) tumor size and type are significant disease-related characteristics. Larger tumors (T4) can have a substantial effect on PEG tube retention.

Anticancer therapies also cause nutritional problems involving reduced caloric intake and increased metabolic stressors. The majority of patients with head and neck cancer will receive radiation with or without surgery or chemotherapy. Radiation therapy causes significant dysfunction that is typically late in onset and may be affected by treatment (eg, total radiation dose, fraction size, treatment technique) or functional changes (eg, xerostomia, fibrosis). PEG tube retention was six-fold higher in patients who had primary treatment with radiation therapy.<sup>2</sup>

## Postoperative infections are common in head and neck cancer

Treatment of head and neck cancer is complex and provides several opportunities for intervention and promotion of resumption of a normal diet. Nutritional intervention is particularly important in the perioperative period to reduce the incidence of nosocomial infections. A retrospective cohort analysis of patients with head and neck cancer reported a 31% incidence of site-specific postoperative infection and a 16-day increase in length of hospital stay.<sup>3</sup>

## Immunonutrition improves post-surgical outcomes

Several studies have evaluated the benefits of immunonutrition in patients with head and neck cancer. Immuno-enhanced enteral nutrition (EN) formula has been shown to decrease postoperative infections in patients undergoing head and neck cancer surgery.<sup>4,5</sup> In the largest of these studies, perioperative immunonutrition (Oral Impact®, Nestlé Health Science) in patients with head and neck cancer (n=261) significantly reduced postoperative infections compared with standard nutritional support (p=0.04).<sup>4</sup> Evidence also suggests that the timing of nutritional support may be important. Preoperative nutritional support given for 7 to 10 days reduces postoperative complications by 10% in malnourished patients with weight loss of ≥10%.<sup>6</sup>

Recommended supplementation protocols for chemoradiation and surgery are presented in Figure 1.

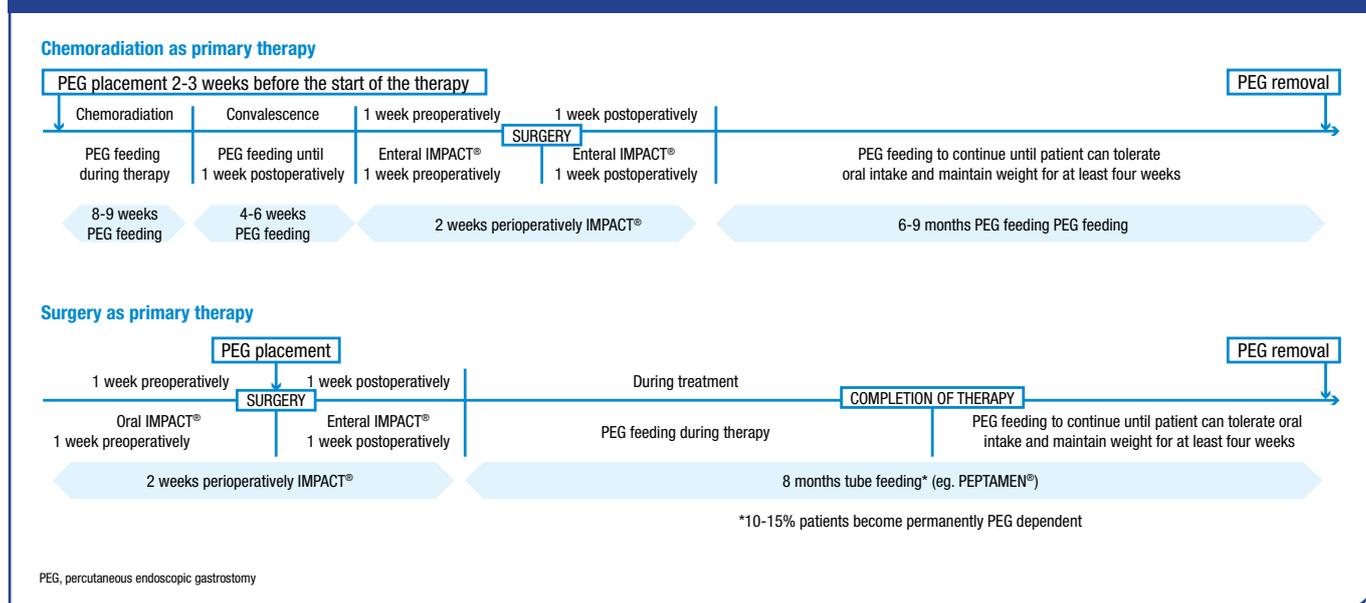
“Preoperative immunonutrition reduces postoperative complications.”

