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Manipulations of the Metabolic Response for Management of Patients with Severe Surgical Illness: Review

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Abstract. The metabolic response to severe surgical illness is complex and varied. Much recent laboratory and clinical research has focused on increasing our understanding of the metabolic response and the development of new therapies designed to modify this response. Antiinflammatory agents can target harmful aspects of the metabolic response; the immune system can be stimulated; and anabolic factors can be used in an attempt to enhance recovery. The nutritional support of the surgical patient remains crucial, but the effects of new additives are being studied in a variety of surgical conditions. As yet, few of these "novel" agents have found an established role in the management of surgical patients. This review focuses on many "novel" agents or those that do not yet have a clearly defined role in surgical illness. Clinical trials in the areas of severe sepsis, major surgical trauma, and major elective surgery have been emphasized.

The cornerstone of management of severe surgical illness has been prudent, timely surgical intervention coupled with the intensive support of failing organs. With our current knowledge of the metabolic responses to severe surgical illness, the range of new or novel therapies has expanded in the hope of significantly enhancing patient recovery from severe surgical illness.

Severe sepsis, major trauma, and major elective surgery together represent some of the greatest challenges faced by surgeons and intensivists. These areas highlight the vital need for integration between basic scientific research and clinical practice.

Agents designed to manipulate the metabolic response to severe surgical illness are broadly designed to either block the harmful effects of the metabolic response or promote beneficial processes such as boosting the immune system or stimulating protein synthesis. Restoration and maintenance of tissue perfusion and oxygenation remain crucial to the metabolic recovery of the surgical patient.

Severe Sepsis

Severe sepsis is characterized by a significant inflammatory and catabolic response frequently associated with multiorgan dysfunction, which ultimately may result in multiorgan failure and death [1]. Because of the central role of inflammatory mediators in the development and maintenance of severe sepsis, much research has focused on developing strategies of antiinflammatory blockade. It is important to note that randomized studies of new therapies for severe sepsis have included patients with a variety of illnesses. No trial of new therapy has purely enrolled *surgical* patients alone; therefore the exact role of these agents in surgical practice is undefined.

Glucocorticoids

The use of high-dose glucocorticoids in patients with severe sepsis has been studied over a number of decades. Two meta-analyses [2, 3] reviewed all the randomized trials published on the use of systemic glucocorticoids in sepsis. Only one trial showed an advantage, and overall there were no data to support routine use of glucocorticoids for management of septic patients. There was, however, some evidence of a slight benefit in patients with gram-negative septicemia [2].

Delayed administration of glucocorticoids in septic patients requiring catecholamine support has been studied. In a randomized trial of 41 patients, glucorticoid administration was commenced only after patients had required catecholamines for more than 48 hours [4]. The trial showed a greater degree of reversal of shock over 7 days in the treatment cases compared with that of the controls. There was also a reduction in 28-day mortality for the steroid group compared with controls.

Routine use of glucocorticoids in sepsis cannot be supported yet. Further investigation is needed to examine subsets of patients who may benefit.

Endotoxin Blockade

Endotoxin is released predominantly during gram-negative sepsis and is central to much of the initiation of the cytokine cascade that accompanies severe gram-negative sepsis [5]. Blockade with antibody has been tested in a number of randomized trials.

The initial report of a large randomized trial of the human monoclonal antibody HA-1A concluded there was a survival advantage in patients with gram-negative bacteremia treated with the antibody [6]. However, on review by the U.S. Food and Drug Administration (FDA) [7], concerns were raised regarding the

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trial and its conclusions. In particular, the FDA review concluded that any benefit from HA-1A was confined to patients with bacteremia *and* shock. This resulted in a second trial of HA-1A being undertaken [8] only in shocked patients with gram-negative bacteremia. There was no reduction in 14-day mortality between the treatment and control groups, and the authors concluded that HA-1A had no role in clinical practice.

