In this issue

Cancer therapy-induced mucositis: Where are we now?

Clinical nutrition abstracts

Highlights of Critical Care Medicine Summer Conference
Feature article

Cancer therapy-induced mucositis: Where are we now?
Linda J Wedlake and Gayle Loader

Clinical nutrition abstracts

- Cancer
- Critical care
- Immunonutrition
- Inflammatory bowel disease
- Nutrition support
- Pancreatitis
- Pediatrics
- Pre- and probiotics
- Trauma and burns

Highlights of Critical Care Medicine Summer Conference
14–16 June 2007

Conference calendar
Introduction

Mucositis is a general term for the erythematous, erosive, inflammatory and ulcerative lesions that occur in the mucosal lining of the mouth, pharynx, esophagus and entire gastrointestinal tract secondary to cytotoxic treatment. Mucositis compromises cancer treatment and impacts healthcare costs through increased length of hospital stay, need for nutritional support and the requirement for pharmaceutical prescription. It can result in death, indirectly through severe malnutrition and attendant complications or directly due to sepsis.

The aims of this article are to: 1) highlight recent progress that has been made towards an improved understanding of the incidence, pathogenesis and measurement of cancer therapy-induced mucositis; 2) draw attention to new clinical guidelines for the management of cancer therapy-induced mucositis; and 3) examine the potential role of nutritional interventional strategies in the prevention and treatment of alimentary mucositis.

Mucositis: Definitions, incidence and impact

Oral mucositis has long been recognized as a common and potentially serious complication of cancer treatment. Inflammation and ulceration of the oral mucosa impairs the ability to swallow, eat and drink; thus, contributing to anorexia and weight loss. Breakdown of the oral mucosal barrier results in painful lesions and increased risk of oral and systemic infection. Gastrointestinal mucositis can occur in response to systemic chemotherapy or radiotherapy, and causes symptoms such as diarrhea, bloating, urgency, fecal incontinence and abdominal pain.

Historically, mucositis was characterized as oral or gastrointestinal, depending on its location. However, during the development of clinical guidelines for mucositis management, it was argued that this division was artificial since the gastrointestinal tract is one structure embryologically and, thus, mucositis can occur at any point with different manifestations being due to localized specialized differentiation required for specific function. New terminology subsequently emerged. ‘Alimentary mucositis’ became the preferred overarching term to describe inflammation of mucosal tissue resulting from cancer therapy that can arise at any point in the gastrointestinal tract from mouth to anus.

Deriving incidence data for mucositis is not straightforward. It is complicated by the different characteristics of the patient groups (eg, tumor type and site) and their treatment modality (eg, transplantation, chemotherapy, radiotherapy, combined regimens). Only recently has mucositis begun to be defined as a primary endpoint in clinical trials. In addition, procedures for assessing the severity of mucositis are rarely stated, making it difficult to judge the quality of the data.

Table 1 shows the reported incidence of mucositis in patients receiving cancer therapy. HSCT patients are at high risk of mucositis because of the particularly toxic nature of pretransplant conditioning regimens comprising high-dose chemotherapy and total body irradiation (TBI). In allograft patients, there is an additional risk of mucositis developing as a manifestation of graft-versus-host disease (GvHD). Thus, although only 4% of all reported mucositis occurs in transplant patients, its incidence in this patient group can reach 100%.

The high incidence of alimentary, lower gastrointestinal mucositis in pelvic radiotherapy settings is also striking, especially as it may be under-reported for the following reasons:

- The term gastrointestinal mucositis is not yet adopted in clinical practice. More commonly used terms are ‘gastrointestinal toxicity’ or radiation-induced ‘procitis’.
- Tangible evidence of gastrointestinal mucositis is only obtainable histologically via biopsy. Research into non-invasive markers of damage is underway but none are yet proven.
- Radiation-induced gastrointestinal mucositis is defined in terms of acute and chronic toxicity. This is because the severity of the acute inflammatory response predisposes to the
The severity of the late reaction – which can be severe or life-threatening.10,11

The economic burden of oral mucositis is considerable. Figures from the USA indicate a doubling of costs associated with caring for patients undergoing cancer therapy who develop oral mucositis versus those who do not.12 Specific costs include those associated with: 1) delayed or aborted treatment (in 35% of patients chemotherapy is delayed and in 30% discontinued); 2) nutritional support (87% of stem cell transplant patients require feeding tubes); 3) prescription of pharmaceutical preparations, including antibiotic therapy or opioid analgesics (80% of stem cell transplant patients receiving high-dose chemotherapy require opioid analgesia); and finally 4) increased hospital stay (in patients with solid tumors receiving myelosuppressive therapy, mucositis doubled the number of hospital days per cycle).2,12

In a report that examined peak Oral Mucositis Assessment Scale (OMAS: score range 0–5) scores and their relationship with economic outcomes in HSCT patients, a 1-point increase in peak OMAS score was associated with 1.0 additional day of fever (p < 0.01), a 2.1-fold increase in the risk of significant infection (p < 0.01), 2.7 additional days of total parenteral nutrition (p < 0.001), 2.6 additional days in hospital (p < 0.01), 2.6 additional days of injectable narcotic therapy (p < 0.0001), US$23,405 in additional hospital charges (p < 0.0001), and a 3.9-fold increase in 100-day mortality risk (p < 0.01).13 Furthermore, mean hospital charges were US$42,749 higher for patients with evidence of ulceration than those without ulceration (p = 0.06). Therefore, reducing the incidence and severity of oral mucositis may potentially improve clinical outcomes and reduce the economic burden associated with its treatment.

A further study, which evaluated the cost of illness in colorectal cancer patients hospitalized for severe chemotherapy-induced diarrhea, demonstrated that severe diarrhea developed after the first cycle of chemotherapy in 58% of patients.14 This contributed to a dose reduction (9.5% of patients), change (15.9%) or discontinuation (34.2%) of chemotherapy, a median length of hospital stay of 8 days, and a mean cost of Can$8,230 per patient. Determining potential risk factors and early identification may thus reduce the morbidity and costs associated with severe diarrhea in cancer patients.

The economic burden of radiotherapy-induced gastrointestinal mucositis has not been formally studied, but it is likely that the costs of chronic gastrointestinal damage and dysfunction are significant. As the number of long-term survivors of pelvic radiotherapy continues to grow (an estimated 300,000 patients are treated worldwide each year),15 the physical and social costs of late toxicity are becoming considerable.16

### Mechanisms and pathophysiology

The mechanisms that initiate and perpetuate mucositis are not fully elucidated. Importantly, the kinetics of mucositis in

<table>
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<tr>
<th>Table 1. Incidence of oral and gastrointestinal mucositis among cancer patients</th>
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<tbody>
<tr>
<td><strong>Incidence of oral mucositis</strong></td>
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<tr>
<td>Radiotherapy for head and neck cancer</td>
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<tr>
<td>Stem cell transplantation</td>
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<td>Solid tumors with myelosuppression</td>
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<tr>
<td><strong>Incidence of acute gastrointestinal mucositis in radiotherapy patients</strong></td>
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<tr>
<td>Adult patients (n=107) receiving radical pelvic radiotherapy over 5 weeks for tumors of a pelvic origin, including gynecological, urological and gastrointestinal tumors.</td>
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<tr>
<td><strong>Incidence of chronic gastrointestinal complications in radiotherapy patients</strong></td>
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<tr>
<td>Long-term follow-up of a mixed group of adult patients receiving radical pelvic radiotherapy for tumors of a gastrointestinal, anal, gynecological, prostate and urological origin.</td>
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QoL, quality of life
different areas of the gastrointestinal tract are probably very different, as are the clinical endpoints. Rapidly renewing stratified squamous mucosa predominates in the upper gastrointestinal tract, while columnar epithelium predominates in the lower tract with crypt and villus morphology. What is clear is that the development of mucositis is unlikely to be a simple linear process confined to the epithelium; rather it is a complex pan-tissue phenomenon involving multiple interacting pathways at all levels of the mucosa. This complex, pan-tissue mechanism involving mediators of gene transcription, amplification of intercellular signaling through pro-inflammatory cytokines and positive feedback loops forms the basis of Sonis’s recently proposed five-stage model of oral mucositis (Figure 1). A comprehensive model of the pathophysiology of gastrointestinal mucositis has yet to be formulated, although it is postulated that (as in oral mucositis) a complex interactive series of events are responsible. The effects of chemotherapy regimens are systemic, whereas radiotherapy has more local or loco-regional effects (i.e., side effects are clinically manifest in tissues and organs that have been irradiated). Chemotherapy-induced diarrhea occurs in up to 10% of patients treated for advanced cancers.

Functionally, both chemotherapy and pelvic radiotherapy affect rapidly dividing mucosal cells causing changes in villus/crypt morphology, possibly by interrupting the normal apoptotic (i.e., programmed cell death) cycles. The integrity of the tight intracellular junctions may be breached, thus increasing the risk of intestinal permeability. Damage to the intestinal villi coupled with rebound crypt hyperplasia (i.e., immature crypt cells reaching the villus tip) results in reduced absorptive capacity. Brush-border (disaccharide) enzymes can be adversely affected with resulting (transient) lactose intolerance. Reduction of absorptive surface area in the terminal ileum may result in bile salt malabsorption and thus diarrhea, and also in deficiency of vitamin B12 and folate. Bacterial overgrowth resulting from changing luminal pH conditions may cause bloating (through early and inappropriate fermentation of nutrients) and abdominal discomfort.

In pelvic radiotherapy (for malignancies of a gynecological, urological or gastrointestinal origin), the bowel remains an important dose-limiting organ. Acute damage to this structure can have serious long-term consequences. Explanations for radiation-induced damage to the gastrointestinal mucosa were originally based on a radiobiological model of direct cell killing, the so-called ‘target cell hypothesis’ in which depopulation and apoptosis of crucial cell populations resulted in functional deficiency. However, this model has been largely superseded by one in which radiation-induced mucosal damage is now seen as a complex (and iterative) injury process mediated by a variety of molecules including pro-inflammatory eicosanoid enzyme cyclo-oxygenase-2 (COX-2) and transcription factor nuclear factor (NF)-κB.

