Cell Response to Surgery

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Objectives: To describe the profound alterations in host immunity that are produced by major surgery as demonstrated by experimental and clinical studies, and to evaluate the benefits of therapeutic strategies aimed at attenuating perioperative immune dysfunction.

Data Sources: A review of the English-language literature was conducted, incorporating searches of the MEDLINE, EMBASE, and Cochrane collaboration databases to identify laboratory and clinical studies investigating the cellular response to surgery.

Study Selection: Original articles and case reports describing immune dysfunction secondary to surgical trauma were included.

Data Extraction: The results were compiled to show outcomes of different studies and were compared.

Data Synthesis: Current evidence indicates that the early systemic inflammatory response syndrome observed after major surgery that is characterized by proinflammatory cytokine release, microcirculatory disturbance, and cell-mediated immune dysfunction is followed by a compensatory anti-inflammatory response syndrome, which predisposes the patient to opportunistic infection, multiple organ dysfunction syndrome, and death. Because there are currently no effective treatment options for multiple organ dysfunction syndrome, measures to prevent its onset should be initiated at an early stage. Accumulating experimental evidence suggests that targeted therapeutic strategies involving immunomodulatory agents such as interferon-γ, granulocyte colony-stimulating factor, the prostaglandin E2 antagonist, indomethacin, and pentoxifylline may be used for the treatment of systemic inflammatory response syndrome to prevent the onset of multiple organ dysfunction syndrome.

Conclusions: Surgical trauma produces profound immunological dysfunction. Therapeutic strategies directed at restoring immune homeostasis should aim to redress the physiological proinflammatory–anti-inflammatory cell imbalance associated with major surgery.

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Surgical trauma produces alterations in the hemodynamic, metabolic, and immune responses of patients in the postoperative period. Like most physiological responses, the injury response is a dynamic process that follows a specific pattern that has been defined based on clinical and scientific observations. The initial proinflammatory immune response, or systemic inflammatory response syndrome (SIRS), is mediated primarily by the cells of the innate immune system. This is followed by a compensatory anti-inflammatory or immunosuppressive phenotype that is mediated primarily by cells of the adaptive immune system and predisposes the host to septic complications. In some susceptible individuals, this can lead to multiple organ dysfunction syndrome (MODS) and death. The SIRS–compensatory anti-inflammatory response syndrome–MODS paradigm is shown in Figure 1. Sepsis, SIRS, and MODS contribute significantly to postoperative mortality in the intensive care setting. Because treatment of MODS is largely supportive, it is reasonable to suggest that therapies directed at modulating SIRS or at blocking compensatory anti-inflammatory response syndrome, thereby preventing the onset of MODS, will prove more beneficial than efforts to treat MODS once it has ensued. Whereas protective immunity is critically dependent on adequate cytokine balance as well as macrophage–T-cell interaction, surgical trauma–induced immune dysfunction results from disruption of these homeostatic mechanisms. An increased understanding of the mechanisms responsible for postoperative immune dysfunction may lead to the development of targeted preventive and therapeutic strategies for the benefit of surgical patients in the future. This review

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outlines the acute-phase response, counterinflammatory response, and metabolic stress response associated with major surgery. It also describes the potentially beneficial immunomodulatory strategies that might be applied following major trauma. Owing to the vast nature of this important topic, related issues including injury-induced activation of the coagulation cascade and the roles of the sympathetic nervous system, high-mobility group box 1 protein, and the innate immune response are not discussed in detail here. It should be noted, however, that these related issues are relevant to the pathophysiology of the response to injury, inflammation, and infection, and they provide an additional dimension of complexity to the topic that is beyond the scope of this review.

ACUTE-PHASE RESPONSE

The cytokine cascade activated in response to surgical trauma consists of a complex biochemical network with diverse effects on the injured host. Whereas elements of the immune system are stimulated to an excessive degree following major surgery, other functions such as that of cell-mediated immunity are dramatically paralyzed.