Two large trials have been reported of a murine monoclonal antibody (E5). The first study, with 468 patients [9], reported a reduction in mortality and alleviation of organ failure in nonshocked patients. The second trial [10], which studied nonshocked patients only, showed no reduction in mortality but did show a significant improvement in organ failure resolution compared to that in the placebo group. The study also showed that E5 significantly prevented the onset of respiratory and central nervous system failure compared with placebo. The conclusion of this second study was that further research was necessary to determine more accurately who may benefit from the E5 antibody.

Taurolidine is an antiendotoxin amino acid derivative that has antiadherent and bactericidal properties. A randomized trial has shown no difference in mortality and no advantage with organ failure resolution for those receiving the drug compared with placebo [11].

Overall, no survival advantage has been found with the use of antiendotoxin therapies. However, some advantage in the resolution of organ failure may exist with the E5 antibody.

Antibody to Tumor Necrosis Factor-α (TNFα)

TNFα is central to many of the manifestations of severe sepsis [12]. A number of antibodies have been tried in patients with severe sepsis.

The North American Sepsis Trial (NORASEPT) [13] and the International Sepsis Trial (INTERSEPT) [14] used the same mouse-derived monoclonal antibody, BAY × 1351. Both trials randomized patients to one of two doses of anti-TNFα or to placebo. The NORASEPT results in 971 patients showed no overall difference in survival between treatment and control groups; but when analyzed for the presence of shock, there was a significant reduction in mortality at day 3 for both treatment groups. However, this advantage did not extend over 28 days [13]. On the basis of these results, the INTERSEPT trial stopped enrolling nonshocked patients. The results of INTERSEPT involving 553 infused patients showed no significant difference in survival between anti-TNFα treatment and placebo but did show a significantly quicker reversal of shock in the treatment groups compared with placebo. In addition, fewer patients in the treatment arms developed organ failure of any type [14].

Another study was conducted in patients with septic shock in the NORASEPT II trial involving 1879 patients [15]. There was no survival advantage conferred by antibody administration.

In a randomized study of the murine antibody MAK 195F involving 122 patients with severe sepsis, there was no overall survival benefit [16]. However, at day 14, those patients with initial interleukin-6 (IL-6) concentrations >1000 pg/ml treated with a high dose of MAK 195F showed a significant survival advantage over those given placebo. In addition, there was a trend toward increased survival in the high-dose IL-6 group at day 28.

Another murine anti-TNFα antibody, CB0006, has undergone trials and the results suggested some benefit in patients with high circulating TNFα levels [17], but there was no impact on survival in a study of 80 patients. Antibody administration and left ventricular function in patients with septic shock has also been studied [18]. Some transient improvement was seen in left ventricular function and arterial oxygenation in 6 of 10 patients studied.

In our own facilities, we studied the effects of a chimeric antibody on protein loss, energy expenditure, and extracellular fluid expansion in a double-blind randomized trial of 56 patients with severe sepsis. Physiologic changes were studied at the height of critical illness and over successive days in a unique facility purposely built to allow the study of critically ill patients. We found no benefit from anti-TNFα administration in the physiologically and metabolically crucial areas of protein loss, energy expenditure, and extracellular fluid expansion [19].

In an attempt to avoid the development of anti-murine antibodies, a "humanized" anti-TNFα antibody has been developed. CDP571 was randomly tested in 42 patients and was shown to cause a decrease in circulating TNFα levels with increasing dose of the antibody [20]. The authors concluded that further study of this therapy was indicated to examine the impact on survival.

Overall, there is no evidence to support the routine administration of anti-TNFα therapy in septic patients. However, subsets of patients may benefit in terms of organ failure/function and possibly survival. Further clinical study is indicated.