The inability to observe events directly within the gastrointestinal tract has meant that much research in this area has focused on tests of physiological function and potential surrogate markers of mucosal damage (see box). This search for early indicators of damage is at present confined to the research setting, but is ultimately aimed at identifying those patients who may be most at risk so that early interventions can be initiated to delay or dampen the inflammatory response. Longitudinal studies of patients receiving radical pelvic radiotherapy, in which biopsies of bowel mucosa have been obtained over the course of treatment, typically lasting 5–7 weeks, indicate that maximal inflammation occurs within the first 2 weeks of starting radiotherapy treatment. This is in contrast to symptoms, which are most severe towards the end of treatment.

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**Figure 1. Five-stage model of pathogenesis of oral mucositis**

- **Initiation**: Activation of reactive oxygen species (ROS), clonogenic cell death, stimulation of transcription factor (NF-κB), up-regulation of cytokines: TNF-α, IL-1β, IL-6, increased expression of adhesion molecules.
- **Up-regulation of messenger signals**: Activation of COX-2 pathways and consequent angiogenesis.
- **Signaling and amplification**: Activation of pathways causing tissue injury, initiation of stimulation of ceramide and caspase pathways by TNF-α. Further production of pro-inflammatory cytokines IL-1β and IL-6.
- **Ulceration**: Initiation of feedback loops and signal amplification leading to prolonged tissue injury.
- **Healing**: Most markedly symptomatic phase with destruction of basal epithelial cells and breakdown of oral mucosa. Ulcerative lesions become focal for bacterial invasion. Secondary infection is common. High risk of sepsis in neutropenic patients.

**Based on Sonis et al. (2005)**

COX-2: cyclo-oxygenase-2; IL-1β: interleukin-1β; TNF-α: tumor necrosis factor-α; NF-κB: nuclear factor-κB.
Clinical assessment and measurement of mucositis

In research and care settings, the importance of being able to accurately describe, classify and measure the severity of mucositis cannot be overestimated. Thus, scoring systems for mucositis must be objective, comprehensive and validated (ie, have construct and content validity). They must also be reproducible, which implies that adequate (operator) training is a necessary precursor. Unfortunately, no single scale meets all these criteria or is accepted universally.

The value of adequate training has recently been demonstrated in the Prospective Oral Mucositis Audit (POMA) of 200 hematology patients attending transplant centers across Europe, in which the duration of severe oral mucositis (World Health Organization [WHO] grade 3 or 4, see Table 2) was a primary endpoint. The results of this audit (in publication) have indicated the value of a ‘train the trainer approach’ in standardizing the assessment and scoring of oral mucositis.

The WHO and National Cancer Institute – Common Toxicity Criteria (NCI-CTC) oral mucositis scoring tools remain the most widely used scales in current practice, with an estimated 38% of studies using the WHO scale and 43% the NCI scale. The Radiation Therapy Oncology Group (RTOG) tool employs a similar five-stage scale and is used to assess the severity of radiation-induced gastrointestinal symptoms. Its lack of sensitivity has been challenged in comparison with other scoring tools for assessing both acute and late symptoms; however, its widespread use in oncology settings allows for retrospective comparison of toxicity findings between studies.

Updated guidelines were published in 2007. Major changes included a recommendation (level 1, grade A) for the use of keratinocyte growth factor-1 (KGF-1) Kepivance (Amgen) for the prevention of oral mucositis in HSCT patients and a recommendation against the use of systemic (ie, parenterally administered) glutamine. Transient lactose intolerance and the presence of bacterial pathogens were recognized as complications in patients with gastrointestinal mucositis.

These guidelines represent a major step forward in our understanding of mucositis and they will undoubtedly inform future research. However, clinical uptake of the guidelines is not encouraging. A recent survey found that only a small percentage of practitioners had actually heard of the guidelines and a ‘disappointingly low percentage had put them into practice’, thus highlighting the need for more effective dissemination and promulgation in the future.

### Table 2. World Health Organization scale for assessment of oral mucositis

<table>
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<tr>
<th>Code</th>
<th>Description</th>
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<tr>
<td>0</td>
<td>None</td>
</tr>
<tr>
<td>1</td>
<td>Soreness and erythema</td>
</tr>
<tr>
<td>2</td>
<td>Erythema, Ulcers, Patient can swallow solid diet</td>
</tr>
<tr>
<td>3</td>
<td>Ulcers, Extensive erythema, Patient cannot swallow solid diet</td>
</tr>
<tr>
<td>4</td>
<td>Mucositis to extent that alimentation not possible</td>
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From reference 27
Mucositis: A role for nutritional intervention?

It is impossible within the scope of this article to provide a comprehensive review of all nutritional interventional studies relating to the prevention and treatment of mucositis. Three promising areas of research are outlined.

a) Dietary manipulation in patients treated with radiotherapy for pelvic malignancy

In patients receiving radiotherapy and chemo-radiotherapy for pelvic malignancies, malnutrition or frank weight loss is not common. Nutritional intervention in this group has therefore been directed towards preventing acute gastrointestinal mucositis and thus chronic complications. A recent review of nutritional interventions in pelvic radiotherapy patients (n = 2,646) concluded that low-fat diets, medium-chain triglycerides (MCTs), probiotics and elemental diets were worthy of further investigation.36

Since 2002 the authors’ research group, under the direction of a consultant gastroenterologist who specializes in pelvic radiation disease, has been investigating the role of simple nutritional interventions in protecting the bowel from acute and consequential long-term radiation-induced damage.37 The use of non-invasive biological markers of gastrointestinal damage and their correlation with symptom scores is also being investigated.38

On the basis of earlier compelling animal research, which had shown the potential of elemental formulas to reduce pancreatic and biliary secretions, both of which may be pro-irritant in the irradiated gut, a series of studies focusing on the role of elemental formula in patients receiving pelvic radiotherapy treatment was commenced.

Results of initial palatability39 and tolerability studies40 were encouraging (Figure 2), although the number of patients managing to consume an elemental diet throughout their treatment period fell from 92% at week 1 to 46% at week 5 (Figure 3).40

A randomized controlled trial was subsequently performed in 50 patients, with elemental formula (composition: 35% fat, of which 35% was MCTs) replacing one third of normal caloric intake. Although median intakes of elemental formula remained relatively stable during treatment, no benefit was demonstrated compared with a control group. In future studies, a 100% replacement of normal diet with very low fat elemental formula ($\leq$5% fat) may be required. Only four other clinical studies in humans using elemental interventions have been undertaken,41-44 two of which showed a benefit.41,42 In these studies, the composition and delivery point of the intervention differed, as did its contribution to daily caloric intake.

Two studies have claimed efficacy for low-fat regimens (20–40 g fat/day) in reducing treatment-induced diarrhea;45,46 however, both studies were confounded by additional manipulations, namely MCT supplementation45 and lactose restriction.46 The authors are currently investigating the (independent) contribution of low- and MCT-supplemented diets on gastrointestinal symptoms during radiotherapy. Probiotic supplementation, using a preparation containing 450 billion/g mixed viable lyophilized bacteria (lactobacillus, bifidobacteria and streptococcal strains) has recently been shown to be effective in preventing radiation-induced diarrhea in patients (n = 490) undergoing postoperative pelvic radiation therapy.47
The role of fiber continues to remain controversial, with a complete lack of evidence to support either low (<10 g/d) or high (>20 g/d) fiber manipulation during radiotherapy treatment. In the near future, the authors’ group, in collaboration with King’s College, London, plans a large randomized controlled trial to investigate the effect of high- and low-fiber dietary interventions in this patient group.

b) Novel oral supplements in chemotherapy and radiotherapy settings: Glutamine and TGF-β

The role of glutamine in the prevention of chemo- and radiotherapy-induced toxicity continues to evolve. Glutamine is a conditionally essential amino acid with multiple well-defined functions in human biologic processes. In addition to its role in regulating intracellular redox potential (as a precursor to glutathione), glutamine may reduce the production of pro-inflammatory cytokines and cytokine-related apoptosis.

Cytotoxic chemotherapy increases cellular glutamine demand such that it may become conditionally essential. Externally provided glutamine may thus be beneficial. Table 3 summarizes recent research regarding the administration of oral glutamine for the prevention of mucositis in various cancer therapy settings.29,30,49-57

Casein, a protein found in dairy products, is a rich source of transforming growth factor beta (TGF-β). TGF-β (which exists in three isoforms) can be classified as both a cytokine and a growth factor and is involved in the regulation of a number of processes, including cell cycle control and wound healing. Casein-containing nutritional supplements, rich in TGF-β, have been shown to be effective in the

