

# 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  $\gamma$ , granulocyte colony-stimulating factor, the prostaglandin  $E_2$  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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**S**URGICAL 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.<sup>1</sup> 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.<sup>2</sup> 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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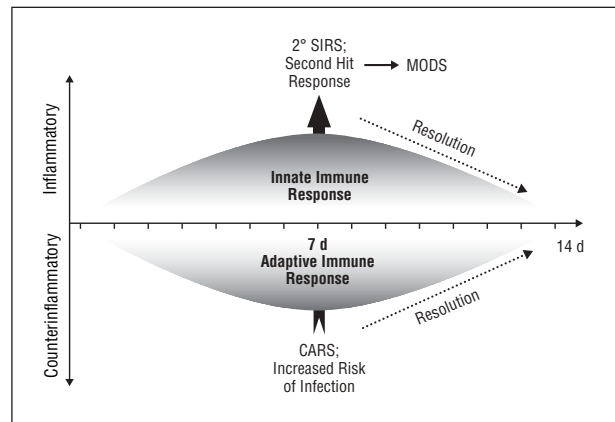
outlines the acute-phase response, counterinflammatory response, and metabolic stress response associated with major surgery. It also describes the potentially beneficial immunomodulatory strategies that might be applied following major trauma. Owing to the vast nature of this important topic, related 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.<sup>3</sup> These cytokines include tumor necrosis factor  $\alpha$  (TNF- $\alpha$ ) and interleukin 1 $\beta$  (IL-1 $\beta$ ), which are primarily responsible for the nonhepatic manifestations of the acute-phase response, including fever and tachycardia. In turn, TNF- $\alpha$  and IL-1 $\beta$  stimulate the production and release of other cytokines, including IL-6.<sup>4,5</sup>

Interleukin 6 primarily regulates the hepatic component of the acute-phase response resulting in the generation of acute-phase proteins, including C-reactive proteins.<sup>3</sup> 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.<sup>6</sup> Circulating levels of several other acute-phase proteins, including serum amyloid A,<sup>7</sup> procalcitonin,<sup>8</sup> C3 complement,<sup>9</sup> and haptoglobin,<sup>9</sup> 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 antiproteinases and fibrinogen, which are involved in nonspecific and specific immunity as inflammatory mediators, scavengers, and protease inhibitors.<sup>3</sup> Accordingly, increased levels of IL-6 in surgical trauma are associated with marked elevations of levels of C-reactive proteins and neutrophil elastase.<sup>10,11</sup> 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.<sup>12</sup> Clinically, the release of IL-6 has been shown in studies by Shen-

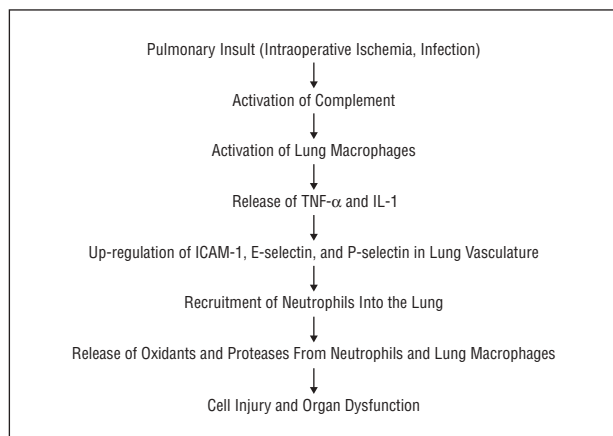


**Figure 1.** Model of injury for systemic inflammatory response syndrome (SIRS), compensatory anti-inflammatory response syndrome (CARS), and multiple organ dysfunction syndrome (MODS). Patients surviving the early proinflammatory SIRS response to major surgery may develop a counterinflammatory response of CARS. This is associated with the onset of postoperative immunosuppression and predisposes patients to the development of opportunistic infection. In a sizeable minority of patients, this may lead to MODS and death.

kin et al<sup>13</sup> and Mokart et al<sup>14</sup> 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<sup>15</sup> 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<sup>16</sup> and colonic resections.<sup>17</sup> Additionally, elevations in IL-6 levels have been correlated with the subsequent development of postoperative complications.<sup>4</sup>

### 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,<sup>18</sup> 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.<sup>19</sup> The mechanisms involved in surgical trauma-induced microvascular inflammation are thought to include endogenous