Cytokines are immune mediators that direct the inflammatory response to sites of injury and infection and are essential for wound healing. An exaggerated production of proinflammatory cytokines from the primary site of injury, however, can manifest systemically as hemodynamic instability or metabolic derangements. Proinflammatory cytokine production in the intraoperative and early postoperative periods is initiated by macrophages and monocytes at the initial site of injury as part of the acute-phase response. These cytokines include tumor necrosis factor-α (TNF-α) and interleukin 1β (IL-1β), which are primarily responsible for the nonhepatic manifestations of the acute-phase response, including fever and tachycardia. In turn, TNF-α and IL-1β stimulate the production and release of other cytokines, including IL-6.4,5

Interleukin 6 primarily regulates the hepatic component of the acute-phase response resulting in the generation of acute-phase proteins, including C-reactive proteins. C-reactive protein levels rise approximately 4 to 12 hours after surgery and peak at 24 to 72 hours. Subsequently, C-reactive protein levels remain elevated for approximately 2 weeks. Circulating levels of several other acute-phase proteins, including serum amyloid A, procalcitonin, C3 complement, and haptaglobin, have also been shown to increase after traumatic insult, providing further evidence of a systemic host response. Interleukin 6 is also a primary effector in the production of other acute-phase proteins, including antiproteases and fibrinogen, which are involved in nonspecific and specific immunity as inflammatory mediators, scavengers, and protease inhibitors. Accordingly, increased levels of IL-6 in surgical trauma are associated with marked elevations of levels of C-reactive proteins and neutrophil elastase. It has been suggested that IL-6 may influence polymorphonuclear leukocyte (PMNL)–mediated inflammation via its role in stimulating the proliferation of PMNL progenitors in the bone marrow. Clinically, the release of IL-6 has been shown in studies by Shen

kin et al and Mokart et al to correlate with the duration of surgery and the requirement for postoperative ventilation. High levels of IL-6 have been associated with an increased severity of tissue trauma in a number of studies, including a series by Cruickshank et al that demonstrated higher levels of IL-6 in the serum of patients undergoing abdominal aortic and colorectal surgery than in those undergoing hip replacement despite similar operating times. Lower levels of IL-6 have also been observed in patients undergoing laparoscopic procedures when compared with those undergoing open surgery such as cholecystectomy and colonic resections. Additionally, elevations in IL-6 levels have been correlated with the subsequent development of postoperative complications.

MICROCIRCULATORY DYSFUNCTION

Microcirculatory disturbances are common in patients who have undergone prolonged hypoperfusion secondary to significant intraoperative blood loss. The initial response to severe blood loss is mediated through the sympathetic nervous system and results in vasoconstriction of arterioles and venules. This results in reduced capillary blood flow with a resulting increase in hydrostatic pressure. The local microcirculatory inflammatory response is characterized by a pronounced leukocyte accumulation and adherence to the endothelial lining of blood vessels. This is associated with an increase in microvascular permeability, reflecting the underlying disruption of endothelial integrity, and can lead to MODS. This surgically induced inflammatory response may be further enhanced by manual handling of the tissues. Animal studies have indicated that exteriorization of the mesentery following initial laparotomy results in a marked increase of venular leukocyte accumulation secondary to enhanced rolling and adhesion interactions. The mechanisms involved in surgical trauma–induced microvascular inflammation are thought to include endogenous...
TNF-α release, as in vivo analysis of the microcirculation has shown that both the leukocytic response and the endothelial injury can be attenuated by the administration of a monoclonal antibody directed against this proinflammatory cytokine. Several studies have indicated that the adhesion molecules implicated in inflammatory processes, namely the selectins, leukocytic β2-integrin CD11b/CD18, and endothelial intercellular adhesion molecule 1, also appear to be involved in the immune response to trauma. It has been shown that major surgery elevates serum levels of P-selectin, E-selectin, intercellular adhesion molecule 1, and vascular cell adhesion molecule 1 (Figure 2). During the initial phase of adherence, selectins on leukocytes (L-selectin), endothelial cells (E-selectin), and platelets (P-selectin) interact to produce leukocyte “rolling.” Subsequently, up-regulation of leukocyte integrins such as CD11a/CD18, CD11c/CD18, and intercellular adhesion molecule 1 or vascular cell adhesion molecule 1 on endothelial cells can be observed after surgical injury. Combined with the capillary leakage caused by proinflammatory cytokine release and increased nitric oxide production, the interaction of these adhesion molecules leads to a stable cell-cell contact with PMNL attachment, a so-called sticking of PMNLs, resulting in microcirculatory obstruction and failure of transcapillary exchange. This altered endothelial microenvironment produces a severe, widespread vascular dysfunction with tissue and cell damage resulting from cellular hypoxia and accumulation of metabolites.