<table>
<thead>
<tr>
<th>Reference</th>
<th>Intervention</th>
<th>Patient group / cancer site</th>
<th>Key findings</th>
</tr>
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<tbody>
<tr>
<td>Galvez E (2001)</td>
<td>16 g oral glutamine / day</td>
<td>70 patients receiving chemotherapy for colorectal cancer</td>
<td>Incidence of diarrhea and use of loperamide reduced in glutamine arm</td>
</tr>
<tr>
<td>Yoshida S (1999)</td>
<td>30 g oral glutamine / day</td>
<td>50 patients with locally advanced esophageal cancer receiving chemotherapy</td>
<td>Reduced lymphocytic counts in glutamine arm</td>
</tr>
<tr>
<td>Aquino VM (2009)</td>
<td>8 g oral glutamine / day</td>
<td>120 pediatric patients undergoing HSCT</td>
<td>Reduced use of morphine in glutamine arm</td>
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<tr>
<td>Huang EY (2001)</td>
<td>Oral glutamine suspension</td>
<td>117 head and neck cancer patients receiving radiotherapy</td>
<td>Reduced duration of oral mucositis ≥ grade 1, 2 or 3 in glutamine arm</td>
</tr>
<tr>
<td>Anderson PM (1998)</td>
<td>Oral glutamine suspension</td>
<td>24 adult and pediatric patients with sarcoma undergoing chemotherapy</td>
<td>Reduced duration of mucositis in glutamine arm</td>
</tr>
<tr>
<td>Anderson PM (1998)</td>
<td>Oral glutamine suspension</td>
<td>193 BMT patients comprising a mixed donor group (ie, allograft, autograft and matched sibling donors)</td>
<td>Reduced duration and severity of mucositis and reduced use of morphine in autologous patients in glutamine arm</td>
</tr>
<tr>
<td>Peterson DE (2007)</td>
<td>Saforis oral glutamine suspension</td>
<td>326 patients with ≥ grade 2 oral mucositis (WHO scale) receiving chemotherapy for breast cancer in cross-over study design</td>
<td>Reduced incidence of severe mucositis in Saforis arm</td>
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Key findings

<table>
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<tr>
<th>Studies demonstrating a beneficial effect of oral glutamine on mucositis</th>
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<tr>
<td>Patient group / cancer site</td>
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<tr>
<td>129 patients receiving pelvic radiotherapy</td>
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<tr>
<td>28 patients with advanced metastatic gastrointestinal cancer receiving chemotherapy</td>
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<tr>
<td>134 patients receiving chemotherapy</td>
</tr>
<tr>
<td>65 patients with advanced breast cancer receiving chemotherapy</td>
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TGF-β, transforming growth factor beta; WHO, World Health Organization; BMT, bone marrow transplant; HSCT, hematopoietic stem cell transplant; TPN, total parenteral nutrition; WHO, World Health Organization.
induction of remission in Crohn’s disease in humans69, possibly through a direct effect on reducing mucosal inflammation.69 In animal models, TGF-β-enriched feeds have been shown to be protective against intestinal inflammation.69,70

The therapeutic efficacy of TGF-β in the prevention and treatment of mucositis has yet to be fully evaluated in the clinical setting. Research in this area must include definitive studies to allay fears that this interesting polypeptide has dual tumor suppressive and oncogenic effects.62

c) Nutritional management in HSCT patients at high risk of mucositis

Mucositis is one of the most significant side effects of treatment for patients undergoing HSCT, particularly for those receiving TBI as part of their conditioning regimen, impacting on ability to eat, drink, swallow or talk, and increasing the use of opioid analgesics.63 However, this group of patients often have a highly complex condition, with a number of side effects such as decreased appetite, xerostomia, nausea, vomiting, taste changes, lethargy and diarrhea63–69 all impacting on nutritional status; these symptoms often relating to the degree of mucositis experienced. In clinical practice, the management of these patients is highly challenging. Nutritional interventions can vary both between and within centers largely due to a poor evidence base for interventions. Traditionally, parenteral nutrition has been the focus of research in this area; however, in recent years this has shifted because of the considerable disadvantages associated with this form of nutrition support including increased risk of central venous catheter-related infection,66 increased potential side effects, on reaching stage 4 mucositis (WHO classification) parenteral nutrition remains the only means of nutritional support, and thus continues to have a valid and important role for patients undergoing HSCT, helping to prevent malnutrition.66

While enteral nutrition is now routinely used in transplant centers throughout the United Kingdom, little research has been published on the use of enteral nutrition in the adult setting. It is suggested that enteral nutrition is a safe and effective method of feeding following allogeneic transplantation;67 although further randomized studies are needed in this area. Perhaps key to the use of enteral nutrition in this setting is the timing of introduction of the feeding tube and commencement of feeding,68 as following the development of alimentary mucositis it can become very difficult for patients to tolerate the insertion of a feeding tube. It can also be very difficult to assess the side effects of feeding compared with the side effects of treatment and thus to determine the tolerance to feeding.

Much of the work in the pediatric setting has focused on the use of elemental nutrition70 with the hypothesis that in patients with alimentary mucositis it may be easier to absorb an elemental formula; this may be relevant in the adult setting and is a useful consideration for developing feeding regimens in the clinical setting. Another approach to increasing tolerance of enteral nutrition in this setting has been the use of nasojejunal feeding, with the aim of reducing vomiting associated with enteral formulas.71 Whatever approach is used, it is clear that there must be strong multidisciplinary working to ensure maximum symptom control and thus increased ability to tolerate and continue enteral nutrition.

Certainly, it is possible to hypothesize from the limited research in this area that enteral nutrition is a feasible option in patients with mucositis following HSCT.72 Indeed, it may also be advantageous to continue some degree of enteral nutrition.73 With the current level of knowledge in the clinical setting, it appears the most appropriate approach would be to combine oral, enteral and parenteral nutrition based on individual need rather than using a ‘one size fits all’ approach. In this way, patients’ individual nutritional status, oral intake and clinical condition can be used to identify the most suitable feeding regimen taking into account individual wishes and beliefs.

Conclusions

Reducing the incidence and improving the treatment and management of cancer therapy-induced mucositis could lead to substantial financial and quality-of-life gains. The development of clinical management guidelines for mucositis represents a major advance. Not only have they prompted an improved understanding of the condition itself, but also they have highlighted the need for more robust research together with improved scoring and assessment. The need for clearer research direction and improved research tools is critical, and timely, given the wide array of new target molecules at which novel preventative strategies may be directed.

The new terminology ‘alimentary mucositis’ encourages a more holistic view of the condition and demands that effective research encompasses a range of clinical disciplines spanning oncology, gastroenterology, nutritional research, radiotherapy and chemotherapy. Such truly effective cross-discipline research cannot be achieved without mutual respect, open dialog and discussion, improved understanding of the knowledge base and, of course, adequate funding. Encouragingly, there is evidence to suggest that specific nutritional substrates (ie, oral glutamine) can confer benefit in the prevention of mucositis in discrete patient groups. However, the weight of evidence is not yet sufficient to merit its inclusion in clinical guidelines. Appropriate nutritional management has long been a critical aspect of cancer care and may yet emerge as a key therapy in the prevention and treatment of both oral and gastrointestinal mucositis.
References


Severe mucositis: How can nutrition help?  
Kerth GM, Ruskin G, D’Onofrio L, Gibson RJ.  
Royal Adelaide Hospital Cancer Centre, Royal Adelaide Hospital, Discipline of Medicine, Faculty of Health Sciences, University of Adelaide, Adelaide, South Australia, Australia.

PURPOSE OF REVIEW: To review the recent evidence on the effect of nutrition on the incidence and severity of mucositis following anticancer treatment. RECENT FINDINGS: There have been many recent publications on mucositis and on nutrition in cancer, but very few on nutrition and mucositis in cancer. It is difficult to establish a definite link between nutritional status, nutritional interventions and mucositis. Malnutrition is probably a risk factor for mucositis, however, and some of the interventions that improve nutrition in cancer patients and reduce the risk of cancer in the general population work via mechanisms that might positively affect the development and course of mucositis. Whilst it can be tempting to extrapolate these findings to suggest that nutritional support can reduce the incidence and severity of mucositis, this would be premature. SUMMARY: There may well be a link between nutritional status, nutritional supplementation, anticancer treatment and mucositis, but it is not yet proven; mechanism-based, prospective, randomized studies are required to answer the question. This is likely to be an area of increased study in the future.

Postoperative complications in gastrointestinal cancer patients: The joint role of the nutritional status and the nutritional support  
Clin Nutr 2007 Jul 31; [Epub ahead of print].  
Bozzetti F, Gianotti L, Braga M, Di Carlo V, Moriani L.  
Department of Surgery, Hospital of Prato, Prato, Italy.

BACKGROUND AND AIMS: This study investigated the effects of nutritional support on postoperative complications, in relation with demographic and nutritional factors, intraoperative factors, type and routes of nutritional regimens. METHODS: A series of 1,410 subjects underwent major abdominal surgery for gastrointestinal cancer and received various types of nutritional support: standard intravenous fluids (SIF; n = 149), enteral nutrition (EN; n = 368), enteral nutrition (TPN; n = 386), enteral nutrition (EN; n = 393), and immune-enhancing enteral nutrition (IEEN; n = 500). Postoperative complications, considered as major (if lethal or requiring re-operation, or transfer to intensive care unit), or otherwise minor, were recorded. RESULTS: Major and minor complications occurred in 101 (7.2%) and 446 (31.6%) patients, respectively. Factors correlated with postoperative complications at multivariate analysis were pancreatic surgery, (p < 0.001), advanced age (p = 0.002), weight loss (p = 0.019), low serum albumin (p = 0.019) and nutritional support (p = 0.001). Nutritional support reduced morbidity versus SIF with an increasing protective effect of TPN, EN and IEEN. This effect remained valid regardless the severity of risk factors identified at the multivariate analysis and it was more evident by considering infectious complications only. CONCLUSIONS: Pancreatic surgery, advanced age, weight loss and low serum albumin are independent risk factors for the onset of postoperative complications. Nutritional support, particularly IEEN, significantly reduced postoperative morbidity.

Mechanisms underlying feed intolerance in the critically ill: Implications for treatment  
Deane A, Chapman MJ, Fraser RJ, Bryant LR, Burggraaf I, Nguyen HO.  
Intensive Care Unit, Royal Adelaide Hospital, Adelaide, Australia.