TNFα Receptor Fusion Protein

The TNFα binds to receptors on cell surfaces and thereby triggers many of the effects seen during severe sepsis. Two cellular receptors have been identified, and both have been shown to exist in a soluble form. During sepsis there appears to be an increase in soluble TNFα receptors, which aim to bind circulating TNFα and therefore reduce cellular binding. Two double-blind randomized trials of the administration of receptor fusion protein during severe sepsis have been reported [21, 22]. Administration of the type II protein in a study of 141 patients produced no survival benefit over placebo [21]. Moreover, mortality appeared to increase significantly with higher doses of the protein. The second study of 498 patients used the type I receptor protein p55 [22]. There was no overall difference in mortality between the treatment and control patients. However, there was a nonsignificant increase in mortality among those receiving low-dose therapy compared with placebo. This finding led to discontinuation of the low-dose arm in the trial. Final analysis showed a trend toward improved 28-day survival in patients with nonrefractory shock treated with high-dose p55.

There are significant pharmacokinetic differences between the type I and type II TNFα receptors, particularly with regard to the binding of TNFα [22], which may well explain many of the differences in results between the two studies. Further investigation of the role of the p55 protein during sepsis is warranted.

Interleukin-1 (IL-1) Receptor Antagonist

IL-1 is a potent cytokine that can induce many of the features of the systemic response to sepsis [23]. The IL-1 receptor antagonist (IL-1ra), a naturally occurring protein produced during sepsis, functions by binding IL-1, thereby blocking the binding of IL-1 to cellular receptors [23]. Recombinant human IL-1ra administration has been tried during severe sepsis. In an open-label study of

99 septic patients, a survival advantage was shown with increasing dosage and in patients with septic shock at the time of entry into the study. Patients with gram-negative sepsis also showed a benefit from IL-1ra compared with placebo [24]. A large, randomized, double-blind trial involving 893 patients [25] failed to show an overall survival advantage for varying doses of IL-1ra and placebo but did suggest that patients with increasing likelihood of death may benefit from treatment. The role of IL-1ra in reversing severe sepsis and septic shock was further evaluated in a trial of 696 patients [26]. This study showed no significant reduction in mortality for those treated with IL-1ra compared with placebo. More than 50% of the patients in both the treatment and control arms of this study were in septic shock at the time of enrollment; no benefit was seen from IL-1ra administration in these patients. At this point in time, there is no defined role for the use of IL-1ra in patients with severe sepsis.

Bradykinin Blockade

Bradykinin is an early mediator in the inflammatory pathway triggered by sepsis. Blockade using a competitive antagonist, CP-0127, has been tried in a double-blind study of 504 patients [27]. Overall there was no significant effect on mortality, but there was a marked decrease in mortality among those patients with gram-negative sepsis treated with the highest dose of CP-0127. Further study of this therapy is indicated, particularly in the presence of gram-negative sepsis.

Platelet-activating Factor (PAF) Blockade

PAF is an alkylating lipid produced by a wide variety of inflammatory cells and platelets. It forms part of the activation pathway of other inflammatory mediators and acts to increase capillary permeability; it also causes arteriolar vasoconstriction, leading to pulmonary hypertension and systemic hypotension [28]. A clinical trial of the PAF antagonist BN52021 in 262 patients demonstrated no significant reduction in mortality during severe sepsis [29]. However, a retrospectively defined subset of patients with gram-negative sepsis did show a significant reduction in mortality for treatment compared with placebo. Patients in gram-negative shock at the time of enrollment also had a significant reduction in mortality with PAF antagonist treatment. Following this trial, a confirmatory study was conducted in 608 patients with suspected gram-negative sepsis [30]. It failed to show any survival advantage overall, although patients weighing more than 70 kg appeared to gain some benefit from the treatment. In a randomized trial of another PAF antagonist, TCV-309, respiratory failure was significantly alleviated in the treatment arm; but the overall 28- and 56-day mortality rates were not influenced by the agent [31]. Further clinical investigation in this subset of patients is indicated.

It is concluded that PAF antagonists do show some promise. Further research, particularly in those with gram-negative sepsis, seems warranted.