In conclusion, identification of patterns and correlates of long-term dependence on PEG-tube feeding following treatment for head and neck cancer is critical in developing interventions that may prevent or shorten long-term dependence on PEG-tubes in these patients. In patients with head and neck cancer, immunonutrition plays a beneficial role in improving post-surgical outcomes.

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Figure 1. A practical approach to nutritional support for head and neck cancer patients.



## Nutritional evaluation and morbidity in colorectal cancer surgery



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### Preoperative nutritional status is an indicator of surgical risk

Progress over the last decade has led to reduced morbidity and mortality after general surgery. However, despite these efforts, complication rates are still around 20 to 40% after abdominal surgery. Nutritional status is a major risk factor for determining patient outcomes in colorectal cancer surgery. In one study, 54% of patients with colon cancer experienced weight loss over a 6-month period.<sup>1</sup> There is substantial evidence that deterioration in a cancer patient's preoperative nutritional state adversely affects outcomes, reflected by increased mortality rates (Figure 2), increased complications and reduced QoL.<sup>1-4</sup>

Impaired nutritional status before major surgery is related to an increased incidence of nosocomial infections, longer duration of hospitalization, and higher mortality rates.<sup>1-4</sup> In general surgery patients, malnutrition was associated with an increased length of hospital stay (15 days;  $p < 0.01$ ) and a 25% increase in the complication rate ( $p < 0.01$ ).<sup>3</sup> In patients with colon cancer receiving chemotherapy, weight loss significantly reduced median survival by approximately 50% ( $p < 0.01$ ).<sup>1</sup>

Figure 2. Preoperative weight loss is a basic indicator of surgical risk.<sup>4</sup>