Malnutrition is associated with poor outcomes in critically ill patients. Although nutritional support is yet to be proven to improve mortality in non-malnourished critically ill patients, early enteral feeding is considered best practice. However, enteral feeding is often limited by delayed gastric emptying. The best method to clinically identify delayed gastric emptying and feed intolerance is unclear. Gastric residual volume (GRV) measured at the bedside is widely used as a surrogate marker for gastric emptying, but the value of GRV measurement has recently been disputed. While the mechanisms underlying delayed gastric emptying require further investigation, recent research has given a better appreciation of the pathophysiology. A number of pharmacological strategies are available to improve the success of feeding. Recent data suggest a combination of intravenous metoclopramide and erythromycin to be the most successful treatment, but novel drug therapies should be explored. Simpler methods to access the duodenum and more distal small bowel for feed delivery are also under investigation. This review summarizes current understanding of the factors responsible for, and mechanisms underlying, feed intolerance in critical illness, together with the evidence for current practices. Areas requiring further research are also highlighted.
Protein and the critically ill: Do we know what to give?


Stroud M.
Institute of Human Nutrition, University of Southampton, Southampton General Hospital, Southampton, United Kingdom.

The National Institute for Health and Clinical Excellence (NICE) has recommended that nutrition support in seriously ill or injured patients should start at ≥50% of the estimated target energy and protein needs.

This recommendation has caused some concern, since taking the NICE approach leads to these sick individuals receiving an initial N provision of only 0.12 g N/kg per d, as opposed to levels of approximately 0.25 g N/kg per d that have been widely recommended by other expert groups. The basis of the recommendation for lower levels of N provision is that feeding at levels of 0.25 g N/kg per d reduces the inevitable net N loss of catabolism and hence minimizes overall lean tissue wasting. However, although it has always been assumed that better N balance must equate with better outcome, there are teleological arguments that question the wisdom of providing more N to sicker patients and studies that imply that best N balance might not equate with best clinical progress. Furthermore, current evidence suggests that in most critical illness low initial intakes of both energy and N lead to improved survival. It therefore seems logical to aim, in the first instance, to feed the seriously ill at only modest levels. Further research is required to determine whether lower-energy, higher-N feeding would prove better or worse than this approach in terms of clinical benefit rather than just better N retention. Investigations to explore the use of feeds that are specifically designed to match the amino acid needs of illness are also required.

Prospective randomized control trial of intermittent versus continuous gastric feeds for critically ill trauma patients


Nicolaidis JR, Letton J, Houghton D, Roland C, Doherty J, Cohn SM, Barquist EI.
Department of Surgery, Emory University, Atlanta, Georgia, USA.

BACKGROUND: This study compared an intermittent feeding regimen (one sixth of daily needs infused every 4 hours) with a continuous (drip) feeding regimen for critically ill trauma patients. There were two outcome variables: time to reach goal volume and the days on 100% of caloric needs via an enteral route in the first 10 days of the intensive care unit stay. Adverse events were also tallied. METHODS: A prospective randomized trial was conducted in the trauma intensive care unit in a university Level I trauma center. A total of 164 trauma patients, 18 years of age and older, were admitted to the trauma intensive care unit with a noninjured gastrointestinal tract and required more than 48 hours of mechanical ventilation. Patients were randomized to receive enteral nutrition via an intermittent feeding regimen versus a continuous feeding regimen. A single nutritionist calculated caloric and protein goals. A strict protocol was followed where hourly enteral intake, interruptions and their causes, diarrhea and pneumonia were recorded, as well as standard guidelines for intolerance. RESULTS: A total of 164 patients were randomized and 139 reached their calculated nutritional goal within 7 days. There were no statistical differences in complications of tube feeding. The patients intermittently fed reached the goal faster, and by day 7 had a higher probability of being at goal. Furthermore, although it has always been assumed that better N balance must equate with better outcome, there are teleological arguments that question the wisdom of providing more N to sicker patients and studies that imply that best N balance might not equate with best clinical progress. Furthermore, current evidence suggests that in most critical illness low initial intakes of both energy and N lead to improved survival. It therefore seems logical to aim, in the first instance, to feed the seriously ill at only modest levels. Further research is required to determine whether lower-energy, higher-N feeding would prove better or worse than this approach in terms of clinical benefit rather than just better N retention. Investigations to explore the use of feeds that are specifically designed to match the amino acid needs of illness are also required.

Is it now time to promote mixed enteral and parenteral nutrition for the critically ill patient?


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BACKGROUND: Intensive care outcome measured by morbidity and mortality is altered in the severely malnourished ICU patient, and nutritional support of the critically ill is accepted as a standard of care. Current recommendations suggest starting enteral feeding as soon as possible wherever the gastrointestinal tract is functioning. The disadvantage of enteral support is that inadequate energy and protein intake can occur. The present commentary focuses on some recent findings regarding the nutritional support of critically ill patients and proposes to promote mixed nutrition support by enteral nutrition (EN), and by parenteral nutrition (PN) whenever EN is insufficient. RECENT FINDINGS: An increasing nutrition deficit during a long ICU stay is associated with increased morbidity (increased infection rate or impaired wound healing). Evidence shows that EN can result in underfeeding and that nutrition goals are reached only after 5–7 days. Contrary to former beliefs, recent meta-analyses of studies in the ICU showed that PN is not related to excess mortality but may even be associated with improved survival. CONCLUSIONS: Optimizing the increased substrate requirement for the critically ill by initiating timely nutrition support and ensuring tight glycemic control with insulin is now considered central for improved intensive care outcomes. Supplemental PN combined with EN could be an effective alternative to achieve 100% of energy and protein targets at day 4, when EN alone fails to achieve goals greater than 60% by day 3. Whether such combined nutrition support provides additional benefit on overall outcome has to be ascertained in further studies.
Preoperative immunonutrition suppresses perioperative inflammatory response in patients with major abdominal surgery – A randomized controlled pilot study


BACKGROUND: Prevention of relapse is a major issue in the management of Crohn’s disease. Corticosteroids and 5-ASA preparations are not effective for the maintenance of remission. Methotrexate, infliximab, 6-mercaptopurine and its prodrug, azathioprine, may be effective in maintaining remission, but these drugs may cause significant adverse events. OBJECTIVES: To conduct a systematic review to evaluate the efficacy of enteral nutrition for the maintenance of remission in Crohn’s disease. SEARCH STRATEGY: MEDLINE (1966 to January 2007), EMBASE (1984 to January 2007) the Cochrane Central Register of Controlled Trials from the Cochrane Library (Issue 4, 2006) and the IBD/FBD Review Group Specialized Trials Register were searched. The articles cited in each publication were hand searched. SELECTION CRITERIA: Randomized controlled trials which compared enteral nutrition with no intervention, placebo or with any other intervention were eligible for inclusion. DATA COLLECTION AND ANALYSIS: Data extraction and assessment of methodological quality of included studies were independently performed by two authors. The main outcome measure was the occurrence of clinical or endoscopic relapse as defined by the primary studies. Odds ratios and 95% confidence intervals were calculated for dichotomous outcomes. MAIN RESULTS: Two studies were identified that met the inclusion criteria and were included in the review. Statistical pooling of the results of these studies was not possible because the control interventions, and the way outcomes were assessed, differed greatly between the two studies. In one study (Takagi 2006), patients who received half of their total daily calorie requirements as elemental diet and the remaining half by normal food) were equally effective for maintenance of remission, but these drugs may cause significant adverse events. Whereas larger studies are needed to confirm these findings, enteral nutritional supplementation could be considered as an alternative or as an adjunct to maintenance drug therapy in Crohn’s disease.
consistent, quality care. This led to the creation of an Acute Assessment Unit (AAU) where all patients are assessed by the Allied Health team on admission. This study aimed to: (i) determine the nutritional status of patients admitted to the AAU using the scored Patient Generated-Subjective Global Assessment (PG-SGA); and (ii) determine the association between nutritional status and length of stay (LOS).

METHODS: A prospective, observational study was conducted in 64 patients (mean age 79.9 ± 11 years, 76% female). Nutritional status was assessed within 48 h of admission and LOS data were collected prospectively. RESULTS: According to PG-SGA global scores, 53% (n = 34) of patients were malnourished. There was a weak association between PG-SGA score and LOS (r = 0.230, p = 0.046). The malnourished patients had a longer LOS by 1 day compared with well-nourished patients, and while this did not reach statistical significance (z = -0.988, p = 0.323), it has implications for healthcare costs. LOS overall was short at a median of 4.5 days (range 1–24). CONCLUSIONS: A significant proportion of patients admitted to the AAU is malnourished. There was a trend for these patients to have a longer LOS, indicating a critical need for nutritional management; however, LOS as a whole was short. While nutrition support in hospital is useful in reinforcing dietary education, the short LOS emphasized the importance of discharge education and follow-up.

Controversies in the determination of energy requirements

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To avoid any negative outcomes associated with under- or overfeeding it is essential to estimate nutrient requirements before commencing nutrition support. The energy requirements of an individual vary with current and past nutritional status, clinical condition, physical activity and the goals and likely duration of treatment. The evidence-base for prediction methods in current use, however, is poor and the equations are thus open to misinterpretation. In addition, most methods require an accurate measurement of current weight, which is problematic in some clinical situations. The estimation of energy requirements is so challenging in some conditions, eg. critical illness, obesity and liver disease, that it is recommended that expenditure be measured on an individual basis by indirect calorimetry. Not only is this technique relatively expensive, but in the clinical setting there are several obstacles that may complicate, and thus affect the accuracy of, any such measurements. A review of relevant disease-specific literature may assist in the determination of energy requirements for some patient groups, but the energy requirements for a number of clinical conditions have yet to be established. Regardless of the method used, estimated energy requirements should be interpreted with care and only used as a starting point. Practitioners should regularly review the patient and reasseess requirements to take account of any major changes in clinical condition, nutritional status, activity level and goals of treatment. There is a need for large randomized controlled trials that compare the effects of different levels of feeding on clinical outcomes in different disease states and care settings.

Is there a difference in metabolic outcome between different enteral formulas?