Pentoxifylline

Pentoxifylline, a methylxanthine derivative, has been advocated by some for use in chronic limb ischemia because of its purported rheologic actions. It is also known to be an inhibitor of phosphodiesterase and as a result can inhibit TNF gene transcription. In a clinical observation trial of the use of pentoxifylline in intensive care patients, significant hemodynamic improvements were seen with the use of the agent in septic patients compared to nonseptic patients [32]. A prospective double-blind trial has recently been reported of this agent verses placebo in patients with sepsis and septic shock [33]. Fifty-one patients were enrolled. Although not a primary endpoint, the overall 28-day mortality was not significantly reduced. Alleviation of organ dysfunction was noted in the treatment group. The authors noted that this study should be viewed as a pilot and that further, larger clinical trials are needed to determine the role, if any, of pentoxifylline in clinical practice.

Interferon Therapy

Initiation of the cytokine cascade early in the course of sepsis and the accompanying hyperinflammatory response lead to end-organ damage, but equally deleterious is a later hypoinflammatory phase, or "immunoparalysis" state. Protective mediators such as interferon-γ (INFγ) are inhibited during critical illness [34], and it is in this setting that further blockade of proinflammatory mediators could be harmful to the patient. The concept of boosting the immune response with INFγ was tested in a pilot study of nine septic patients with reduced human lymphocyte antigen-DR (HLA-DR) monocyte expression [35]. Compared with a historical control group, HLA-DR expression and TNF production capacity were rapidly returned to normal upon administration of INFγ. Further investigation is required to define the role, if any, of INFγ in sepsis.

Inhibition of Nitric Oxide (NO) Synthesis

NO, a free radical and potent vasodilator, is produced in increased quantities in a number of settings including sepsis [36]. Blockade is possible, and N$^{\omega}$-nitro-L-arginine methylester (L-NAME) was recently studied in 11 patients with "severe" septic shock [37]. The study found that L-NAME administration resulted in an initial increase in mean arterial pressure and systemic vascular resistance, but cardiac output and oxygen delivery were decreased. Of the 11 patients, 7 died. The study concluded that NO plays a role in the cardiovascular effects seen with sepsis, but further investigation is needed to study the role of NO blockade in sepsis.

Granulocyte Colony Stimulation

Much research has been done on the use of granulocyte colony-stimulating factor administration for a variety of hematologic cancers and for treatment of neonatal sepsis. Although shown to be of some benefit, further clinical research is needed. At present, there are no randomized clinical data from adult surgical sepsis patients.

Administration of Growth Factors

Sepsis is marked by a gross catabolic state; therefore the use of anabolic agents has theoretic appeal. Growth hormone (GH) has a promising role in the stimulation of host defenses to infection. GH promotes myeloid cell maturation and migration of phagocytes [38]. Only a limited number of clinical studies have been

conducted, each looking at various metabolic effects of recombinant human growth hormone (rhGH) in septic patients. In one study, rhGH was shown to reduce net protein catabolism significantly and lower the mean systolic and diastolic pressures in five septic surgical patients requiring parenteral nutrition [39]. A similar study in eight patients, however, failed to show any significant difference in whole-body protein turnover with a 1-week course of rhGH [40]. In a randomized study of septic patients requiring intensive care support, 3 days of rhGH administration led to improved nitrogen balance, but the positive effects were lost following the end of treatment [41].

Insulin-like growth factor-1 (IGF-1) is the agent via which GH expresses most of its anabolic effects. Early clinical experience with recombinant human IGF-I has now been published [42].

Much more research is required for both rhGH and IGF-I administration in septic patients before any significant conclusions can be drawn. However, it is important to note that a large phase III study of the effects of rhGH on catabolism in a variety of intensive care patients has raised significant questions regarding the safety of the agent (L.D. Plank, 1997, personal communication).