The sequence and effects of these events in the lung are summarized in Figure 3. Experimental studies have shown that the application of a monoclonal antibody directed against CD18 significantly reduces leukocyte adhesion and microcirculatory dysfunction that are due to surgical trauma.

### INCREASED INTESTINAL PERMEABILITY

Alterations in intestinal permeability have been described following major surgery and have been attributed to the generalized hyperpermeability seen with this state. This results in a breakdown of the gut mucosal barrier as well as leakage of luminal bacteria and endotoxin into the portal and systemic circulation. The translocation process involves the initial attachment of the microbe to the gut wall, which then elicits production of cytokines and initiates the inflammatory response. Once intact organisms penetrate the mucosa, they may be transported to distal organs or the systemic circulation; this has been shown to occur in patients with illness ranging from mild to critical. The development of SIRS and MODS in the absence of an identifiable focus of infection in patients after major surgery has led to the hypotheses that microorganisms from the intestinal tract may be the causative organisms and that endotoxin is involved in the pathogenesis and pathophysiological findings of these syndromes.

### METABOLIC STRESS RESPONSE

The stress, fear, and pain often observed in the surgical patients following major surgery produce metabolic alterations that adversely affect the host. Major surgery results in reduced metabolism for approximately 24 hours postoperatively. This is followed by a catabolic phase of up to 2 weeks’ duration and a final reparative phase characterized by anabolic metabolism. During this anabolic phase, increased levels of amino acids are required for the synthesis of acute-phase proteins in the liver. The hypothalamic release of corticotropin-releasing hormone results in increased corticotropin secretion, which in turn raises serum steroid levels. Increased glucocorticoid production results in inhibition of protein synthesis, increased muscular protein degradation, and mobilization of fats by lipolysis. Additionally, increased serum steroid levels limit inflammatory reactivity of mononuclear cells and suppress antibody production. The anti-inflammatory effects of glucocorticoids include decreased TNF-α and IL-1 transcription, inducible cyclooxygenase 2 generation, and adhesion molecule expression.
pression. In different inflammatory cell types, glucocorticoids increase the intracellular expression of IκB-α–inhibitory protein κB-α, which inhibits the activation of nuclear factor κB. The influence of glucocorticoids on inflammatory cells appears to be cell specific. In vitro animal studies have shown dexamethasone to be capable of inducing apoptosis in T lymphocytes, with thymocytes being most sensitive and CD8+ T cells being more sensitive than CD4+ T cells. In contrast, in vitro dexamethasone exposure delays apoptosis in normal neutrophils and prolongs their functional responsiveness. In healthy human subjects, glucocorticoid administration immediately before or concomitantly with endotoxin infusion has been shown to attenuate the systemic inflammatory response partly by altering cytokine expression. A randomized trial by Bollaert et al in which patients requiring catecholamines for more than 48 hours postoperatively were administered glucocorticoids showed attenuation of shock over 7 days as compared with controls who were treated with catecholamines but not glucocorticoids. There was also a reduction in the 28-day mortality for the steroid group compared with controls who were treated with catecholamines but not glucocorticoids. There was also a reduction in the 28-day mortality for the steroid group compared with controls. In patients undergoing coronary artery bypass, methylprednisolone administration preoperatively appears to reduce IL-6 and IL-8 production whereas IL-10 and IL-1 production remain unchanged.46