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BACKGROUND: Despite appropriate enteral nutrition, many elderly patients do not reach a good metabolic outcome. Two nutrition formulas are commonly used in Israel with no evidence-based medicine to indicate preference of one over the other. METHODS: We describe a 2-month observational study of patients fed by one of the two formulas. The first (Osmolite, Abbott Company, Abbott Park, IL, USA) is without fiber, and the second (Easy Fiber, Easyline Company Givatam, Israel) in addition to containing fiber is also richer in protein, vitamins and minerals. The formula was selected by the primary care physician before enrollment in the study and was not influenced by the investigators. Routine blood tests as well as body weight were monitored at the start of enteral feeding and during the 2 months following as part of the regular follow-up. RESULTS: Fifty-seven patients were fed with the regular formula and 77 with the enriched one. No statistically significant differences were noted between the groups during the follow-up period, in body weight, cholesterol levels, total lymphocyte count, renal function tests, or electrolyte balance. However, in the enriched formula group there was a significant decrease in glucose (p < 0.05), and increase in albumin (p < 0.05) and hemoglobin (p = 0.01) levels. CONCLUSIONS: Enteral feeding with enriched formula appears to improve albumin and hemoglobin levels as well as diabetic control, thus it may be more appropriate than the non-fiber diet for use in long-term care patients.

Nutritional assessment of patients before gastrointestinal surgery and nurses’ approach to this issue

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AIMS AND OBJECTIVES: This study was conducted to evaluate the nutritional status of patients before gastrointestinal surgery and to reveal nurses’ opinions about this issue. BACKGROUND: Although there is increasing awareness that malnutrition constitutes an important problem, especially when it accompanies diseases, malnutrition in hospitalized patients is not being diagnosed or treated. DESIGN: This study was descriptive. METHODS: Subjective global assessment and anthropometric/biochemical measurements were used to evaluate the nutritional status of 57 patients hospitalized for gastrointestinal surgery. Related opinions of eight nurses were obtained via semi-structured interviews. RESULTS: The malnutrition rate was high in patients before gastrointestinal surgery, and the nurses were not able to evaluate nutritional status properly.
Furthermore, the nurses lacked knowledge. CONCLUSIONS: This study indicates the importance of evaluating the nutritional status of patients before surgery and the necessity of developing nutritional support plans. RELEVANCE TO CLINICAL PRACTICE: Our study showed that subjective global assessment is an easy and useful scale for evaluating the nutritional status of patients. Nurses are suitable team members for continuous nutritional care and therefore must not delegate this role.

The effect of nutritional management on the mood of malnourished patients
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BACKGROUND AND AIMS: Starvation and weight loss are common accompaniments of severe illness. The functional consequences of such malnutrition include not only physical changes but also psychological changes such as depression, anxiety, irritability, apathy, poor sleep pattern and loss of concentration. We carried out a pilot observational study in 22 undernourished patients at the time of referral to the nutritional team and after 8 days of nutritional support, using the Profile of Mood States Score (POMS) questionnaire to determine whether measurable and clinically significant changes in mood occurred with treatment. METHODS: Twenty-two undernourished patients with gastrointestinal disease were studied during the first week of treatment by the nutrition team. Psychological assessment was performed using a structured and standardized questionnaire assessing mood states (tension, depression, anger, vigor, fatigue, confusion). The questionnaire was administered to the patients by the same interviewer on days 1 (start of treatment by the nutrition team) and 8. RESULTS: Median (IQR) scores for tension, depression, anger, vigor, fatigue and confusion were 21.5 (11.5), 23.0 (15.8), 15.0 (11.8), 6.0 (7.5), 20.0 (8.5) and 12.0 (7.0) respectively on day 1. Corresponding scores on day 8 were 4.0 (8.8), 3.5 (6.0), 1.0 (1.8), 20.0 (7.5), 10.0 (8.8) and 2.5 (6.8). The improvement in scores seen on day 8 was statistically significant (p < 0.01). CONCLUSION: Nutritional status and treatment have important effects on the psychology of patients and formal measurements of mood of malnourished patients may improve the clinical outcome of SAP, reducing postoperative complications. CONCLUSIONS: CRAI and EN may improve the clinical outcome of SAP, reducing postoperative complications.

Randomized clinical trial of the impact of early enteral feeding on postoperative ileus and recovery
In J Surg 2007 May;84(5):555-561
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BACKGROUND: Postoperative convalescence is mainly determined by the extent and duration of postoperative ileus. This randomized clinical trial evaluated the effects of early oral feeding on functional gastrointestinal recovery and quality of life. METHODS: One hundred twenty-eight patients undergoing elective open colorectal or abdominal vascular surgery participated in the trial. Of these, 67 were randomized to a conventional return to diet, and 61 to a regimen allowing resumption of an oral diet as soon as tolerated (free diet group). RESULTS: Reinsertion of a nasogastric tube was necessary in 20% of the free diet group and 10% of the conventional group (p = 0.213). The complication rate was similar for both groups, as was return of gastrointestinal function. A normal diet was tolerated after a median of 2 days in the free diet group compared with 5 days in the conventional group (p < 0.001). Quality of life scores were similar in both groups. CONCLUSION: Early resumption of oral intake does not diminish the duration of postoperative ileus or lead to a significantly increased rate of nasogastric tube reinsertion. Tolerance of oral diet is not influenced by gastrointestinal functional recovery. As there is no reason to withhold oral intake following open colorectal or abdominal vascular surgery, postoperative management should include early resumption of diet.

PANCREATITIS

Treatment strategy against infection: Clinical outcome of continuous regional arterial infusion, enteral nutrition, and surgery in severe acute pancreatitis
J Gastroenterol 2007 Aug;42(8):681-689
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BACKGROUND: In severe acute pancreatitis (SAP), infectious complications are the main contributors to high mortality. Since 1995, we have performed continuous regional arterial infusion of protease inhibitor and antibiotics (CRAI) and enteral nutrition (EN) as prevention therapies against infection. When infected pancreatic necrosis was proven, surgical intervention was adapted. The aim of this study was to investigate the clinical outcome of these treatments. METHODS: We examined the relationship between the historical change of treatment strategy and clinical outcome. We divided 84 patients with acute necrotizing pancreatitis into two groups, CRAI(−) and EN(−), and compared the outcome. We divided 145 patients with SAP into two groups, EN(−) and EN(+), and compared the outcome. We also analyzed the outcome of surgical treatment. RESULTS: In the CRAI(+) group, the incidence of infection, the frequency of surgery, and the mortality rate were lower than those in CRAI(−) group: 34% vs 51%, 27% vs 63% (p < 0.05), and 37% vs 54%, respectively. In the EN(+) group, the frequency of surgery and the mortality rate were lower than those in the EN(−) group: 23% vs 32% and 19% vs 35% (p < 0.05), respectively. These improvement effects were manifest in stage 3 (9 ≤ Japanese Severity Score ≤ 14). Treatment outcome of necrosectomy for infected pancreatic necrosis was still poor. Blending and abscess-gut fistula were life-threatening postoperative complications. CONCLUSIONS: CRAI and EN may improve the clinical outcome of SAP, reducing infection and averting pancreatic surgery.
Influence of enteral versus parenteral nutrition on blood glucose control in acute pancreatitis: A systematic review

Din D et al. 2007 Jan 6; [first draft at print].

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BACKGROUND AND AIMS: There is increasing evidence that tight glucose control may reduce infectious complications and mortality in surgical critically ill patients. However, data regarding the influence of artificial nutrition on glycemic homeostasis are limited. Our aim was to review all randomized controlled trials on enteral versus parenteral nutrition in acute pancreatitis to determine whether the route of feeding can affect the glucose control in the setting of this disease. METHODS: Relevant literature cited in three electronic databases (Cochrane Central Register of Controlled Trials, EMBASE and Medline) were systematically reviewed. A meta-analysis was carried out using a random effects model. RESULTS: Thirteen randomized controlled trials on enteral versus parenteral nutrition in acute pancreatitis were identified. Seven studies were excluded from analysis, leaving 6 trials in which a total of 264 non-diabetic patients with acute pancreatitis were treated. Intake of nutrients did not differ among enterally and parenterally fed patients in five of six randomized controlled trials. Enteral nutrition reduced the risk of hyperglycemia (relative risk 0.53, 95% confidence interval 0.29–0.98; p = 0.04) and insulin requirement (relative risk 0.74, 95% confidence interval 0.24–0.70; p = 0.001). CONCLUSIONS: Enteral nutrition, when compared with parenteral nutrition, is associated with better blood glucose control in patients with acute pancreatitis.

Impact of nutrient density of nocturnal enteral feeds on appetite: A prospective, randomized crossover study

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OBJECTIVE: To determine whether the energy density of isocaloric nocturnal enteral feeds (NEF) influences daily nutrient intake in children. METHOD: In a 6-week, randomized, crossover trial, the impact on spontaneous nutrient intake of manipulating the energy density of two isocaloric overnight feeds (1.0 kcal/mL and 1.5 kcal/mL) was compared in a group of 32 children aged 1–10 years (or 8–2.5 kg body weight) on long-term, overnight enteral feeding at home. Total daily oral energy, protein, fat and carbohydrate intake were assessed using 3 day food diaries. Anthropometric data were also recorded during the study. RESULTS: Spontaneous intakes of energy, protein, fat and carbohydrate from food were 20–30% greater when receiving the lower nutrient density feed (1 kcal/mL). This was due to a gender effect; males consumed twice as much protein from food than females and had slightly higher (but not significant) energy and fat intakes when on the larger volume feed. All children increased in weight, height and mid-upper arm circumference in the 6-week period. CONCLUSIONS: Children appear to tolerate and grow equally well, irrespective of the nutrient density and volume of NEF taken. However, it appears that children will consume a more energy- and nutrient-dense oral diet when given their NEF as a higher density feed. This is particularly so for boys, while for girls the volume of NEF or feed concentration appeared to have no impact on quantity of oral diet taken. However, further blinded studies with larger subject numbers would be useful to support these findings.