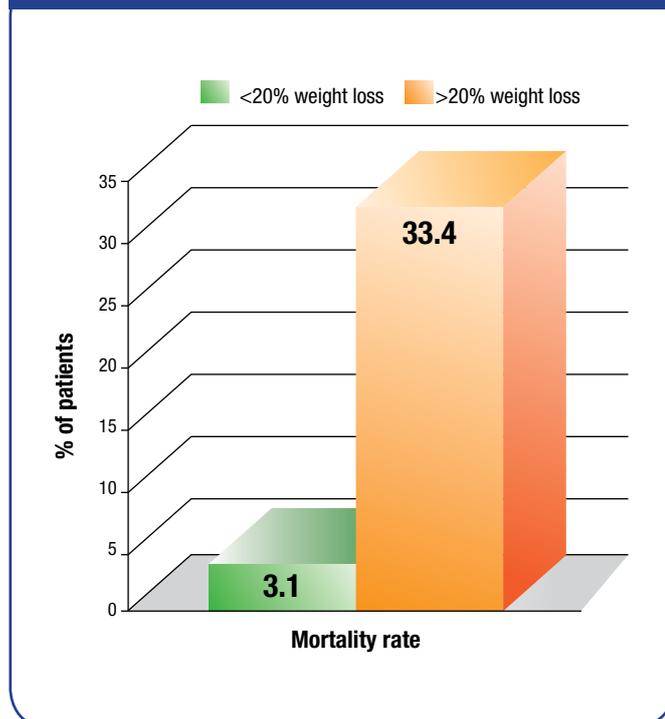
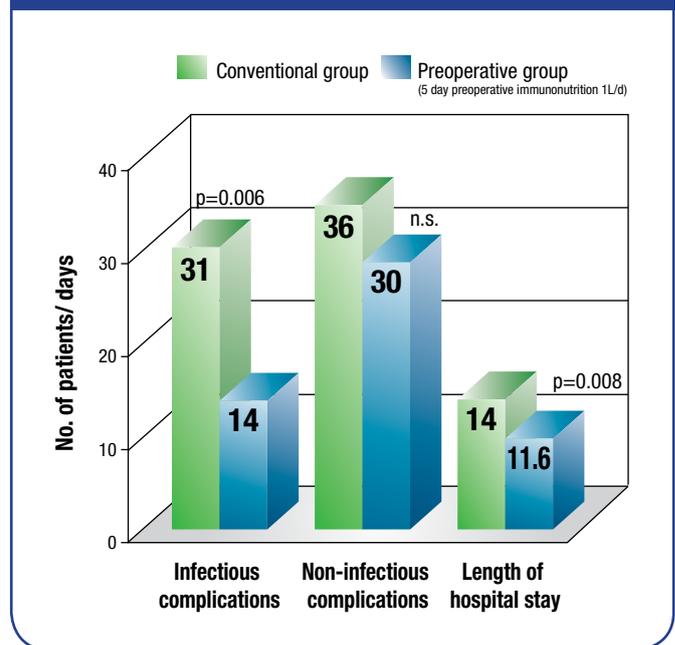


Figure 3. Incidence of infections following 5 days of preoperative immunonutrition in surgical cancer patients (n=204).<sup>11</sup>



### Minimizing postoperative complications is essential

These factors have economic implications for the healthcare system, both in terms of direct costs and costs related to the management of complications.<sup>5</sup> Therefore, minimizing the risk of potential complications in the preoperative phase is of great importance. The stress of surgery or trauma additionally increases protein and energy requirements by creating a hyper-metabolic, catabolic state. As a result, identifying and treating malnutrition in colorectal cancer patients prior to surgery is critical to achieve favorable patient outcomes.

## “Deterioration in preoperative nutritional state adversely affects patient outcomes”

### Careful preoperative screening of nutritional status is advised

Several comparisons between different nutritional screening instruments have been published but there is no consensus regarding the best instrument to predict outcome. Careful preoperative nutritional screening should include an evaluation of the nutritional status based on four variables – pathological weight loss, BMI, general condition and amount of food intake in the preceding week – and a determination of the level of stress of the underlying disease.<sup>6</sup> For this purpose, a simple, reliable, easily applied and reproducible scoring system, such as the Nutritional Risk Screening 2002 (NRS 2002) tool developed by the ESPEN working group, could be used.<sup>7</sup>

A recent study investigated whether implementation of NRS 2002 at hospital admission could predict mortality and complications after colorectal cancer surgery.<sup>8</sup> A total of 39% of patients were deemed to be

at nutritional risk, and based on the NRS, there was a significant difference in the rate of postoperative complications (62% vs 39.8%;  $p=0.004$ ). Nutritional risk was identified as an independent predictor of postoperative complications ( $p=0.002$ ).

## ESPEN recommend preoperative nutritional support

As malnutrition affects both the treatment and outcomes of patients with colorectal cancer perioperatively, timely intervention to assess and improve nutritional status has enormous importance. Enhanced patient recovery after surgery (ERAS) has become an important focus of perioperative management. The objective is to provide the best preoperative nutritional support for these patients, according to ESPEN evidence-based recommendations.<sup>9</sup>