COUNTERINFLAMMATORY RESPONSE

Although IL-6 functions as a proinflammatory cytokine in the early postoperative period, it can also exert anti-inflammatory effects by attenuating TNF-α and IL-1 activity while promoting the release of IL-1Ra and soluble TNF receptors. By binding to the proinflammatory cytokines TNF-α and IL-1β, these serve to attenuate the proinflammatory response. Also, via its central role in the acute-phase response, IL-6 induces macrophages to release prostaglandin E2, a powerful endogenous immunosuppressant. The effects of prostaglandin E2 include the inhibition of T-cell mitogenesis, IL-2 production, and IL-2 receptor expression. In addition, via intracellular activation of cyclic adenosine monophosphate, prostaglandin E2 further abrogates the inflammatory response through negative control of macrophage TNF-α and IL-1β synthesis. Prostaglandin E2 also stimulates the release of the potent anti-inflammatory cytokine IL-10. These profound anti-inflammatory effects result in a dramatic cytokine imbalance that is clinically referred to as the compensatory anti-inflammatory response syndrome. This syndrome is characterized by low levels of the proinflammatory cytokines TNF-α, IL-1β, IL-12, and interferon γ (IFN-γ) but markedly elevated levels of the anti-inflammatory cytokines IL-6, IL-10, and IL-1Ra. It is associated with an immunosuppressed state. Immune incompetence under these conditions is further contributed to by the deactivation of monocytes, which is characterized by markedly reduced HLA-DR antigen receptor expression, a loss of antigen-presenting capacity, and a reduced ability of these cells to produce TNF-α on stimulation with lipopolysaccharide (LPS) in vitro. The depression of monocytic HLA-DR antigen expression caused by major surgical trauma is also thought to correlate with sepsis severity and outcome. This monocytic deactivation is thought to involve IL-10, as studies have demonstrated that LPS-induced proinflammatory cytokine production is restored with administration of a neutralizing antibody against IL-10. Furthermore, it has been shown that surgery-induced reduction of monocyte HLA-DR antigen expression closely correlates with IL-10 gene expression. Evidence also exists that transforming growth factor β may additionally contribute to the monocytic deactivation induced by surgical trauma. Increased serum levels of transforming growth factor β, which are associated with a marked depression of macrophage antigen presentation, are seen following major surgery. Experimental studies have shown that the administration of a transforming growth factor β1, 2, and 3–neutralizing antibody restores macrophage antigen presentation. Major surgical trauma also produces alterations in innate immune homeostasis. In fact, innate immune function is now thought to be significantly attenuated by surgical insult and is reflected by a marked reduction in total systemic CD4+ and CD8+ T-lymphocyte counts. Studies have shown this lymphocyte depression to correlate closely with the duration of surgery and the volume of intraoperative blood loss and have suggested that it may be secondary to the dysregulation of apoptotic cell death and survival factors known to be associated with surgical trauma. Delogu et al demonstrated a significantly higher frequency of CD4+ and CD8+ T-cell apoptosis at 24 hours after surgery. They also showed that the rate of CD8+ T-cell apoptosis correlated with the rate of infectious complications manifested during the postoperative course. T-helper cell dysfunction has also been implicated in the development of postoperative immunosuppression. The initial proinflammatory phase of the host response to injury during the early postoperative period is followed by anti-inflammatory cytokine production by Th2-type lymphocytes, including IL-10, at approximately 10 days after surgery. While the initial proinflammatory cytokine response is associated with an increased rate of adult respiratory distress syndrome, MODS, and mortality, surgery-induced immunosuppression predisposes the host to sepsis and is also associated with significant morbidity and mortality. Postoperative immunosuppression can be further exacerbated by blood transfusion, which can induce a shift toward a Th2 phenotype associated with a fall in lymphocyte count, down-regulation of antigen-presenting cells, and release of cortisol and soluble TNF receptor. The release of Th1-type cytokines and granulocyte-macrophage colony-stimulating factor sometimes induced by transfusion can produce a deleterious inflammatory response resulting in transfusion-related graft-vs-host disease. Importantly, the immunosuppressed state has also been associated with an increased rate of tumor progression and metastasis formation in patients with malignant disease.1, 2, 3–neutralizing antibody restores macrophage antigen presentation, are seen following major surgery. Experimental studies have shown that the administration of a transforming growth factor β1, 2, and 3–neutralizing antibody restores macrophage antigen presentation. Major surgical trauma also produces alterations in innate immune homeostasis. In fact, innate immune function is now thought to be significantly attenuated by surgical insult and is reflected by a marked reduction in total systemic CD4+ and CD8+ T-lymphocyte counts. 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The effects of laparoscopic techniques on postoperative immune function and inflammatory responses have been the focus of much investigation during the last 2 de-
pressed natural killer and lymphokine-activated killer cell-mediated tumor growth after laparotomy correlates with supraventricular paralysis and postoperative sleep disturbances have been associated with laparoscopic surgery. Laparoscopic surgery has also been shown to attenuate the fall in lymphocyte count and to abrogate the decrease of monocytic HLA-DR antigen expression associated with major surgical trauma. Reduced rates of atelectasis and respiratory tract infections have been observed in laparoscopic surgery groups as compared with open surgery groups; however, it should be noted that postoperative pulmonary dysfunction is most prominent after upper abdominal surgery, a finding also relevant to laparoscopic procedures when performed in the upper abdomen. Reduced gastrointestinal paralysis and postoperative sleep disturbances have been associated with laparoscopic surgery as compared with open surgery, although the reduced opioid requirement of patients undergoing laparoscopic surgery as compared with the open surgery group remains a confounding factor in these studies. Additionally, laparoscopic surgery has been demonstrated to significantly reduce the rate of tumor progression when compared with laparotomy. It has been suggested that this may be owing to an attenuated immune dysfunction following the minimally invasive approach, as the accelerated tumor growth after laparotomy correlates with suppressed natural killer and lymphokine-activated killer cell cytotoxicity. While numerous prospective clinical trials have been established to investigate the effect of pentoxifylline on tumor growth in surgical patients, 1 group has already demonstrated a reduced rate of growth of lung metastases after laparoscopy as compared with open surgery. Further evidence will be necessary to determine whether this effect is attributable to the reduction in surgical trauma associated with the minimally invasive approach or whether other as-yet-undefined mechanisms may be involved.