Nutrition

The development of nutritional support for surgical patients has been one of the greatest advances in surgical care during the twentieth century. Much research has been done to determine the best route of administration of nutritional support. It has become increasingly clear that the gut can be an important source of sepsis, although use of the gut to give nutrition seems, theoretically at least, to be ideal [43]. However, the enteral route is clearly not always available, particularly so in severely septic patients. Under such circumstances, total parenteral nutrition (TPN) is necessary.

Nutritional support is given to patients who cannot, for whatever reason, eat and absorb sufficient nutrients to supply their energy needs. In addition to supplying "metabolic fuel," nutrition has important effects on immune function and host defense against infection [43].

Although not "novel," much research continues into the metabolic effects of varying additives in nutritional supplements. During sepsis infection is already established; therefore the role of nutritional support is to aid recovery and, if possible, avoid further septic complications. These aims vary somewhat from those during major trauma or elective surgery where *prevention* of infection is one of the key aims of nutritional support.

Results from septic animal experiments have, in fact, shown some adverse effects from enteral nutrition (EN), possibly due to increased protein availability for cytokine production [44]. Recently, however, the use of "immune enhancing" agents has been tried in a variety of patients. Emphasis has been placed on arginine, nucleotides, and omega-3 fatty acid additives. In a prospective, randomized study of immune-enhanced EN versus standard EN in 398 ICU patients, a significant reduction in morbidity, particularly pulmonary problems, was seen with the enhanced diet, although overall mortality was not reduced [45]. The benefits of the enhanced diet were limited to those in whom enteral feeding was established early. It must be noted, however, that this study enrolled a heterogeneous group of patients—not only those with sepsis. Another randomized trial of similar immune-enhancing agents compared with standard EN showed a significant reduction in nosocomial infections and overall hospital stay in the septic subgroup of patients treated with the enhanced diet [46].

Research on the use of parenteral nutrition in septic patients has involved the use of high-proportion branched-chain amino acid solutions. In a study of 69 septic patients, of whom 54 had intraabdominal sepsis, mortality was significantly reduced in the groups receiving more branched-chain amino acids compared to those receiving "standard" TPN [47]. The authors postulated that the beneficial effects of branched-chain-rich TPN may be due to the preservation of higher levels of certain amino acids, particularly glutamine and arginine.

The long-term benefits of glutamine-enhanced parenteral nutrition have been studied. In a randomized trial of 84 intensive care patients requiring parenteral nutrition, a significant survival advantage was seen at 6 months for the glutamine-enhanced group [48]. Benefit was particularly significant in patients requiring TPN for more than 10 days.

The mechanisms via which enhanced nutritional formulas affect the metabolic response seen during severe sepsis are not fully determined. It seems, however, that altered gut mucosal barrier function and improved immune function are at least partly responsible [43].

Major Trauma

The metabolic response to trauma is designed to restore the "normality" of physiology rapidly; however, when trauma is severe, the hypermetabolic responses that accompany the trauma can themselves be harmful to the patient [49]. Appropriate resuscitation, wound débridement, fracture stabilization, and organ support remain the mainstays of surgical treatment. Recently, much clinical research has focused on the use of anabolic agents and protecting the patient from infection (particularly from endogenous sources) as ways of manipulating the metabolic response.

Administration of Growth Factors

Growth factors are anabolic agents; hence their use during trauma is appealing. Both rhGH and IGF-I have been studied. In a randomized trial of 14 patients with multiple injuries, 7 days of rhGH significantly increased serum IGF-I levels and the levels of IGF-I binding protein-3 (IGFBP-3), but no significant anabolic effects were noted [50]. The authors concluded that some form of growth hormone resistance exists early in the posttrauma phase despite the apparent stimulation of IGF-I levels by the rhGH. Similar findings and conclusions were reached in a study of 16 head or spinal trauma patients who were each receiving enteral nutrition and who were randomized to rhGH or placebo [51]. IGF-I itself has also been tried. A significant fall in protein breakdown was observed in a study of eight burn patients [52]. Clearly, the interaction of anabolic agents and the control of catabolism in trauma patients remains to be determined, and there is much ongoing research.