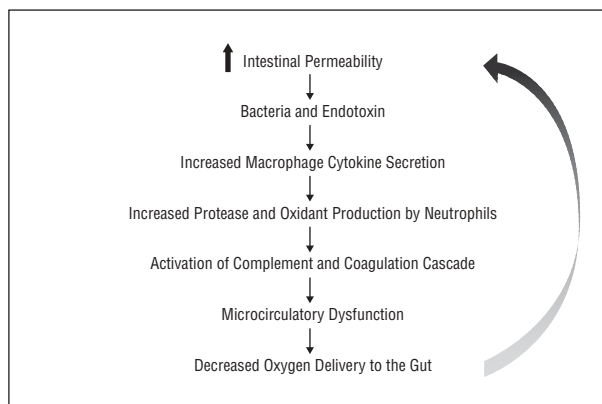
**Figure 2.** Model of lung injury induced by immune dysfunction. TNF- $\alpha$  indicates tumor necrosis factor  $\alpha$ ; IL-1, interleukin 1; ICAM-1, intercellular adhesion molecule 1.

TNF- $\alpha$  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.<sup>18</sup> Several studies<sup>20</sup> have indicated that the adhesion molecules implicated in inflammatory processes, namely the selectins, leukocytic  $\beta$ 2-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<sup>21-23</sup> as well as increases expression of leukocytic CD11a and CD11b, endothelial intercellular adhesion molecule 1, and vascular cell adhesion molecule 1 (**Figure 2**).<sup>24-27</sup> During the initial phase of adherence, selectins on leukocytes (L-selectin), endothelial cells (E-selectin), and platelets (P-selectin) interact to produce leukocyte “rolling.”<sup>28</sup> 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.<sup>28</sup> Combined with the capillary leakage caused by proinflammatory cytokine release and increased nitric oxide production,<sup>29</sup> 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<sup>19</sup> 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<sup>30</sup> and have been attrib-



**Figure 3.** Effects of injury-induced gastrointestinal hyperpermeability. Increased intestinal permeability results in the translocation of bacteria from the gut lumen into the systemic circulation. This stimulates increased cytokine secretion by macrophages, which in turn activates neutrophil proteases and induces oxidant release. These activate the complement cascade, which adversely affects the microcirculation and results in decreased oxygen delivery to the gut, further aggravating the hyperpermeable state.

uted to the generalized hyperpermeability seen with this state.<sup>31</sup> 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.<sup>32</sup> 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<sup>33</sup>; this has been shown to occur in patients with illness ranging from mild to critical.<sup>34</sup> 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.<sup>35</sup>

#### 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.<sup>36</sup> 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.<sup>37</sup> Increased glucocorticoid production results in inhibition of protein synthesis, increased muscular protein degradation, and mobilization of fats by lipolysis.<sup>37,38</sup> Additionally, increased serum steroid levels limit inflammatory reactivity of mononuclear cells and suppress antibody production.<sup>38</sup> The anti-inflammatory effects of glucocorticoids include decreased TNF- $\alpha$  and IL-1 transcription, inducible cyclooxygenase 2 generation, and adhesion molecule ex-

pression.<sup>39</sup> 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.<sup>40</sup> 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<sup>+</sup> T cells being more sensitive than CD4<sup>+</sup> T cells.<sup>41</sup> In contrast, in vitro dexamethasone exposure delays apoptosis in normal neutrophils and prolongs their functional responsiveness.<sup>42</sup> 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.<sup>43,44</sup> A randomized trial by Bollaert et al<sup>45</sup> 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. 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.<sup>46</sup>

#### 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.<sup>47</sup> 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 E<sub>2</sub>, a powerful endogenous immunosuppressant.<sup>48</sup> The effects of prostaglandin E<sub>2</sub> include the inhibition of T-cell mitogenesis, IL-2 production, and IL-2 receptor expression.<sup>49</sup> In addition, via intracellular activation of cyclic adenosine monophosphate, prostaglandin E<sub>2</sub> further abrogates the inflammatory response through negative control of macrophage TNF-α and IL-1β synthesis.<sup>49</sup> Prostaglandin E<sub>2</sub> also stimulates the release of the potent anti-inflammatory cytokine IL-10.<sup>50</sup> These profound anti-inflammatory effects result in a dramatic cytokine imbalance that is clinically referred to as the compensatory anti-inflammatory response syndrome.<sup>14</sup> 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.<sup>14,51,52</sup> 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.<sup>53</sup> The depression of monocytic HLA-DR antigen expression caused by major surgical trauma<sup>54,55</sup> is also thought to