**IMMUNE MODULATION AFTER SURGICAL TRAUMA**

Immune dysfunction induced by surgical trauma may comprise either an inappropriately exaggerated inflammatory response or a profound suppression of cell-mediated immunity. Although careful surgical technique, the use of a minimally invasive approach, adequate fluid replacement, and antibiotic therapy minimize surgical risk, immune dysfunction requires aggressive management once established. Immune modulation should comprise restoration of depressed immune responses as well as down-regulation of hyperinflammation. The major goal of immunotherapy should be the prevention of bacterial sepsis in patients with SIRS. Although several strategic approaches aimed at preventing the development of MODS have been tested, these have not shown any clear benefit. Clinical trials in patients with gram-negative sepsis who have used therapeutic tools such as anti-LPS monoclonal antibodies, anti-TNF antibodies, soluble TNF receptors, or an IL-1 receptor antagonist have not shown a clinically significant treatment benefit. Therefore, alleviation of SIRS before the onset of septic complications may prove to be the most efficacious approach to avoiding an irreversible, autodestructive inflammatory process. Recombinant granulocyte-macrophage colony-stimulating factor has been demonstrated to attenuate LPS-inducible TNF-α and IL-1β release by 50% within 20 hours of administration to healthy volunteers. By contrast, LPS-inducible soluble TNF receptor p75 was not detectable in incubated blood from untreated donors but increased dramatically 44 hours after granulocyte-macrophage colony-stimulating factor treatment. After LPS challenge, the IL-1Ra level was increased 10-fold by granulocyte-macrophage colony-stimulating factor treatment. These findings led to the conclusion that granulocyte-macrophage colony-stimulating factor treatment converts peripheral leukocytes to an anti-inflammatory state characterized by attenuation of IL-1 and TNF-releasing capacity and augmentation of the release of cytokine antagonists. Interferon γ therapy has also been proposed as a therapeutic strategy for the treatment of surgically induced immune dysfunction. The first clinical application of IFN-γ was tested on patients with sepsis. Because monocyte activation requires delivery of IFN-γ, the treatment resulted in the restoration of deficient monocytic HLA-DR antigen expression and ex vivo LPS-induced TNF-α secretion. These findings are in concert with those of a number of other experimental studies that show that IFN-γ administration to patients with surgical infections is associated with an improved outcome. Decreased rates of bacterial translocation following transfusion, and reduced susceptibility to sepsis following hemorrhagic shock. Further prospective randomized trials will be necessary, however, to confirm the benefits of IFN-γ in the clinical setting. Recovery of monocyte function was associated with clearance of sepsis in this study. Another promising approach for the attenuation of an excessive systemic inflammatory response includes the use of xanthine derivatives such as pentoxifylline. This substrate selectively inhibits the formation of TNF by inhibiting TNF gene transcription. Furthermore, pentoxifylline is able to counteract neutrophil adherence to the endothelium and thereby protect against increased pulmonary vascular permeability. Consequently, pentoxifylline has been found to improve survival in various models of hemorrhagic and endotoxic shock. In a clinical observation trial, the use of pentoxifylline in intensive care patients was associated with significant hemodynamic improvements in patients with sepsis as compared with patients without sepsis. Another study by Staubach et al involving patients with sepsis and septic shock demonstrated alleviation of organ dysfunction in the treatment group as compared with controls. The effect of blockade of the anti-inflammatory mediator, prostaglandin E2, in counteracting immunosuppression after surgical trauma has also been analyzed. Early studies by Faist et al and Marke-