Preoperative immunonutrition has been shown to improve outcomes in malnourished patients with cancer.<sup>10,11</sup> When compared with conventional therapy, 7 days of preoperative EN feeding, enriched with arginine,  $\omega$ -3 fatty acids and RNA, reduced the rate of major (12 vs 9 patients) and infectious complications (12 vs 8 patients) and the length of hospital stay (15.3 vs 13.2 days;  $p=0.001$ ) in patients with gastrointestinal cancer and  $\geq 10\%$  weight loss over a 6-month period.<sup>10</sup> Similar outcomes were reported in surgical patients with gastrointestinal cancer and with  $< 10\%$  weight loss over the preceding 6 months (Figure 3).<sup>11</sup> In these patients, preoperative immunonutrition was found to be cost-effective, reducing nutritional costs, complication costs and total costs per patient ( $p=0.04$ ).<sup>11</sup>

## “Preoperative immunonutrition reduced major and infectious complications in malnourished cancer patients.”

In conclusion, preoperative malnutrition is associated with increased postoperative morbidity and mortality. Preoperative nutritional support is beneficial in malnourished patients, and evidence demonstrates that preoperative immunonutrition improves outcomes in colorectal surgery.

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## Nutrition as part of the treatment plan in GI cancer surgery



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In patients with esophageal, gastric or pancreatic cancer, the prevalence of malnutrition following surgery is 20 to 50%.<sup>1</sup> A number of mechanisms are involved in the development of malnutrition including physical obstruction by the tumor, systemic effects of the tumor, and the impact of anticancer therapies – particularly those used in combination or in the preoperative setting. Malnutrition is a risk factor for decreased responsiveness to chemotherapy, increased toxicity and postoperative complications. Malnutrition is also an independent predictor of postoperative morbidity and mortality, leading to a longer duration of hospital stay and increased healthcare costs.

## “Malnutrition independently predicts postoperative morbidity and mortality.”

### Prevention of postoperative complications is a major issue

As rates of nosocomial infections continue to increase, the prevention of infection is a major surgical issue. Infectious surgical complications may be due to primary surgical pathology, the type and magnitude of the operation or relative immune suppression due to the surgical insult.

There is a growing trend for the use of neoadjuvant therapy, in the form of preoperative chemotherapy or radiation therapy, to improve surgical outcomes. However, neoadjuvant-related toxicities result in presurgical patients who are more malnourished and immunocompromised. There is a higher risk of postoperative complications among these patients. As a result, there has been increasing recognition of the importance of improving nutrition and immune status prior to surgery.

## “Improving nutrition and immune status is important in surgical cancer patients.”

### Nutritional support should be included in oncology treatment plans

All efforts should be directed towards including nutritional support in active oncology treatments. A meta-analysis ( $n=2,552$ ) suggests that early EN after elective GI surgery offers improved outcomes compared with parenteral nutrition (Table 1).<sup>2</sup> However, there is an increased risk of vomiting ( $p<0.001$ ).

Table 1. Enteral versus parenteral nutrition following GI surgery<sup>2</sup>

Patient outcome	Relative risk	P-value
Any complication	0.85	p=0.04
Any infectious complication	0.69	p=0.001
Anastomotic leak	0.67	p=0.03
Intra-abdominal abscess	0.63	p=0.03
Duration of hospital stay	–	p=0.02

Over the past few years, the standard EN has been modified to contain specific nutrients (eg, glutamine, arginine, polyunsaturated fatty acids, nucleotides, taurine, vitamin A, vitamin E, vitamin C) to develop **immunonutrition**. Immunonutrition has a number of benefits:

- Upregulation of host immune response
- Control of the inflammatory response
- Improvement of nitrogen balance and protein synthesis after injury.