Interferon Therapy

With infection being recognized as a serious risk for patients suffering from major trauma, immune boosting with INFγ has

attracted much interest. Three large randomized trials have been published. In a study of 213 patients, those treated with IFNγ had higher monocyte counts, but septic complications did not differ significantly between the groups [53]. There were, however, fewer septic complications requiring therapeutic intervention in the IFNγ group. A second study involving 416 patients reported similar findings [54]. In addition, there were significantly fewer sepsis-related deaths in the INFγ-treated patients compared to those in controls. The authors of this second study noted that the results closely resembled those of one center in the study, and an "unidentified imbalance" may have significantly affected the results. The third major randomized study of INFγ administration during trauma examined 216 burn patients [55]. There was no reduction in 90-day mortality with INFγ treatment, nor was there a reduction in septic complications. At present, no data support the routine use of INFγ in trauma patients.

Nutrition

The role of nutritional support during major trauma is not only to provide for the caloric needs of the patient but also to act as prophylaxis against infection. The gut is now recognized as a significant source of sepsis in the injured patient. Gut permeability is increased after major trauma, and coupled with this is the risk of serious metabolic consequences secondary to the onset of a systemic inflammatory response [56]. As a result, considerable attention has been paid to the best route of administration for nutritional support. Several large studies of EN versus TPN after major abdominal trauma have been conducted and were reviewed in the *World Journal of Surgery* [43]. Two studies showed a significant reduction in septic complications for the EN groups, and a third study with only 22 patients showed a nonsignificant fall in septic complications for EN patients. Only one of the four studies showed no difference between the groups. In all these studies, most of the complications were respiratory, and this complication was reduced the most by EN compared with TPN. As a result of the above studies coupled with increased understanding of the importance of the gut as a source of sepsis, EN has become the preferred route of administration in trauma patients requiring nutritional support.

As noted above, much recent nutritional research has centered around immune-enhanced enteral nutrition (IEEN). In a randomized trial of 98 severely traumatized patients, those who received IEEN had significantly higher T lymphocyte counts, significantly fewer intraabdominal abscesses, and significantly fewer episodes of multiple organ failure [57]. Similar results were seen in a smaller study of patients who required laparotomy to treat trauma [58]. The latter study showed the significant benefit of any form of early EN over no (or delayed) nutrition is similarly injured patients. A third randomized trial of enhanced enteral feed versus standard EN, however, did not show any benefit from the enhanced formula [59], emphasizing the need for continued research into the composition and timing of nutritional support. A randomized trial in 51 burn patients also failed to show any benefit of enhanced EN over standard EN [60].

In our department, we have conducted a blinded, randomized trial of glutamine-enriched enteral nutrition and standard EN in predominantly head-injured patients. We demonstrated no significant difference in septic complications or in total body protein levels between the two groups (in preparation).

Major Elective Surgery

The metabolic response to major elective surgery is characterized by significant fat and protein loss and by marked postoperative fatigue [61]. Major postoperative complications, particularly respiratory ones, are closely related to the degree of protein loss experienced by the surgical patients [62, 63]. Emphasis on modifying this response has been in a number of areas, each designed to minimize the effects of major surgery or enhance the restoration of normal structure and function.

Growth Factors

The anabolic effects of growth factors have been outlined above. A number of studies have investigated both GH and IGF-I in a variety of types of major elective surgery. In a randomized study of 38 patients who had undergone major gastrointestinal surgery, increased protein synthesis was seen in those treated with rhGH and TPN versus TPN alone [64]. The same group studied protein synthesis and immune function in 180 patients undergoing open gallbladder surgery again treated with TPN or TPN plus rhGH and showed that an improved nitrogen balance could be achieved early during the postoperative phase of rhGH administration. In addition, immunoglobulin levels were preserved in the rhGH group [65]. Improved nitrogen balance was achieved by rhGH use in a randomized study of 15 malnourished patients requiring TPN after major abdominal surgery [66]. Similar results were shown in a randomized study of 18 patients following gastrectomy or colectomy [67].