Reducing the risk of wrong route errors

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Infants in the neonatal intensive care unit are at particular risk from clinical errors because of their fragility and vulnerability, as well as the complex nature of medication and other treatment regimens. Wrong route errors have been well documented, particularly related to enteral...
Enteral resuscitation and early enteral feeding in children with major burns – Effect on McFarlane response to stress


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AIM: Early enteral feeding has become standard practice for burned patients. The aim of this study was to determine whether early enteral feeding could be used as an avenue for resuscitation and feeding and the effect it would have on the induction/amelioration of the hormonal stress response. METHOD: Eighteen children with ≥20% TBSA were randomly assigned to either early enteral feeding and resuscitation, or intravenous resuscitation with the induction of enteral feeding delayed. The enteral fluid volume was incrementally increased every 3 h with a simultaneous reduction in the intravenous fluid volume until all the calculated intravenous fluid requirements for resuscitation and maintenance could be administered entonally. In the second group, intravenous resuscitation continued for 48 h when enteral feeding was introduced. Parameters measured were the clinical responses and outcome as well as the concentrations of insulin, insulin-like growth factor 1, glucagon, corticosterone and growth hormone. The estimated and calculated energy expenditure was measured calorimetrically and bowel permeability was assessed using a dual sugar absorption test. RESULTS: Three children were excluded from the study because of early death from organ failure or carbon monoxide poisoning. Early enteral resuscitation and feeding (ER/EEF) was initiated within a median of 10.7 h post-burn in nine children and late enteral feeding and resuscitation (LEF) introduced on an average 54 h post-burn. The ER/EEF group showed an anabolic response with significantly higher energy expenditure was not different amongst the groups. Small bowel permeability (lactulose:rhamnose [L-R] ratios) decreased significantly over time (p = 0.02) in both study groups. No pulmonary aspiration was found. Diarrhea in the ERF/EEF settled quickly (2–4 days), whereas in the LEF group it persisted for longer than a week. The LEF group lost a median of 7.7% (acceptable range ± 5%) of admission body weight, whereas the ER/EEF group lost a median of 3.01%. Patients in the LEF group required antibiotic treatment for a longer period (p = 0.08) and their hospital stay was longer, though not significant. CONCLUSIONS: Enteral resuscitation and early enteral feeding is a safe and effective method and particularly suited for children in developing countries. It resulted in the amelioration of the hormonal stress response and improved outcome. Enteral resuscitation should not be introduced in a patient in shock or with existing gastrointestinal disease. Complications were minimal.

PRE- AND PROBIOTICS

Improvement of nutritional status and incidence of infection in hospitalized, enterally fed elderly by feeding of fermented milk containing probiotic Lactobacillus johnsonii La1 (NCC533)


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Probiotics have potential to improve host immunity; however, there is less evidence showing their efficacy against infections and nutritional status in the elderly. We conducted a double-blind feeding trial in the elderly to elucidate the effect of fermented milk containing Lactobacillus johnsonii La1 (LC1*) on infections and nutritional status. Twenty-four completely enterally fed elderly in-patients aged over 70 years were randomly assigned into two groups. All subjects were administered 3,768 kJ (900 kcal)/d of total enteral nutrition (EN) through tube feeding for 12 weeks. Subjects in the LC1 group were administered 373 kJ (89 kcal)/d of LC1 fermented milk after feeding of 3,395 kJ (811 kcal)/d of EN for 12 weeks. In the control group, 373 kJ/d of the same EN was replaced from the fermented milk. In the LC1 group, the percentage of days with infections during the run-in observation period was 15.4 (SD 17.3%), which significantly decreased to 5.7 (SD 8.1%) during the intervention period (p = 0.018), and the reduction was larger than that of the control group (p = 0.047). Blood Hb increased (p < 0.05), and there was a tendency towards an increase in serum albumin and a decrease in TNF-α (a pro-inflammatory cytokine) in the LC1 group. There was a trend towards an increase in blood phagocytic activity (a natural immunity marker) in the subjects whose initial level was low in the LC1 group. There were no changes in those parameters in the control group. Administration of fermented milk containing the probiotic L. johnsonii La1 may contribute to suppressing infections by improving nutritional and immunological status in the elderly.
Effect of enteral nutrition and synbiotics on bacterial infection rates after pylorus-preserving pancreatoduodenectomy: A randomized, double-blind trial


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OBJECTIVE: Patients undergoing pancreas resection carry several risk factors for nosocomial bacterial infections. Probiotics and prebiotics reduce the risk of nosocomial infection. The objective of the current study was to evaluate the effect of synbiotics on the bacterial colonization rates after pylorus-preservation pancreatoduodenectomy (PPPD).

METHODS: Nineteen patients were randomized to receive synbiotics (prebiotics and probiotics) as synbiotic, synbiotics as placebo (i.e., fibers only), or placebo. The synbiotic mixture contained Lactobacillus plantarum, Bifidobacterium longum, and beneficial fibers. Bacterial colonization was measured in the stool and skin.

RESULTS: Synbiotic treatment was associated with a reduced bacterial colonization rate compared to placebo. The synbiotic group showed significantly lower colonization rates compared to the placebo group (p < 0.05–0.01). No significant differences were found between the synbiotic groups.

CONCLUSION: Synbiotics are effective in reducing bacterial colonization rates after pylorus-preserving pancreatoduodenectomy.

Trace element supplementation after major burns increases burned skin trace element concentrations and modulates local protein metabolism but not whole-body substrate metabolism


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BACKGROUND: After major burns, patients exhibit an intense catabolism, and the wounds require surgery and grafting for closure. Complications, such as weight loss and delayed wound healing, are worsened by trace element (TE) deficiencies. OBJECTIVE: We aimed to assess the effects of TE supplements on systemic substrate turnover and local protein metabolism during wound healing after major burns.

METHODS: This was a prospective, randomized, placebo-controlled trial in 21 patients aged 35 ± 11 y with burns on 45 ± 16% of their body surface area; 12 had skin biopsies performed on days 3, 10 and 20, and 10 patients underwent a stable-isotope investigation on day 10.

RESULTS: The patients' mean age and burn severity did not differ significantly between the groups. Plasma TE concentrations were significantly higher in the TE group. In the burned areas, the skin contents of selenium and zinc were increased, and the wounds required surgery and grafting for closure.

CONCLUSION: Trace element supplementation after major burns increases burned skin trace element concentrations and modulates local protein metabolism but not whole-body substrate metabolism.
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S McClave (Louisville, KY, USA)

Differences in the availability of parenteral nutrients, as well as unique patient populations and practice settings in Europe versus North America, sometimes lead to different approaches to nutrition support. For example, use of parenteral nutrition (PN), alone or with early enteral nutrition (EEN), in the first week of intensive care unit (ICU) hospitalization is more common in Europe where an intravenous omega-3 fat source is available, than in North America where the only intravenous fat option is an omega-6 lipid-based formula.

Both European and North American clinicians support the use of EEN (<36 hours) recognizing that a narrow window of opportunity exists for EEN to positively impact outcomes in the ICU. However, gaps exist between consensus and practice. In North America, few patients (15%) reach nutrition goals within 3 days and 22% of patients remain NPO longer than 3 days; the net effect is patients continue to receive only 50% of goal volume. The same pattern is seen in Europe where patients frequently do not start feedings until day 3 and receive less than 50% of target calories in the first week (Villet S, et al. Clin Nutr 2005;24:502-509).

While there is strong agreement that glutamine supplementation decreases ICU mortality rates, it is rarely used in North America. Free glutamine is unstable in liquids, but can be provided as glutamine dipeptides; this option is costly. Glutamine supplementation is widely used in Europe where an intravenous dipeptide glutamine source is readily available. There is also strong consensus on the benefits of arginine in patients with trauma and following major elective surgery, and that a low-arginine, omega-3–enriched formula benefits patients with acute respiratory distress syndrome. Clinicians disagree on the use of arginine in patients with sepsis and burns, and on the need for omega-3 fatty acid supplementation in all ICU patients.

Using meta-analyses and systematic reviews to develop evidence-based guidelines and protocols drives improvements in practice. At the same time, Dr Wernerman urges caution when interpreting results to develop guidelines. While the majority of patients in intensive care stay less than 5 days, those who stay longer than 5 days may have disproportionately higher complication rates and hospital costs, and a 10-fold higher mortality rate. Pooling data from these patient populations may yield misleading results. Therefore, clinicians should carefully consider the results from each distinct group when developing guidelines.

In the next decade, nutrition therapy should no longer be considered adjunctive supportive therapy; rather it should be recognized as proactive primary therapy that can modulate the stress response and systemic immunity.

Controversy I: Omega-3 fatty acids
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R Chiolero (Lausanne, Switzerland)

While strong evidence from large epidemiological studies supports the use of fish oil supplements to decrease the risk of cardiovascular disease and cancer, and promote fetal and neonatal brain growth, the use of fish oils in adult respiratory distress syndrome (ARDS), acute lung injury (ALI) and sepsis is more controversial.


While these studies showed significant clinical benefits in patients with severe sepsis and ARDS/ALI, they do have limitations. First, the combination of omega-3 fatty acids, glutamine, arginine and antioxidant vitamins in the enteral formula made it difficult to distinguish the benefit of fish oils compared with other nutrients. Second, the control diet was high in fat (35.2% of calories) and omega-6 fatty acids, which are known to depress immunity and alter pulmonary
gas exchange (Gottschlich MM, et al. *JPEN J Parenter Enteral Nutr* 1999;23:225-236; Garrel DR, et al. *JPEN J Parenter Enteral Nutr* 1995;19:482-491). Third, two studies excluded a large number of patients from the final analysis due to protocol violations, and did not include intention-to-treat (ITT) analyses. Clinical effectiveness may be overestimated if an ITT analysis is not done. Finally, the studies were single center studies.


