

Immunonutrition in patients after multiple trauma

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Severe trauma threatens the life of the victim, both directly and indirectly via immunological dysregulation during the subsequent clinical course. Inflammatory or infectious episodes may complicate the clinical course and ultimately result in sepsis and multiple organ failure, which have mortality rates of up to 80%. Immunomodulatory intervention aims to ameliorate the early hyperinflammatory phase (systemic inflammatory response syndrome, SIRS) to avoid the development of sepsis. One of the immunomodulation strategies is enteral feeding supplemented with specific nutrients, such as glutamine, *n*-3-polyunsaturated fatty acids, and nucleotides ('immunonutrition'), because changes in the GALT (gut-associated lymphoid tissue) immune response may contribute to intestinal dysfunction and increase susceptibility to post injury gut-derived sepsis. In a prospective, randomized, double-blind, controlled study in twenty-nine patients suffering severe trauma we were able to show that immunonutrition (arginine, *n*-3-fatty acids, and nucleotides) significantly reduces the number of SIRS days per patient, and also lowers the multiple organ failure (MOF) score on day 3 and days 8–11 ($P < 0.05$). Other studies have reported a reduction in septic complications and MOF rates, shortened hospital stay, and reduction in the use of antibiotics in patients randomized to the immune-enhancing diet. This improved clinical outcome was reflected in a reduction in hospital costs. In the recovery period after trauma (1–72 h after injury) a limitation of the inflammatory response of immunocompetent cells must be achieved as quickly as possible (<72 h). The only strategy available to clinicians caring for trauma patients is immunonutrition, and this should be strongly considered as a rational approach improving immune function and reducing septic complications in critically ill or injured patients.

Immunonutrition: Multiple trauma

The most common cause of death in polytraumatized patients is multiorgan failure. If the systemic inflammatory reaction syndrome (SIRS) and subsequent immunosuppression has not already resulted in the development of multiorgan failure at an early stage, a second traumatic event can initiate a late multiorgan failure. In this process, the intestine has a particular role to play as a 'motor'. The bowel, damaged by ischaemia during the shock process and subsequently reperfused, acts as a 'primer' for neutrophil granulocytes. Activated and resistant to apoptosis, these granulocytes can attach to capillary endothelial cells – for example in the pulmonary blood vessels. With persistent disruption of bowel permeability, a relatively small second trauma – for example, surgical treatment of a fractured limb – suffices to initiate, via bacterial translocation or endotoxaemia, the liberation of oxygen free radicals and lytic enzymes from the neutrophil granulocytes (respiratory burst). The consequence is organ injuries as, for example, acute respiratory distress syndrome (ARDS). A critical

phase for the development of delayed multiorgan failure must be considered to be postinjury days 7–14 (Biffi *et al.* 1999; Moore *et al.* 1994; Swank & Deitch, 1996; Weimann *et al.* 1999). Thus, already in the acute phase, treatment is focused on preserving the bowel mucosa with the aim of avoiding bacterial translocation. This implies the earliest possible initiation of enteral nutrition. Although the numerous mechanisms at the cellular level when the intestinal barrier is disrupted remain obscure, supplementation with immunomodulating substrates (immunonutrition) is nevertheless considered to be of importance. In addition to aiding regeneration of the epithelial cells of the bowel mucosa, further therapeutic goals are the exertion of a favourable influence on the inflammatory reaction, and the stimulation of the immune system. The major substrates used for enteral nutrition are arginine, *n*-3 fatty acids and ribonucleotides, together with glutamine. Currently, empirical data from clinical studies investigating the effects of the antioxidants vitamins A, C and E, are not available.

Abbreviations: SIRS, systemic inflammatory response syndrome.

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Practical problems

After initial management and stabilization of the patient, an access must be created for early enteral nutrition, if possible within the first 24 h. Frequently, pronounced and persistent gastric atony can be expected. For this reason, attempts to place a duodenal or jejunal tube are mandatory. The use of a multichannel tube permitting decompression of the stomach is recommended. In many cases, placement of the tube can be effected only via an endoscope. Should a laparotomy prove necessary, and if the duration of enteral nutrition is expected to be more than 10 days, a thin-needle catheter jejunostomy should, if possible, be applied. In the event of a severe head injury and a predicted duration of enteral nutrition of more than 4 weeks, consideration should be given to percutaneous endoscopic gastrostomy (PEG) or jejunostomy (PEJ).

In particular in the case of sepsis, it must be remembered that the metabolism of exogenous substrates might be impaired. The use of catecholamines, necessitated by the need to support the circulation, may also enhance existing intestinal atony, making it impossible to secure the caloric requirement via the nutrition. Also, in many cases, only small amounts (25 ml/h) can be provided via the enteral route. In such a situation, a combination of enteral and parenteral nutrition is recommended. Depending on tolerance, the volume of enteral feed can be increased in steps of 25 ml/h; at a delivery rate of 75 ml/h, parenteral nutrition can be reduced.