correlate with sepsis severity and outcome.<sup>56,57</sup> This monocytic deactivation is thought to involve IL-10, as studies<sup>58</sup> 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.<sup>59</sup> Evidence also exists that transforming growth factor β may additionally contribute to the monocytic deactivation induced by surgical trauma.<sup>60,61</sup> Increased serum levels of transforming growth factor β, which are associated with a marked depression of macrophage antigen presentation, are seen following major surgery.<sup>60</sup> Experimental studies<sup>60</sup> 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.<sup>62</sup> 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<sup>+</sup> and CD8<sup>+</sup> T-lymphocyte counts.<sup>63</sup> Studies<sup>63</sup> 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<sup>64</sup> demonstrated a significantly higher frequency of CD4<sup>+</sup> and CD8<sup>+</sup> T-cell apoptosis at 24 hours after surgery. They also showed that the rate of CD8<sup>+</sup> 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.<sup>2,65-67</sup> 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 55.<sup>68,69</sup> Also, 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.<sup>68</sup> Importantly, the immunosuppressed state has also been associated with an increased rate of tumor progression and metastasis formation in patients with malignant disease.<sup>70</sup>

#### BENEFITS OF LAPAROSCOPIC SURGERY

The effects of laparoscopic techniques on postoperative immune function and inflammatory responses have been the focus of much investigation during the last 2 de-

caes. Experimental studies<sup>11,71</sup> have demonstrated a reduced impairment of the delayed-type hypersensitivity response, ie, the release of oxygen free radicals and TNF, for the laparoscopic approach as compared with conventional open surgery. Laparoscopic cholecystectomy has been shown to produce a reduced inflammatory response with lower C-reactive protein and IL-6 levels when compared with the open procedure.<sup>72,73</sup> Studies have also demonstrated that a reduction of surgical trauma by the use of a minimally invasive approach restores the decreased IL-2, IFN- $\gamma$ , and TNF- $\alpha$  production by T cells observed with open surgery.<sup>71</sup> 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.<sup>55</sup> Reduced rates of atelectasis and respiratory tract infections have been observed in laparoscopic surgery groups as compared with open surgery groups<sup>74,75</sup>; 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<sup>76-78</sup> and postoperative sleep disturbances<sup>79</sup> 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.<sup>80,81</sup> 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.<sup>80</sup> While numerous prospective clinical trials have been established to investigate the effect of pneumoperitoneum 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.<sup>81</sup> 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 develop-

ment 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,<sup>82</sup> anti-TNF antibodies,<sup>83,84</sup> soluble TNF receptors,<sup>85,86</sup> or an IL-1 receptor antagonist<sup>87</sup> 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- $\alpha$  and IL-1 $\beta$  release by 50% within 20 hours of administration to healthy volunteers.<sup>88</sup> 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. 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  $\gamma$  therapy has also been proposed as a therapeutic strategy for the treatment of surgically induced immune dysfunction. The first clinical application of IFN- $\gamma$  was tested on patients with sepsis. Because monocyte activation requires delivery of IFN- $\gamma$ , the treatment resulted in the restoration of deficient monocytic HLA-DR antigen expression and ex vivo LPS-induced TNF- $\alpha$  secretion.<sup>55</sup> These findings are in concert with those of a number of other experimental studies that show that IFN- $\gamma$  administration to patients with surgical infections is associated with an improved outcome,<sup>89</sup> decreased rates of bacterial translocation following transfusion,<sup>90</sup> and reduced susceptibility to sepsis following hemorrhagic shock.<sup>91</sup> Further prospective randomized trials will be necessary, however, to confirm the benefits of IFN- $\gamma$  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.<sup>92</sup> 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,<sup>93</sup> 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<sup>94</sup> 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 E<sub>2</sub>, in counteracting immunosuppression after surgical trauma has also been analyzed. Early studies by Faist et al<sup>95</sup> and Marke-

witz et al<sup>96</sup> demonstrated that administration of the cyclooxygenase 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<sup>+</sup>:CD8<sup>+</sup> 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 hysterectomy by lowering IL-6–induced C-reactive protein levels<sup>97</sup> and by reducing postoperative infectious complications in patients following acute colorectal surgery.<sup>98</sup> 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.<sup>99</sup> 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.<sup>99</sup> 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.<sup>100</sup> Experimental animal studies have, however, shown some adverse effects from enteral nutrition possibly owing to increased protein availability for cytokine production.<sup>101</sup> Use of immune-enhancing agents including arginine, nucleotides, and omega-3 fatty acid derivatives has been tried in various patients. One prospective, randomized study<sup>102</sup> 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.<sup>103</sup> 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<sup>104</sup> 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<sup>105</sup> 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.<sup>100</sup>