**Controversy II: Arginine**

R Martindale (Portland, OR, USA) J Ochoa (Pittsburgh, PA, USA)


D Martindale suggests arginine supplementation at 15–30 g/d is safe and should be considered in all ICU patients when they are hemodynamically stable (within 24–48 hours). He recommends giving arginine as part of a complete nutrition formula with an arginine content of 12–15 g/L.

In contrast, D Ochoa gives arginine supplements only in diseases associated with an arginine deficiency syndrome (eg, trauma/surgery, sickle cell anemia and some cancers). He concludes that sepsis is not associated with arginine deficiency based on observations that plasma arginine levels are normal in sepsis (Chiarla C, et al. *Amino Acids* 2006;30:81-86).

Arginine is toxic to the non-perfused mucosal surface and is contraindicated in hemodynamically unstable patients with poor gut perfusion (Kozar RA, et al. *J Trauma* 2004;57:1150-1156).

**Glutamine: What is the science?**

P Wischmeyer (Denver, CO, USA) J Wienerman (Stockholm, Sweden)


Glutamine also maintains the intestinal mucosal barrier, reduces bacterial translocation, controls nitric oxide formation, and preserves glutathione and antioxidant function (Kelly D, Wischmeyer PE. *Curr Opin Clin Nutr Metab Care* 2003;6:217-222).

Intravenous administration of glutamine provides uniform distribution and certain delivery. The uptake and delivery of enterally administered glutamine is uncertain, especially in patients with gut failure. While some studies showed enteral glutamine lowered the risk of infectious morbidity and reduced hospital costs (Conjeever R, et al. *Nutrition* 2002;18:716-721), another found it had no benefit (Hall J, et al. *Intensive Care Med* 2003;29:1710-1716).

Glutamine treatment has not been associated with adverse effects in any study of ICU patients. Recommendations call for giving glutamine supplementation at doses adequate to normalize plasma concentrations. Glutamine supplementation is especially important in ICU patients with anticipated long stays (Goetters C, et al. *Crit Care Med* 2002;30:2032-2037).
Prebiotics/probiotics in the ICU: Food fad or “bacterial therapy”?  
R Martindale  
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Critical illness is associated with altered gut flora, including reduced beneficial flora and increased pathogenic flora (Shimizu K, et al. J Trauma 2006; 60:126-133). Prebiotics and probiotics can mitigate or treat many negative effects attributed to changes in the gut flora during critical illness.

Prebiotics are clearly beneficial in diarrheal diseases (Rabbani G, et al. Gastroenterology 2001; 121:554-560); prebiotics show promise, but the effect is very dependent on the strain and quantity used. More recent studies support prebiotics for Clostridium difficile diarrhea (CDD), especially in recurrent cases (McFarland LV. Am J Gastroenterol 2006;101:812-822).

Probiotic use decreases infection rates in the ICU. Their benefit has been shown in postoperative infections following gastrointestinal surgery, including for gastrointestinal cancer, and hepatic transplants (Rayes N, et al. Z Gastroenterol 2002;40:869-876; Rayes N, et al. Am J Transplant 2005;5:125-130). In more recent studies, live Lactobacillus rhamnosus GG cleared vancomycin-resistant enterococci (Manley KJ, et al. Med J Aust 2007;186:454-457) and reduced clinical ventilator-associated pneumonia from 45% to 35% and mortality from 24% to 14% compared with a control group (Presented at: Society for Critical Care Medicine, 2007).


Probiotics warrant careful evaluation prior to use in the ICU given the lack of guidelines governing their use, extravagant claims that are made without supporting research, and inconsistent manufacturing practices. Clinicians should use probiotics only when data support their use and should not extrapolate data from one strain to another. They should carefully identify the optimal strain, fiber and commercially available product. For effectiveness, probiotics must be given at 10^9–10^10 viable cells/d; for prebiotics, at least 20–30 g/d is required.

In the future, probiotics may be used to treat HIV and obesity, or as part of postoperative bowel preparation. Genetically engineered probiotics as drug delivery devices may be on the horizon.

Gut immunity and feeding: When and why?  
K Kudsk  
Milwaukee, WI, USA

Enteral feeding significantly reduces infectious complications in critically ill patients by maintaining mucosal immunity and increasing resistance of the respiratory tract to invasive pathogens. According to the ‘common mucosal immune hypothesis’, upregulation of mucosal T and B cells by the adhesion molecule MadCAM-1 produces immunoglobulin A (IgA), which is transported to the lungs and other sites and halts the invasion of bacteria (Kudsk KA. Am J Surg 2003;185:16-21; Genton I, et al. JPEN J Parenter Enteral Nutr 2005;29:44-47).

Enteral diets stimulate the expression of lymphoid tissue-β receptor (LTβR) in gut-associated lymphoid tissue (GALT), which, in turn, triggers MadCAM-1 production in the mucosa and increases IgA levels. (Kang W, et al. Ann Surg 2006;244:392-399).

Conversely, a lack of enteral nutrients reduces GALT cell numbers and levels of LTβR and MadCAM-1, leading to reduced T and B cell activation and lowering IgA levels, ultimately leaving the respiratory tract more susceptible to bacteria. This is demonstrated when animals given PN exclusively become immunodeficient and then regain immunity after 3 days of chow feeding (Gomez FE, et al. JPEN J Parenter Enteral Nutr 2007;31:47-52). The effect is also seen in patients with colon cancer where a lack of enteral nutrients reduces GALT cell number (Okamoto K, et al. JPEN J Parenter Enteral Nutr 2005;29:56-58).

Current work is focusing on the role of intestinal polymeric immunoglobulin receptor (pIgR) in maintaining immunity. Enteral feeding increases the expression of pIgR, which facilitates transport of IgA through the mucosal epithelial cell to increase luminal secretory IgA and maintain immunity. Clearly, enteral feeding stimulates defenses and maintains a healthy environment in addition to providing energy.

Antioxidants and trace elements: State of the art  
J Preiser  
Liège, Belgium


While adding antioxidant compounds to nutrition support appears to be physiological, this may not hold true in the ICU. A recent systematic review and meta-analysis of randomized trials of antioxidant supplementation in the ICU concluded that the addition of beta-carotene and vitamins A and E significantly increased the risk of mortality. Vitamin C and selenium warranted further study (Bjelakovic G, et al. JAMA 2007;297:842-857).

Taken together, clinical studies comparing the combined vitamins and trace elements versus standard therapy suggest antioxidants are a promising therapeutic option. However, there is still work to be done to determine the right antioxidant, combination and dose; the appropriate timing; the right patient; and circumstance; and the appropriate assessment of efficacy when using antioxidants.

**Moderated debate – Glycemic control: Target of tight glucose control should be normoglycemia**

J Jacobi (Indianapolis, IN, USA) J Preiser (Liège, Belgium)


However, large multicenter studies on IIT demonstrate that the benefits of IIT must be weighed against the risks of hypoglycemia (Vriesendorp TM, et al. Crit Care Med 2006;34:96-101). Dr Preiser presented unpublished data from the GLUcontrol study that was stopped in March 2006 after results showed severe hypoglycemia (<40 mg/dL) and variability in blood glucose concentrations occurred more often in IIT patients, compared with patients on conventional glucose control, and was associated with a trend toward higher mortality (Devos P. Available at: www.glucontrol.org. Accessed 28 August 2007). The VISEP trial in Germany, another multicenter study on IIT, was stopped because of no difference in mortality (21.9 vs 21.6%; p = 1.0) and frequent hypoglycemia in the IIT arm compared with the standard treatment arm (12.1 vs 2.1%; p < 0.001) (Brunnhorst FM, et al. Infection 2005;33:19-20 [abstract]).

Van den Berghes’ findings may not be applicable to other settings, given the increased workload required for IIT and a lack of benefit in patients with diabetes and in those with short hospital stays. Others question the high percentage of patients receiving steroids, the large amount of parenteral glucose given, a relatively high mortality rate in relation to severity of illness among patients in the control group, and the single-center design of the study (Bellomo R, Egi M. Mayo Clin Proc 2005;80:1546-1548).

A large prospective, multicenter study is under way combining data from the Normoglycemia in Intensive Care Evaluation (NICE) and the Survival Using Glucose Algorithm Regulation (SUGAR) studies. The NICE-SUGAR study will provide information about the effect of normoglycemia in a heterogeneous group of at least 5,000 critically ill patients. Until the publication of NICE-SUGAR, sweeping recommendations for IIT to be applied to all patients may be premature; a blood glucose level of 140–150 mg/dL may be a more acceptable threshold to start intravenous insulin.

**Moderated debate – Permissive underfeeding in the critically ill patient**

J Wernerman (Stockholm, Sweden) D Heyland (Kingston, ON, Canada)

Support for permissive underfeeding comes from observational studies that suggest the optimal nutrition dose in critically ill patients is 25–65% of goal calories (Rubinson L, et al. Crit Care Med 2004;32:350-357; Krishnan JA, et al. JAMA 2003;290:1279-1286). Available at: www.glucontrol.org. Accessed 28 August 2007). The VISEP trial in Germany, another multicenter study on IIT, was stopped because of no difference in mortality (21.9 vs 21.6%; p = 1.0) and frequent hypoglycemia in the IIT arm compared with the standard treatment arm (12.1 vs 2.1%; p < 0.001) (Brennhorst FM, et al. Infection 2005;33:19-20 [abstract]).

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Given alone, EN provides fewer calories; yet a systematic review of studies that supplemented EN with PN found no effect on mortality or infections (DhalIWal R, et al. Intensive Care Med 2004;30:1666-1671). Clinical practice guidelines do not recommend supplementing EN with PN in critically ill patients.

