The pharmacological effects of novel nutrients on the immune system

The role of novel nutrients that appear to have pharmacological effects on the immune system has been studied over the past 20 years. This area of research has been termed immunonutrition. This paper provides an overview of particular novel nutrients – arginine, glutamine, omega-3 fatty acids, and nucleotides – and examines some of the evidence for the effects that they may have on immune function. The benefits to particular patient groups are also considered (Box 1).

**Glutamine** Although traditionally thought of as a non-essential amino acid in healthy individuals, glutamine is now known to be conditionally essential in states of injury or illness (Wischmeyer, 2003). In the catabolic patient, amino acids are released from muscle tissue and it has been reported that up to 70 per cent of these amino acids are composed of glutamine (Brooks et al, 1996).

It is thought that glutamine is released following stress to provide an essential source of fuel for enterocytes (cells in the small intestine) and rapidly dividing macrophages and leukocytes in the immune system. It is also involved in the maintenance of acid base homeostasis in the kidney (Wischmeyer, 2003).

Illness and injury can therefore lead to a significant decrease in plasma levels of glutamine, and severe loss has been correlated with increased mortality (Houdijk et al, 1998). In a wide variety of patient groups, studies have shown that supplements of glutamine can have effects including decreased length of stay, infectious complications, mortality, and other morbidity. These groups include patients with cancer, critical illness (Wischmeyer et al, 2001), trauma (Houdijk et al, 1998), and patients with complications following surgery (Jiang et al, 1999).

**Arginine** Arginine is considered to be a conditionally essential amino acid, meaning that endogenous synthesis (synthesis within the body) may be limited in states of injury or illness (McCowen and Bistrian, 2003). In animal studies, supplementary dietary arginine has been shown to have useful effects on cellular immunity.

In patients with cancer following surgery increased IGF-1 (insulin like growth factor-1) and improved nitrogen balance were observed but no differences in infection rates or clinical outcomes were reported (Daly et al, 1988).

It is difficult to find published work evaluating the effect of arginine supplementation on patients. However, a commercially available enteral feed (Impact) that contains arginine, omega-3 fatty acids, and nucleotides has been well evaluated in a variety of patient groups including those with cancer, trauma, critical illness, and surgical patients (McCowen and Bistrian, 2003). It is important to note that the greatest benefits have been reported in trauma patients (Moore and Jones, 1986) and those who have had surgery for gastrointestinal cancers (Gianotti et al, 2002).

Other feeds commercially available in the UK that enhance immune function are listed in Box 2.

**Omega-3 fatty acids** These polyunsaturated fatty acids (PUFAs) are a constituent of fish oil and are the precursors of eicosanoids (a class of lipid), which include prostaglandins, prostacyclines, leukotrienes, and thromboxanes (McCowen and Bistrian, 2003). Omega-3 fatty acids are thought to be anti-inflammatory since they inhibit the proinflammatory effects of omega-6 fatty acids.

A number of studies of enteral nutrition formulas containing omega-3 fatty acids have shown beneficial outcomes. Increased tolerance of enteral feed has been demonstrated in patients with gastrointestinal cancer (Kenler et al, 1996), while shorter periods of artificial ventilation and reduced rates of infection have been reported in critically ill patients (Gadek et al, 1999).

Further studies in patients with cancer have shown improved ratios of T helper cells (lymphocytes involved in the immune response) to suppressor cells (Gogos et al, 1998). Interestingly, it has been suggested that a diet rich in omega-3 fatty acids, observed in eskimo populations, may predispose the patient to vasdilitation and extended bleeding times (O’Leary and Coakley, 1996). Although studies involving the critically ill and the use of omega-3 fatty acid supplementation have involved relatively small sample sizes, the risk of platelet dysfunction remains an issue of concern (Peck, 1994).

Perhaps of greater concern is the fact that diets rich in polyunsaturated fatty acids can lead to the formation of lipid peroxides. It is known that lipid peroxides cause cellular and tissue damage. This could have a negative effect in the critically ill patient with the development of multiple organ failure (O’Leary and Coakley, 1996). However, it is not known if these are clinically valid concerns and more investigation is needed.