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<sup>106</sup> was considerable. Concerns that isotonic resuscitation might be harmful in itself gave rise to interest in small-volume hypertonic resuscitation regimens.<sup>107</sup> 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.<sup>108</sup> This results in the rapid improvement of mean arterial pressure, cardiac output, and peripheral perfusion.<sup>108</sup> Articles<sup>109</sup> 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.<sup>110</sup> One such group demonstrated augmentation of immune function of healthy T cells using a mouse model.<sup>111</sup> 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.<sup>109,112</sup> 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,<sup>113,114</sup> phago-

cytosis,<sup>115</sup> and cytotoxicity.<sup>111,115</sup> Furthermore, incubation with hypertonic media reduces the expression of surface L-selectin and CD11b on human PMNLs.<sup>114,116,117</sup> 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.<sup>118</sup> 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.<sup>119,120</sup> 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

- Bone RC. Immunologic dissonance: a continuing evolution in our understanding of the systemic inflammatory response syndrome (SIRS) and the multiple organ dysfunction syndrome (MODS). *Ann Intern Med.* 1996;125:680-687.
- Faist E, Schinkel C, Zimmer S. Update on the mechanisms of immune suppression of injury and immune modulation. *World J Surg.* 1996;20:454-459.
- Baumann H, Gaudie J. The acute phase response. *Immunol Today.* 1994;15:74-80.
- Baigrie RJ, Lamont PM, Kwiatkowski D, Dallman MJ, Morris PJ. Systemic cytokine response after major surgery. *Br J Surg.* 1992;79:757-760.
- Desborough JP. The stress response to trauma and surgery. *Br J Anaesth.* 2000;85:109-117.
- Ohzato H, Yoshizaki K, Nishimoto N, et al. Interleukin-6 as a new indicator of inflammatory status: detection of serum levels of interleukin-6 and C-reactive protein after surgery. *Surgery.* 1992;111:201-209.
- Casl MT, Coen D, Simie D. Serum amyloid A protein in the prediction of post-burn complications and fatal outcome in patients with severe burns. *Eur J Clin Chem Clin Biochem.* 1996;34:31-35.
- Dehne MG, Sablotzki A, Hoffmann A, Muhling J, Dietrich FE, Hempelmann C. Alterations of acute phase reaction and cytokine production in patients following severe burn injury. *Burns.* 2002;28:535-542.
- Spies M, Wolf SE, Barrow RE, Jeschke MG, Herndon DN. Modulation of types I and II acute phase reactants with insulin-like growth factor-1/binding protein-3 complex in severely burned children. *Crit Care Med.* 2002;30:83-88.
- Hildebrandt U, Kessler K, Pistorius G, et al. Granulocyte elastase and systemic cytokine response after laparoscopic-assisted and open resections in Crohn's disease. *Dis Colon Rectum.* 1999;42:1480-1486.
- Hildebrandt U, Kessler K, Plusczyk T, Pistorius G, Vollmar B, Menger MD. Comparison of surgical stress between laparoscopic and open colonic resections. *Surg Endosc.* 2003;17:242-246.
- Botha AJ, Moore FA, Moore EE, Sauaia A, Banerjee A, Peterson VM. Early neutrophil sequestration after injury: a pathogenic mechanism for multiple organ failure. *J Trauma.* 1995;39:411-417.