On the other hand, many studies on permissive underfeeding are underpowered and have design flaws that may lead to inconclusive results. For example, 40% of patients in the ACCEPT study received no feeding at all (Martin CM, et al. CMAJ 2004;170:197-204). Delays in starting nutritional support create energy deficits that cannot be compensated for later on, and that correlate with increased incidence of complications (Villet S, et al. Clin Nutr 2005;24:502-509; Dvir D, et al. Clin Nutr 2006;25:37-44).

In a recent meta-analysis that investigated the effect of the quality of EN and PN trials, ITT analyses demonstrated reduced mortality associated with PN. Despite a correlation with increased infectious complications, the findings support using PN in patients who do not tolerate initiation of EN within 24 hours of admission (Simpson F, Doig GS. Intensive Care Med 2005;31:12-23).

Both presenters agreed that complications related to nutritional therapy in the ICU are not acceptable, and that EN is preferable if it can be given without risk. Beyond that, controversy remains and highlights the need for high quality prospective studies.

**Best practice: Aspiration / residual volume**

N Metheny

St Louis, MO, USA

There is no clear definition of excessive gastric residual volume (GRV). While expert consensus considers that GRVs >200 mL seem to be well tolerated and GRVs >500 mL should be held, research yields conflicting results. Moreover, sensitive laboratory assays show that micro-aspirations are common in critically ill patients despite low measured GRVs (McClave SA, et al. Crit Care Med 2005;33:324-330).


The guidelines from the North American Summit on Aspiration in the Critically Ill recommend holding GRVs >200 mL and reassessing tolerance; returning GRVs <500 mL to patient; careful evaluation of patients with GRVs of 200–500 mL using an algorithmic approach to reduce risk; and ongoing evaluation of risk in patients with GRVs <200 mL (McClave SA, et al. JPEN J Parenter Enteral Nutr 2002;26(suppl):S80-S85).

To minimize aspiration risk, consider all critically ill tube-fed patients at risk for aspiration and those with identified high GRVs at even greater risk; keep the head of the bed elevated to 30-45 degrees when feasible; use sedatives as sparingly as possible; use an algorithmic approach to deal with high GRVs, including prokinetics and small bowel tube placement if necessary; and avoid interrupting feedings whenever possible.

**Critical care nutrition survey: Preliminary results**

D Heyland

Kingston, ON, Canada

Preliminary results of the International Nutrition Survey 2007, a point prevalence observational study comparing nutrition practices to the Canadian Nutrition Support Clinical Practice Guidelines, identified opportunities for improvement and illuminated research opportunities. The database included 2,896 patients and 165 ICUs worldwide.

Most hospitals (66%) strongly recommend EN over PN. Use of EN alone was highest in the United Kingdom (UK) (74%) and lowest in Europe (47%). To optimize EN delivery, hospitals use feeding protocols (77%), motility agents (75%), small bowel feedings (68%) and elevate the head of the bed (71%). The average time after admission before enteral feedings were started was 40–50 hours, with a wide range.

Conversely, use of PN alone, though low overall, was highest in Europe (20%) and lowest in the UK (<10%). Use of EN combined with PN was highest in Europe (28%) and lowest in Canada and the USA (<5%). Thirty percent of hospitals use lipid-free PN to optimize PN delivery; less than 10% use a medium-chain triglyceride/long-chain fat mixture or structured lipid.
All groups fell far short of meeting prescribed goals for total and enteral calories and protein. The UK provided the most nutrition (52–66% of prescribed total and enteral calories and protein); the USA and Europe the least. Of concern, a significant number of ICU patients received no nutrition support; the prevalence was lowest in the UK (10%) and highest in the USA (28%).

Eighty-two percent of hospitals use a glycemic control protocol, and 96% reported no episodes of hyperglycemia.

Patients on EN rarely receive arginine (5.3%), glutamine supplementation (7.2%), or an omega-3 fatty acid-supplemented formula (4.1% of ARDS patients). Most patients on EN (91%) receive a polymeric formula. Differences in the use of parenteral glutamine are striking; although overall 75% of all study patients on PN received glutamine supplements, none did in Canada or the USA, while all study patients in the UK, Australia and Asia received glutamine.

More detailed information will be available at www.criticalcarenutrition.com.

How to improve quality of nutritional care in the ICU
P Roberts
Oklahoma City, OK, USA

Quality care is safe, timely, effective, efficient, equitable and patient-centered (Berwick DM. Health Aff 2002;21:80-90), or more simply, the ‘right care, right now’. Organizations measure three components of quality – structure, process and outcomes – to determine current status and make improvements. Measuring structure (the way care is organized) or process (what is done or not done for patients) provides clear feedback about what providers are doing and is easily accomplished using routinely collected data. Measuring outcomes (the results achieved) is most important to patients, but more difficult to do since many processes affect outcomes (Curtis JR, et al. Crit Care Med 2006;34:211-218).

Good quality measures should be important, valid, reliable, responsive, interpretable and feasible. Nutrition support quality measures may include type and amount of available technology, or staffing levels and composition (structure measures); use of evidence-based care bundles (process measure); and morbid events, such as nosocomial infections or adverse drug events, or patient satisfaction (outcomes measures).

Improving quality requires support throughout the organization and begins with understanding the current situation and determining where change needs to occur. Models for change, such as the widely used Plan-Do-Study-Act model, and a basic understanding of statistics and process control tools, such as control charts and flow charts, facilitate the process.

Changes usually spread slowly with the rate influenced by the relative advantage, compatibility, and complexity of the change, as well as environmental factors and the ability of the team to trial and observe the change. Barriers to improvement are excessive autonomy, system flaws, complicated rules and policies, resistance to change, and a lack of data (www.ihi.org).

In the future, nutrition care bundles have the potential to significantly improve quality of nutrition care.

Where do we go from here?
R Martindale
Portland, OR, USA

The goals of nutrition therapy must change from adjunctive care to therapeutic strategy. Current goals should be to attenuate metabolic response; reverse loss of lean body tissue; prevent oxidative stress; favorably modulate immune response using enteral feeding; provide appropriate macro- and micronutrients (including glutamine, arginine, omega-3 fatty acids, and antioxidants); and achieve meticulous glycemic control.


Even so, many pitfalls to optimal ICU nutrition remain: over reliance on PN; the unavailability of physiological parenteral solutions in the USA; failure to predict which patients will need support; and lack of understanding of therapeutic potential of specialized formulas and nutrients, such as arginine, glutamine, omega-3 fatty acids, nucleic acids and antioxidants. Clinicians need more data on specific nutrients, better assessment tools, more effective dissemination and implementation of various guidelines, and more physiologic parenteral nutrition products, especially in the USA.

Future trends in nutrition may include genotype-specific nutrient delivery; pre-insult cellular preparation using carbohydrate loading, arginine, glutamine, or fish oils; more physiologic PN using glutamine dipeptide and new lipid emulsions; new attention to the gut/microbe mutualism; and new nutrient-driven ICU resuscitation fluids.

The views expressed in this newsletter are of the presenters and participants, and Nestlé Nutrition.
### Conference Calendar 2007 – 2008

<table>
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<tr>
<th>Month</th>
<th>Event</th>
<th>Dates</th>
<th>Location</th>
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<tr>
<td>November 2007</td>
<td>Annual Conference of the British Association for Parenteral and Enteral Nutrition (BAPEN) 2007</td>
<td>27–28 November 2007</td>
<td>Harrogate, United Kingdom</td>
<td>Sovereign Conference, Exhibitions &amp; Travel Incentives</td>
<td>+44 (0) 1527 518 777</td>
<td>+44 (0) 1527 518 718</td>
<td><a href="mailto:association@sovereignconference.co.uk">association@sovereignconference.co.uk</a></td>
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<td>December 2007</td>
<td>4th Cachexia Conference</td>
<td>6–9 December 2007</td>
<td>St Petersburg, Florida, USA</td>
<td>LMS Group</td>
<td>+33 1 4253 0303</td>
<td>+33 1 4253 0302</td>
<td><a href="mailto:info@lms-group.com">info@lms-group.com</a></td>
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<td>February 2008</td>
<td>37th Critical Care Congress</td>
<td>2–6 February 2008</td>
<td>Honolulu, Hawaii, USA</td>
<td>Society of Critical Care Medicine</td>
<td>+1 847 827 6888</td>
<td>+1 847 493 6420</td>
<td><a href="mailto:info@sccm.org">info@sccm.org</a></td>
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<td>Clinical Nutrition Week 2008</td>
<td>10–13 February 2008</td>
<td>Chicago, Illinois, USA</td>
<td>American Society for Parenteral and Enteral Nutrition</td>
<td>+1 301 587 6315</td>
<td>+1 301 587 2365</td>
<td><a href="mailto:aspen@nutr.org">aspen@nutr.org</a></td>
<td><a href="http://www.nutritionweek.org">www.nutritionweek.org</a></td>
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<td>March 2008</td>
<td>6th European Oncology Nursing Society (EONS) Spring Convention</td>
<td>27–29 March 2008</td>
<td>Geneva, Switzerland</td>
<td>European Oncology Nursing Society</td>
<td>+32 (2) 779 9923</td>
<td>+32 (2) 779 9937</td>
<td><a href="mailto:eons@village.uunet.be">eons@village.uunet.be</a></td>
<td><a href="http://www.cancerworld.org">www.cancerworld.org</a></td>
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<td>7th International Diabetes Federation Western Pacific Region (IDF WPR) Congress</td>
<td>30 March – 3 April 2008</td>
<td>Wellington, New Zealand</td>
<td>Convention Management Services Ltd</td>
<td>+64 4 479 4162</td>
<td>+64 4 479 4163</td>
<td><a href="mailto:idfwpr@cmsl.co.nz">idfwpr@cmsl.co.nz</a></td>
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www.nestlenutrition-institute.org

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In this issue

Cancer therapy-induced mucositis: Where are we now?

Clinical nutrition abstracts
Highlights of Critical Care Medicine Summer Conference