witz et al\textsuperscript{96} demonstrated that administration of the cycloxygenase inhibitor indomethacin effectively down-regulates the acute phase response. They noted reduced IL-6 release and restored IL-1, IL-2, and IFN-\(\gamma\) synthesis, IL-2 receptor expression, CD4\(^+\):CD8\(^+\) ratio, and lymphocyte proliferation as well as a normalized delayed-type hypersensitivity response in the presence of this agent. The histamine 2 receptor antagonist ranitidine has also been shown to effectively attenuate the postoperative immune response after elective abdominal hysterecmy by lowering IL-6–induced C-reactive protein levels\textsuperscript{97} and by reducing postoperative infectious complications in patients following acute colorectal surgery.\textsuperscript{98} The administration of anabolic agents, including recombinant human growth hormone and insulin-like growth factor 1, to patients with postoperative sepsis has also been investigated.\textsuperscript{99} Because growth hormone promotes myeloid cell maturation and the migration of phagocytes, it might also be expected to stimulate host defenses to infection. Early clinical experience with insulin-like growth factor 1, the agent by which recombinant human growth hormone expresses most of its anabolic effects, has now been published.\textsuperscript{98} However, a large phase 3 study of the effects of recombinant human growth hormone and insulin-like growth factor 1 on catabolism in various intensive care patients has raised significant questions regarding the safety of these agents.

The development of nutritional support for surgical patients has greatly advanced surgical care during the 20th century. It has become increasingly clear that the gut can be an important source of sepsis; however, the enteral route is not always available, especially in patients with severe sepsis. In addition to providing energy, nutrition has important effects on immune function and host defense against infection.\textsuperscript{100} Experimental animal studies have, however, shown some adverse effects from enteral nutrition possibly owing to increased protein availability for cytokine production.\textsuperscript{101} Use of immune-enhancing agents including arginine, nucleotides, and omega-3 fatty acid derivatives has been tried in various patients. One prospective, randomized study\textsuperscript{102} of immune-enhanced enteral nutrition vs standard enteral nutrition in 398 intensive care patients demonstrated a significant reduction in morbidity, particularly pulmonary problems, with the enhanced diet, although overall mortality was not reduced. It should be noted, however, that this study recruited a heterogeneous group of patients, not only those with surgical sepsis. Another randomized trial of similar immune-enhancing agents compared with standard enteral nutrition showed a significant reduction in nosocomial infections and length of hospital stay in the septic subgroup of patients treated with enhanced diet.\textsuperscript{103} Research on the use of total parenteral nutrition in patients with sepsis involving the use of concentrated branched-chain amino acid solutions has also shown patient benefits. In a study\textsuperscript{104} of 69 patients with sepsis, 54 of whom had intra-abdominal sepsis, mortality was significantly reduced in the group receiving more branched-chain amino acids compared with those receiving standard parenteral nutrition. It was thought that this might be owing to the preservation of higher levels of certain amino acids, particularly glutamine and arginine, in the enriched feed. The long-term benefits of glutamine-enhanced parenteral nutrition have also been studied. A randomized trial\textsuperscript{105} of 84 intensive care patients requiring parenteral nutrition demonstrated a significant survival advantage at 6 months for the glutamine-enhanced group. This benefit was particularly marked in patients requiring total parenteral nutrition for more than 10 days. The mechanisms by which enhanced nutritional formulas affect the metabolic response seen during severe sepsis have not been fully elucidated. It seems, however, that altered gut mucosal barrier function and improved immune function are at least partially responsible.\textsuperscript{100}