- Shenkin A, Fraser WD, Series J, et al. The serum interleukin-6 response to elective surgery. *Lymphokine Res.* 1989;8:123-127.
- Mokart D, Capo C, Blanche JL, et al. Early postoperative compensatory anti-inflammatory response syndrome is associated with septic complications after major surgical trauma in patients with cancer. *Br J Surg.* 2002;89:1450-1456.
- Cruickshank AM, Fraser WD, Burns HJ, Van Damme J, Shenkin A. Response of serum interleukin-6 in patients undergoing elective surgery of varying severity. *Clin Sci.* 1990;79:161-165.
- Kloosterman T, von Bloemberg BM, Borgstein P, Cuesta MA, Scheper RJ, Meijer S. Unimpaired immune functions after laparoscopic cholecystectomy. *Surgery.* 1994;115:424-428.
- Ueo H, Honda M, Adachi M, et al. Minimal increase in serum interleukin-6 levels during laparoscopic cholecystectomy. *Am J Surg.* 1994;168:358-360.
- Yamauchi J, Vollmar B, Wolf B, Menger MD. Role of TNF-alpha in local surgical trauma-induced microvascular dysfunction. *Dig Surg.* 1999;16:400-406.
- Fiebig E, Ley K, Arfors KE. Rapid leukocyte accumulation by "spontaneous" rolling and adhesion in the exteriorized rabbit mesentery. *Int J Microcirc Clin Exp.* 1991;10:127-144.
- Menger MD, Vollmar B. Adhesion molecules as determinants of disease: from molecular biology to surgical research. *Br J Surg.* 1996;83:588-601.
- Wildhirt SM, Schulze C, Schulz C, et al. Reduction of systemic and cardiac adhesion molecule expression after off-pump vs conventional coronary artery bypass grafting. *Shock.* 2001;16(suppl 1):55-59.
- Boldt J, Ducke M, Kumble B, Papsdorf M, Zurmeyer EL. Influence of different volume replacement strategies on inflammation and endothelial activation in the elderly undergoing major abdominal surgery. *Intensive Care Med.* 2004;30:416-422.
- Sasajima K, Onda M, Miyashita M, et al. Role of L-selectin in the development of ventilator-associated pneumonia in patients after major surgery. *J Surg Res.* 2002;105:123-127.
- Shijo H, Iwabuchi K, Hosoda S, Wantanabe H, Nagaoka I, Sakakibara N. Evaluation of neutrophil functions after experimental abdominal surgical trauma. *Inflamm Res.* 1998;47:67-74.
- Klava A, Windsor AC, Ramsden CW, Guillou PJ. Enhanced polymorphonuclear leukocyte adhesion after surgical injury. *Eur J Surg.* 1997;163:747-752.
- Sendt W, Amberg R, Schoffel U, Hassan A, von Specht BU, Farthmann EH. Local inflammatory peritoneal response to operative trauma: studies on cell activity, cytokine expression, and adhesion molecules. *Eur J Surg.* 1999;165:1024-1030.
- Hogevold HE, Lyberg T, Kahler H, Reikeras O. Expression of beta-2-integrins and L-selectin by leukocytes and changes in acute phase reactants in total hip replacement surgery. *Eur Surg Res.* 1996;28:190-200.
- Seekamp A, Jochum M, Ziegler M, et al. Cytokines and adhesion molecules in elective and accidental trauma-related ischaemia/reperfusion. *J Trauma.* 1998;44:874-882.
- Bateman RM, Sharpe MD, Ellis CG. Bench-to-bedside review: microvascular dysfunction in sepsis: hemodynamics, oxygen transport, and nitric oxide. *Crit Care.* 2003;7:359-373.