Not all investigations have shown positive results. In a study of 18 patients undergoing elective aortic aneurysm repair, no benefit was seen after 6 days of preoperative rhGH treatment compared with placebo [68]. Our own recently completed pilot study of pre- and postoperative rhGH use in panproctocolectomy patients also failed to show a benefit for minimizing total body protein loss (in preparation). Interestingly, in both these "negative" studies, patients were not receiving supplemental nutrition, in contrast to the studies cited above that showed a benefit from rhGH administration.

Insulin-like growth factor-1 has been tried following large bowel resection [69]. Nineteen patients were randomized to IGF-I or placebo. All patients were receiving TPN in addition to the study agent. Whereas IGFBP-3 levels rose significantly, there was no significant effect on nitrogen balance, although there was a trend toward reduced protein catabolism. No effect on protein catabolism or nitrogen balance was observed in another randomized trial of IGF-I in 30 patients undergoing elective colorectal surgery [70].

It seems that there is evidence of a benefit in protein metabolism from the use of rHGH, particularly when combined with nutritional supplements. Whether it equates with a reduction in surgical morbidity requires further clinical investigation. The dose and duration of treatment must be determined and to whom it should be administered.

Nutrition

As with sepsis and trauma, the role of nutritional support has been investigated extensively for major elective surgery. The route of administration of nutrition in patients deemed in need of support

Table 1. Summary of the effects of various agents on manipulating the metabolic response during surgery.

Agent	Summary of effects	References
Glucocorticoids	No overall benefit in sepsis, but some subgroups may benefit	2, 3, 4
Endotoxin blockade	No survival benefit in sepsis; possible benefit in organ failure resolution during sepsis	6, 8, 9, 10, 11
Anti-TNFα	No survival advantage in sepsis	13, 14, 15, 16, 17, 18, 19, 20
TNFα fusion protein	P55 may be beneficial in sepsis	21, 22
IL-1ra	No significant benefit in sepsis	24, 25, 26
Bradykinin blockade	Possible role in gram-negative sepsis	27
Platelet-activating factor blockade	Possible role particularly in gram-negative sepsis	28, 29, 30, 31
Pentoxifylline	No role in sepsis at present; large studies needed	33
Interferon therapy	Further sepsis studies necessary; no indication for routine use in trauma	35, 53, 54, 55
Inhibition of nitric oxide synthesis	Further studies necessary in surgical patients	37
Growth hormone	Some concern regarding use in critical illness, although some transient benefits in sepsis; no benefit shown in trauma; beneficial effect in major elective gastrointestinal surgery, particularly when combined with nutritional support	39, 40, 41, 50, 51, 64, 65, 66, 67, 68
IGF-1	Further sepsis research necessary; some reduction in protein loss shown in burn patients; no benefit seen in major elective surgery	42, 69, 70
Nutritional support	If required, immune-enhanced formulas show most benefit in a variety of surgical patients	43, 45, 46, 47, 48, 57, 58, 59, 60, 71, 72, 73, 74, 75

TNFα: tumor necrosis factor α; IL-1ra: interleukin-1 receptor antagonist; IGF-1: insulin-like growth factor-1.

has been studied extensively. In general, if the gastrointestinal tract can be used, enteral nutrition is superior to parenteral administration [43].

The role of preoperative nutrition has been studied extensively. In general, severely malnourished surgical patients benefit from preoperative parenteral nutrition [71]. A major study of patients undergoing liver resection has also shown significant benefit from preoperative parenteral nutrition. The most pronounced benefit was in cirrhotic patients [72].