The type of fluid regimen administered after major surgery also bears significant implications for the patient. For several decades, trauma research has sought to uncover the best fluid for resuscitation from hemorrhagic shock. Although massive isotonic crystalloid resuscitation was a major advance in the treatment of hemorrhagic shock, the incidence of associated pulmonary edema and subsequent adult respiratory distress syndrome\textsuperscript{108} was considerable. Concerns that isotonic resuscitation might be harmful in itself gave rise to interest in small-volume hypertonic resuscitation regimens.\textsuperscript{107} The hemodynamic effects of hypertonic saline resuscitation in hemorrhagic shock are well documented. Hypertonic saline solutions restore hemodynamic parameters and effective circulating volume, in part through vasodilatation of precapillary resistance vessels and increases in cardiac preload.\textsuperscript{109} This results in the rapid improvement of mean arterial pressure, cardiac output, and peripheral perfusion.\textsuperscript{108} Articles\textsuperscript{109} in the literature also suggest reductions in postresuscitation complications such as renal failure, coagulopathies, and adult respiratory distress syndrome. The last decade has produced a revived interest in hypertonic saline after some studies demonstrated hypertonic saline–mediated immune protection with associated improved trauma outcomes.\textsuperscript{110} One such group demonstrated augmentation of immune function of healthy T cells using a mouse model.\textsuperscript{111} They showed that hypertonic saline restores function of suppressed T cells in vitro and in vivo and reduces immunosuppression after hemorrhage, thereby protecting mice from subsequent sepsis. These effects attributable to hypertonic saline were thought to be mediated by its direct influence on cellular signaling events through specific signaling pathways that include protein tyrosine kinase and up-regulation of mitogen-activated protein kinase p38. This group also demonstrated that hypertonic saline provides a costimulatory signal that enhances the proliferation of activated T cells and hypothesized that it may be capable of substituting signals lost through blockade resulting from trauma-induced suppressive factors, thereby restoring function of suppressed T cells. In this way, hypertonic saline may represent a simple but effective tool with which to modulate cellular immune function after trauma. In addition, large, randomized, controlled human trials have established the safety and efficacy of hypertonic saline resuscitation of hypovolemic trauma patients.\textsuperscript{109,112} Several in vitro experiments have demonstrated that hypertonic saline alters PMNL structure and function. The PMNLs exposed to hypertonicity before in vitro activation display diminished oxidative burst.\textsuperscript{113,114} phago-
cytosis,115 and cytotoxicity.111,115 Furthermore, incubation with hypertonic media reduces the expression of surface L-selectin and CD11b on human PMNLs.114,116,117 Also, in vivo studies have shown that human volunteers receiving hypertonic saline infusions demonstrate a reduced neutrophil CD11b expression when compared with those receiving Ringer’s lactate solution.118 Direct evidence now exists to implicate hypertonic saline in the attenuation of augmented leukocyte-endothelium interactions seen with standard isotonic resuscitation from shock. Several shock animal models have shown that a reduction in leukocyte-endothelium interactions by hypertonic saline administration can be correlated both spatially and chronologically with a diminution in microcirculatory leakage.119,120 Further research will be required to determine whether these findings will ultimately improve outcome in syndromes of systemic inflammation.