In major randomized, controlled trials, preoperative immunonutrition has been shown to reduce the infection rate in elective surgery patients with GI cancer by approximately 50%.<sup>3-7</sup> In both well-nourished and malnourished patients, EN immunonutrition (eg, Oral Impact<sup>®</sup>, Enteral Impact<sup>®</sup> Nestlé Health Science) has been associated with a significant decrease in postoperative infectious morbidity (Figure 4),<sup>8</sup> reduced length of hospital stay<sup>9-15</sup> and lower healthcare costs compared with standard isocaloric and isoenergetic nutrition.<sup>4,16</sup>

### Early administration of enteral nutrition is beneficial

Traditionally, postsurgical feeding involved the use of nasogastric tubes and avoidance of oral fluid intake to prevent nausea and vomiting and protect anastomosis. However, early EN has been shown to improve tissue healing and reduce septic complications after GI surgery.<sup>17,18</sup> Evidence from a meta-analysis of 11 studies (n=837) demonstrated a lack of any clear advantage to keeping patients nil by mouth after elective GI surgery, and suggested that early oral feeding may be beneficial.<sup>18</sup> Initiation of EN within the first

24 hours versus standard regimens, significantly reduced infectious complications (RR=0.72; p=0.036), anastomotic leaks (RR=0.53), and the median duration of hospital stay (p=0.001). There were also non-significant reductions in wound infections, intra-abdominal abscess, pneumonia and mortality.<sup>18</sup> However, the risk of vomiting was increased among patients receiving early oral EN (p=0.046).

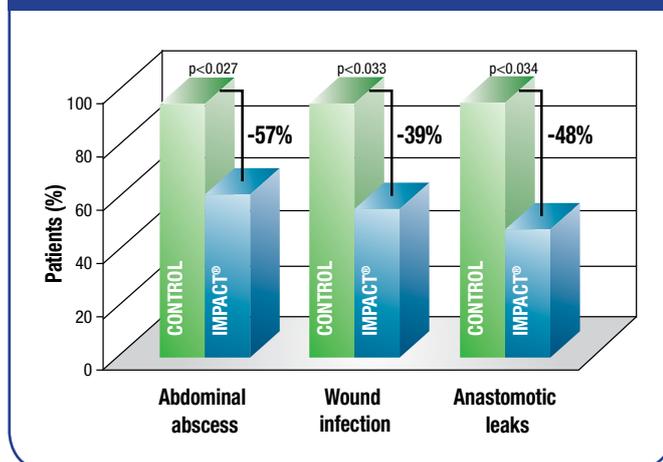
**“ESPEN recommend immune perioperative modulating formula irrespective of nutritional risk in patients undergoing major abdominal cancer surgery.”**

### Immunonutrition is recommended for GI cancer surgical patients

The French Society of Digestive Surgery recommends immunonutrition for 5 to 7 days in the preoperative setting, in all patients who will benefit from elective surgery for GI cancer.<sup>19</sup> During the postoperative period, immunonutrition needs to be continued in all malnourished patients for 7 days in the absence of postoperative complications or until patients can have an oral diet of at least 60% of their needs. In addition, progressive and early EN feeding, in the form of oral dietary supplements of energy and protein within the first 24 hours after surgery, is recommended.<sup>19</sup> These recommendations are similar to the ESPEN guidelines on EN nutrition which state that: immune modulating formula should be administered perioperatively independent of nutritional risk for patients undergoing major abdominal cancer surgery.<sup>20</sup>

In summary, early nutritional support should be included in oncology treatment plans for GI cancer surgical patients. Immunonutrition has been shown to reduce postoperative infectious complications and length of hospital stay, leading to substantial cost-savings. Immunonutrition should be initiated 5 to 7 days prior to elective surgery in both malnourished and well-nourished patients with GI cancer. The surgeon plays a key role in providing nutritional support as part of the therapeutic strategy for GI cancer patients.