Whether enteral nutrition should routinely be prescribed after major surgery has been examined in a randomized study of 195 patients undergoing surgery for esophageal, pancreatic, or bilary cancer [73]. No significant difference was seen in morbidity, mortality, or hospital stay between patients fed enterally with an immune-enhancing solution and those in whom oral intake was restored over a number of days postoperatively. In a study of 164 patients undergoing esophageal, pancreatic, or gastric resection for cancer, patients were randomized to immune-enhanced enteral nutrition or a standard isocaloric, isonitrogenous control diet [74]. The was a significant reduction in late postoperative infections in the enhanced-diet group. In an earlier study of the effects of immune-enhanced enteral feeding after gastrointestinal cancer surgery, postoperative immune function was improved by immune-enhanced enteral feeding versus conventional enteral nutrition [75].

At present there is no uniformity of opinion as to which elective surgical patients, if any, require routine administration of enteral nutrition. When such nutrition is deemed appropriate, the use of immune-enhancing formulas seems to be supported by clinical research.

Conclusions

Many therapies have been tried in an attempt to modify the metabolic response to severe surgical illness (Table 1). That few therapies have consistently proved to be of benefit highlights the complexities of the metabolic response. Not only is there variation among septic, trauma, and elective surgical patients, there is also marked variation among patients within each of these groups. Continued clinical research is needed to identify patients who may benefit from new therapies that alter the metabolic response. In addition, much work remains to identify not only the correct therapies but also the correct dosage and duration of administration of these promising therapies. Surgeons and intensivists must continue to work together to improve our understanding of the metabolic response to surgical illness and the effects of the therapeutic agents use in attempts to modify this response. Finally, it cannot be overemphasized that no amount of metabolic manipulation can compensate for poorly judged or poorly performed surgery.

Résumé

La réponse métabolique à une agression chirurgicale sévère est complexe et variée. Beaucoup de la recherche récente de laboratoire et en clinique ont contribué à améliorer notre compréhension de la réponse métabolique ainsi que dans le développement de nouvelles thérapies désignées à modifier cette réponse. Par l'action des agents anti-inflammatoires, on pourrait cibler les aspects nocifs de la réponse métabolique; on pourrait également stimuler le système immun et des facteurs anaboliques peuvent être utilisés pour essayer d'améliorer la période de récupération. Le soutien nutritionnel du patient chirurgical reste crucial; on étudie également les effets de nouveaux composés qui pourraient agir dans une variété de conditions chirurgicales. Jusqu'à présent, très peu de ces agents «nouveaux» ont trouvé un rôle bien défini dans le traitement des patients en chirurgie. Cette revue vise plusieurs de ces agents «nouveaux» dont le rôle n'est pas encore bien défini dans l'agression chirurgicale. Des essais cliniques dans le domaine du sepsis sévère, du traumatisme chirurgical majeur et de la chirurgie majeure élective sont signalés.

Resumen

La respuesta metabólica a la enfermedad quirúrgica grave es compleja y variada. Mucha de la investigación experimental y clínica reciente se ha orientado a incrementar el conocimiento de la respuesta metabólica y desarrollar nuevas terapias que permitan modificarla. Los agentes antiinflamatorios pueden modificar aspectos nocivos de la respuesta metabólica; el sistema inmunitario puede ser estimulado; y se pueden utilizar factores anabólicos con miras a acelerar la recuperación. El soporte nutricional del paciente quirúrgico sigue siendo crucial, y actualmente se estudia el valor de aditivos en el manejo de determinadas situaciones quirúrgicas. Por lo pronto, muy pocos de estos agentes "noveles" han demostrado un rol definido. La presente revisión se ha enfocado sobre los agentes "noveles" o sobre aquellos agentes que todavía no han demostrado un papel significante en el manejo de la enfermedad quirúrgica. Se hace énfasis sobre los ensayos clínicos en las áreas de la sepsis severa, el trauma quirúrgico mayor y la cirugía electiva mayor.

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