CONCLUSIONS

Experimental and clinical studies have shown that surgical trauma profoundly affects the immune system, including both the innate and adaptive immune responses. Major surgical trauma promotes an immunologic dysfunction that predisposes the patient to significant morbidity. Although decades of basic and clinical research have focused on elucidating the functional effects of trauma on the immune system, much remains to be learned about the interdependent relationship between changes in immune function and predisposition to opportunistic infections following major surgery. The combination of suppressed adaptive immune function and augmented innate immune reactivity directed against invading pathogens after surgical trauma has the potential to set in motion a critical situation with sometimes lethal consequences for the patient. Therapeutic strategies directed at alleviating immune dysfunction in such patients should aim to redress the proinflammatory–anti-inflammatory cytokine imbalance associated with major surgical trauma, thereby restoring immune homeostasis. This will be the major goal of clinical immunotherapeutics for the future.

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REFERENCES


ternational, multicenter, placebo-controlled trial of monoclonal antibody to tu-
mer necrosis factor-α in patients with sepsis. Crit Care Med. 1996;24:1431-
1440.
87. Opal SM, Fischer CJ Jr, Dhaianaut JF, et al; Interleukin-1 Receptor Antagonist Sepsis Investigator Group. Confirmatory interleukin-1 receptor antagonist trial in severe sepsis: a phase III, randomized, double-blind, placebo-controlled, mul-
89. Hershman MJ, Sonnenfeld G, Mays BW, Fleming F, Trachtenberg LS, Polk HC Jr. Effects of interferon-gamma treatment on surgically simulated wound infec-
90. Gennari R, Alexander JW, Eaves-Pyles T. IFN-γ decreases translocation and im-
94. Staubach KH, Schroder J, Stubber F, Gehre K, Traumann E, Zabel P. Effect of pentoxifylline in severe sepsis: results of a randomized, double-blind, placebo-
95. Faist E, Markewitz A, Fuchs D, et al. Immunomodulatory therapy with thymo-
96. Markewitz A, Faist E, Lang S, Endres S, Fuchs D, Reichart B. Successful res-
97. Rasmussen LA, Nielsen HJ, Sorensen S, et al. Ranitidine reduces postopera-
98. Moesgaard F, Jensen LS, Christiansen PM, et al. The effect of ranitidine on post-opera-
99. Yarwood GD, Ross RJM, Medbak S, Coakley J, Hinds CJ. Administration of hu-
102. Atkinson S, Sieffert E, Bihari D. A prospective, randomized, double-blind, con-
103. Bower RH, Cerra FB, Bershadsky B, et al. Early enteral administration of a for-
mula (Impact) supplemented with arginine, nucleotides, and fish oil in inten-
sive care unit patients: results of a multicenter, prospective, randomized, clini-
302.
107. Nakayama Y, Sibley L, Gunther RA, Holcroft JW, Kramer GC. Small-volume re-
110. Coimbra R, Hoyt DB, Juenger WG, et al. Hypertonic saline resuscitation de-
111. Juenger WG, Hoyt DB, Davis RE, et al. Hypertonicity regulates the function of human neutrophils by modulating chemoattractant receptor signaling and ac-
2779.
112. Younes RN, Aun F, Ching CT, et al. Prognostic factors to predict outcome fol-
lowing the administration of hypertonic/hyperoncotic solution in hypovolemic patients. Shock. 1997;7:79-83.
113. Murao Y, Hoyt DB, Loomis W, et al. Does the timing of hypertonic saline re-
suscitation affect its potential to prevent lung damage? Shock. 2000;14:18-
23.
114. Rhee P, Wang D, Ruff P, et al. Human neutrophil activation and increased ad-
116. Rizoli SB, Kapus A, Fan J, Li YH, Marshall JC, Rotstein OD. Immunomodula-
tory effects of hypertonic resuscitation on the development of lung inflamma-
117. Ciesla DJ, Moore EE, Zallen G, Biffi WL, Stillman CC. Hypertonic saline attenu-
120. Pascual JL, Khwaja KA, Ferri LE, et al. Hypertonic saline resuscitation attenu-