**Nucleotides (ribonucleic acid – RNA)** It has been reported that dietary RNA may be necessary to maintain normal immune function as nucleotides increase protein synthesis and participate in the regulation of T-cell mediated immune responses. Unfortunately, no human studies examining the role and benefits of nucleotides in isolation could be found. However, it has been suggested that as nucleotides are traditionally, nutritional support was recommended as a therapy to offset starvation-induced immune dysfunction and muscle wasting (McCowen and Bistrian, 2003). However, more recently attention has focused on particular dietary components and their individual functions. Angie Davidson explains

**KEY WORDS**

Immunonutrition
Enteral nutrition
Parenteral nutrition

**REFERENCES**


It is suggested that immunonutrition should be given to:
- Patients having abdominal or upper gastrointestinal surgery for cancer – ideally this should be given pre- and postoperatively;
- Patients with multiple trauma;
- Critically ill patients with APACHE scores < 20 (McCowen and Bistrian, 2003).

It has been suggested that timing is important and unless immunonutrition is given in advance of surgery, the benefits are difficult to observe. Studies of patients who were given immunonutrition for a week before and after their surgery have shown distinct advantages in terms of reduced infectious complications.

Cost effectiveness Dietetic advice, nutritional supplements, and certain techniques of enteral feeding such as nasogastric feeding are not in themselves expensive. However, increased awareness of nutritional problems and uses of particular nutrients will inevitably increase the use of such services and therapies, so raising overall costs. And there is no dispute that immunonutrition is more expensive than standard feeds.

It is therefore very important that inappropriate use of such services and treatment be minimised and this is best achieved using nutrition support teams (NSTs). NSTs are best placed to implement and monitor nutritional policy and to audit effectiveness including morbidity and costs. They can also ensure the most appropriate method of nutritional therapy for individual patients.

Gianotti et al (2003) conducted a study that calculated the costs of treating postoperative complications such as wound dehiscence, abdominal abscess, fistula, pneumonia, and urinary tract infection. They found that the cost-effectiveness analysis yielded a net saving of approximately £2,180 per patient in the treatment group, far offsetting the cost of the immunonutrition.

**Conclusion and recommendations** Positive outcomes are more likely if immunonutrition can be given early to patients following trauma and pre- and postoperatively to surgical patients.

The amount of nutrition given also appears crucial and this may reflect the poorer outcomes in the most critically ill patients whose rates of feeding were perhaps not progressed in response to their condition, resulting in under-feeding. Progressive enteral feeding protocols are needed to standardise practice and provide a framework for nutritional support.

It is clear that more investigation is needed in the area of immunonutrition to identify what effect specific nutrients have on certain patient groups with particular emphasis on long-term outcomes.

### BOX 1. USE OF IMMUNONUTRITION

- **It is suggested that immunonutrition should be given to:**
  - Patients having abdominal or upper gastrointestinal surgery for cancer – ideally this should be given pre- and postoperatively;
  - Patients with multiple trauma;
  - Critically ill patients with APACHE scores < 20 (McCowen and Bistrian, 2003).

### BOX 2. IMMUNE FUNCTION ENHANCING FEEDS AVAILABLE IN THE UK

<table>
<thead>
<tr>
<th>Feed</th>
<th>Arginine</th>
<th>Glutamine</th>
<th>Nucleotides</th>
<th>Omega-3 FA</th>
</tr>
</thead>
<tbody>
<tr>
<td>AdaminGlu (SHS)</td>
<td>N</td>
<td>Y</td>
<td>N</td>
<td>N</td>
</tr>
<tr>
<td>Alitraq (Ross)</td>
<td>N</td>
<td>Y</td>
<td>N</td>
<td>N</td>
</tr>
<tr>
<td>Impact (Novartis)</td>
<td>Y</td>
<td>N</td>
<td>Y</td>
<td>Y</td>
</tr>
<tr>
<td>Impact Glutamine</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
</tr>
<tr>
<td>Oxepa (Ross)</td>
<td>N</td>
<td>N</td>
<td>N</td>
<td>Y</td>
</tr>
<tr>
<td>Peralite (Ross)</td>
<td>Y</td>
<td>N</td>
<td>N</td>
<td>Y</td>
</tr>
<tr>
<td>Recovon (F.Kabi)</td>
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<td>Y</td>
</tr>
<tr>
<td>Stresson (Nutricia)</td>
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</tr>
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<td>Prosure (Abbott)</td>
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<td>N</td>
<td>N</td>
<td>Y</td>
</tr>
</tbody>
</table>

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**REFERENCES**