Figure 4. Postsurgical infections are reduced with specialized nutritional support.<sup>8</sup>



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## The economic burden of diarrhea in GI cancer patients



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Progress in the development of adjuvant and palliative therapies for patients with cancer, has seen a progressive decline in mortality rates while the number of patients who are coping with chronic disease and the side effects of active treatments have simultaneously increased. GI discomfort is the most frequent of these side effects. In particular, diarrhea (defined as >3 unformed stools/day) is a common and significant clinical concern. It is among the most common GI symptoms in cancer patients both before and during treatment. These adverse effects compromise both the patient's QoL and their ability to derive further benefit from oncology treatments.<sup>1</sup>

**“Diarrhea is a common and significant clinical concern in patients with cancer.”**

### Cancer-related diarrhea is usually treatment related

The mechanisms of cancer-induced diarrhea are numerous but the major contributing factor is the direct effect of treatment on intestinal secretion or motility which can compromise the nutritional status of the patient. Fluoropyrimidines are the most common cause of chemotherapy-related diarrhea. Severe grade 3 and 4 diarrhea occurs in up to 50% of patients with colorectal cancer undergoing chemotherapy as adjunctive or palliative treatment.<sup>2</sup> Targeted therapy-related diarrhea also occurs with the epidermal growth factor receptor tyrosine kinase inhibitors; rates of diarrhea of up to 60% have been reported with erlotinib and gefitinib. Diarrhea may be more severe when these agents are administered in combination with chemotherapy. Radiation-induced diarrhea may be either acute, which usually has a spontaneous resolution, or chronic.

### Antidiarrheal treatments are not ideal

There are a number of therapeutic options for managing diarrhea in patients with GI cancer. The key issues are whether patients are able to receive ambulatory treatment or whether hospital admission is required. Standard antidiarrheal drugs which are relatively low cost include opioids, analgesics or spasmolytic drugs. However, in many patients, more potent and costly anti-secretory drugs, such as octreotide, are necessary. Ambulatory treatment may prove insufficient in very severe cases of diarrhea. Cancer-related diarrhea is a common cause of hospital readmission. In the most severe cases, intravenous rehydration is indicated and parenteral nutrition may also be needed.

## Chemotherapy-induced diarrhea represents a significant economic burden

The cost-benefit approach of cancer treatment has often focused on the impact of active therapy, with the increasing costs of modern therapies being weighed against the rate of survival or the length of disease-free survival. More recently, health economics has begun to address the issue of QoL and supportive care. Emerging data highlight the economic burden of severe chemotherapy-induced diarrhea.<sup>3-7</sup>

**“Nutritional strategies are needed to reduce the burden of diarrhea in patients with GI cancer.”**

In patients with colorectal cancer, grade 3/4 chemotherapy-induced diarrhea developed after the first cycle, with 54% of patients requiring a dose reduction of 20% and a dose delay of 7 days.<sup>5</sup> Approximately one-third of patients required hospital admission, and 25% experienced a recurrence of diarrhea. The mean cost per patient was \$2,559 Canadian dollars.<sup>5</sup> In a subset of patients, 58% experienced severe diarrhea requiring hospitalization after the first course of chemotherapy.<sup>6</sup> Severe diarrhea caused a reduction, change or discontinuation of chemotherapy in 9.5%, 15.9% and 34.2% of patients, respectively. The median length of hospital stay was 8 days, with a median of 3 days of intravenous rehydration. Parenteral support was required in 87% of patients (Table 2). The estimated cost per-patient due to severe diarrhea was \$8,230 Canadian dollars.<sup>6</sup>

Table 2. Supportive care administered in 63 patients admitted to hospital with chemotherapy-induced diarrhea<sup>6</sup>

Parameter	%
<i>Antidiarrheal medication</i>	
Oral antidiarrheals	58.7
Octreotide monotherapy	1.6
Octreotide + oral antidiarrheals	19
None	12.7
<i>Hospital admission</i>	100
Median length of stay (days)	8
Parenteral support	87.3
Median days of IV fluid (days)	3
IV/oral antibiotics administered	79

In conclusion, GI cancer-related diarrhea is frequent and often severe, generating high physical impairment and a significant economic burden. Early innovative nutritional and/or pharmacological strategies are needed to reduce the incidence and severity of this burden prior to the initiation of cancer treatment. The clinical evaluation of such preventative nutritional conditioning of the GI tract should include a cost-efficiency analysis.

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