Clinical experience

Only a few prospective, randomized controlled clinical studies have been performed to investigate the utility of immunomodulating substrates exclusively in traumatized patients. The usefulness of enteral glutamine is currently controversial. Houdijk *et al.* (1998) investigated sixty patients receiving glutamine supplementation and reported a significant reduction in infectious complications, pneumonia, sepsis and bacteraemia in comparison with controls [3]. In a multicentre study involving ninety-eight patients with severe thoracic trauma, Moore *et al.* (1994) compared the effects of a diet enriched with arginine, ribonucleotides and *n*-3 fatty acids and containing glutamine and branched-chain amino acids. These authors observed significantly fewer intra-abdominal abscesses in the treated group in comparison with the control group, in which the abscess rate was 11%. In none of the patients in the test group did multiorgan failure develop, while in the control group, this condition developed in 11% of the cases. In thirty-three patients receiving a diet of similar composition, Kudsk *et al.* (1996) observed a significant reduction in the rate of severe infectious complications, in the need for antibiotic treatment, and in length of hospital stay.

In our own double-blind study involving twenty-nine severely polytraumatized patients receiving a supplementary diet containing arginine, *n*-3 fatty acids and

ribonucleotides, we found a significant reduction in the incidence of SIRS, in particular, in the critical phase between postinjury days 7 and 14 (Weimann *et al.* 1998). Overall, in this particular period, significantly lower MOF scores were also seen. However, as in the report by Moore *et al.* (1994), no effect on the mortality rate, the length of stay in the ICU, or the duration of hospitalization was seen (Weimann *et al.* 1998).

A meta-analysis of the data from the above-mentioned and a further nine studies, including patients undergoing visceral surgery and medical patients, revealed significant benefits of enteral immunonutrition, in particular in surgical patients (Beale *et al.* 1999). These include a reduction in the infection rate, in the requirement for mechanical ventilation in the ICU, and in overall hospital stay. Although no hard clinical data are currently available, the use of parenteral *n*-3 fatty acids during sepsis is presently not recommended, since enhancement of an existing immunosuppression cannot be excluded.

References

- Beale RJ, Bryg DJ & Bihari DJ (1999) Immunonutrition in the critically ill: A systemic review of clinical outcome. *Critical Care Medicine* **27**, 2799–2805.
- Biffi WL, Moore EE, Zallen G, Johnson JL, Gabriel J, Offner PJ & Silliman CC (1999) Neutrophils are primed for cytotoxicity and resist apoptosis in injured patients at risk for multiple organ failure. *Surgery* **126**, 198–202.
- Houdijk AP, Rijnsberger ER, Jansen J, Wesdorp RI, Weiss JK, McCamish MA, Teerlink T, Meuwissen SG, Haarman HJ, Thijs LG & van Leeuwen PA (1998) Randomised trial of glutamine-enriched enteral nutrition on infectious morbidity in patients with multiple trauma. *Lancet* **352**, 772–776.
- Kudsk KA, Minard G, Croce MA, Brown RO, Lowrey TS, Pritchard FE, Dickerson RN & Fabian TC (1996) A randomized trial of isonitrogenous enteral diets after severe trauma. An immune-enhancing diet reduces septic complications. *Annals of Surgery* **224**, 531–543.
- Moore FA, Moore EE, Kudsk KA, Brown RO, Bower RH, Koruda MJ, Baker CC & Barbul A (1994a) Clinical benefits of an immune-enhancing diet for early postinjury enteral feeding. *Journal of Trauma* **37**, 607–615.
- Moore EE, Moore FA, Franciose RJ, Kim FJ, Biffi WL & Banerjee A (1994b) The postischemic gut serves as a priming bed for circulating neutrophils that provoke multiple organ failure. *Journal of Trauma* **37**, 881–887.
- Swank GM & Deitch EA (1996) Role of the gut in multiple organ failure: bacterial translocation and permeability changes. *World Journal Surgery* **20**, 411–417.
- Weimann A, Bastian L, Bischoff WE, Grotz M, Hansel M, Lotz J, Trautwein C, Tusch G, Schlitt HJ & Regel G (1998) The influence of an immune-enhanced enteral diet on systemic inflammatory response syndrome in patients with severe multiple injury. *Nutrition* **14**, 165–172.
- Weimann A, Bastian L, Grotz M, Heine J & Schlitt HJ (1999) Welche Bedeutung besitzt der Darm in der Ätiologie des Multiorganversagens. *Aktuelle Ernährungs-Medizin* **24**, 20–24.