30. Roumen RM, van der Vliet JA, Wevers RA, Goris RJ. Intestinal permeability is increased after major vascular surgery. *J Vasc Surg.* 1993;17:734-737.
31. Pape HC, Dwenger A, Regel G, et al. Increased gut permeability after multiple trauma. *Br J Surg.* 1994;81:850-852.
32. Rush BF Jr. Irreversibility in hemorrhagic shock is caused by sepsis. *Am Surg.* 1989;55:204-208.
33. Balk RA. Severe sepsis and septic shock: definitions, epidemiology, and clinical manifestations. *Crit Care Clin.* 2000;16:179-192.
34. Lemaire LCJM, van Lanschot JJB, Stoutenbeek CP, van Deventer SJH, Wells CL, Gouma DJ. Bacterial translocation in multiple organ failure: cause or epiphenomenon still unproven. *Br J Surg.* 1997;84:1340-1350.
35. Marshall JC, Christou NV, Meakins JL. The gastrointestinal tract: the "undrained abscess" of multiple organ failure. *Ann Surg.* 1993;218:111-119.
36. Woolf PD. Hormonal response to trauma. *Crit Care Med.* 1992;20:216-226.
37. Singer M, De Santis V, Vitale D, Jeffcoate W. Multiorgan failure is an adaptive, endocrine-mediated, metabolic response to overwhelming systemic inflammation. *Lancet.* 2004;364:545-548.
38. Hill AG, Hill GL. Metabolic response to severe injury. *Br J Surg.* 1998;85:884-890.
39. Wissink S, van Heerde EC, van der Burg B, van der Saag PT. A dual mechanism mediates repression of NF- $\kappa$ B activity by glucocorticoids. *Mol Endocrinol.* 1998;12:355-363.
40. Brostjan C, Anrather J, Cszizmadia V, Natarajan G, Winkler H. Glucocorticoids inhibit E-selectin expression by targeting NF- $\kappa$ B and not ATF/c-Jun. *J Immunol.* 1997;158:3836-3844.
41. Ayala A, Herdon CD, Lehman DL, DeMaso CM, Ayala CA, Chaudry IH. The induction of accelerated thymic programmed cell death during polymicrobial sepsis: control by corticosteroids but not tumor necrosis factor. *Shock.* 1995;3:259-267.
42. Liles WC, Dale DC, Klebanoff SJ. Glucocorticoids inhibit apoptosis of human neutrophils. *Blood.* 1995;86:3181-3188.
43. Barber AE, Coyle SM, Marano MA, et al. Glucocorticoid therapy alters hormonal and cytokine responses to endotoxin in man. *J Immunol.* 1993;150:1999-2006.
44. van der Poll T, Barber AE, Coyle SM, Lowry SF. Hypercortisolemia increases plasma interleukin-10 concentrations during human endotoxemia: a clinical research center study. *J Clin Endocrinol Metab.* 1996;81:3604-3606.
45. Bollaert PE, Charpentier C, Levy B, Debouverie M, Audibert G, Larcan A. Reversal of late septic shock with supraphysiologic doses of hydrocortisone. *Crit Care Med.* 1998;26:645-650.
46. Kawamura T, Inada K, Nara N, Wakusawa R, Endo S. Influence of methylprednisolone on cytokine balance during cardiac surgery. *Crit Care Med.* 1999;27:545-548.
47. Tilg H, Trehu E, Atkins MB, Dinarello CA, Mier JW. Interleukin-6 (IL-6) as an anti-inflammatory cytokine: induction of circulating IL-1 receptor antagonist and soluble tumor necrosis factor receptor p55. *Blood.* 1994;83:113-118.
48. Sheeran P, Hall GM. Cytokines in anaesthesia. *Br J Anaesth.* 1997;78:201-219.
49. Phipps RP, Stein SH, Roper RL. A new view of prostaglandin E regulation of the immune response. *Immunol Today.* 1991;12:349-352.
50. Ayala A, Lehman DL, Herdon CD, Chaudry IH. Mechanism of enhanced susceptibility to sepsis following hemorrhage: interleukin-10 suppression of T-cell response is mediated by eicosanoid-induced interleukin-4 release. *Arch Surg.* 1994;129:1172-1178.
51. Ogata M, Okamoto K, Kohriyama K, Kawasaki T, Itoh H, Shigematsu A. Role of interleukin-10 on hyporesponsiveness of endotoxin during surgery. *Crit Care Med.* 2000;28:3166-3170.
52. Biffi WL, Moore EE, Moore FA, Peterson VM. Interleukin-6 in the injured patient: marker of injury or mediator of inflammation? *Ann Surg.* 1996;224:647-664.
53. Docke WD, Randow F, Syrbe U, et al. Monocyte deactivation in septic patients: restoration by IFN-gamma treatment. *Nat Med.* 1997;3:678-681.
54. Hensler T, Hecker H, Heeg K, et al. Distinct mechanisms of immunosuppression as a consequence of major surgery. *Infect Immun.* 1997;65:2283-2291.
55. Walker CB, Bruce DM, Heys SD, Gough DB, Binnie NR, Eremin O. Minimal modulation of lymphocyte and natural killer subsets following minimal access surgery. *Am J Surg.* 1999;177:48-54.
56. Schinkel C, Sendtner R, Zimmer S, Faist E. Functional analysis of monocyte subsets in surgical sepsis. *J Trauma.* 1998;44:743-748.
57. Wakefield CH, Carey PD, Foulds S, Monson JR, Guillou PJ. Changes in major histocompatibility complex class II expression in monocytes and T-cells of patients developing infection after surgery. *Br J Surg.* 1993;80:205-209.
58. Strassmann G, Patil-Koota V, Finkelman F, Fong M, Kambayashi T. Evidence for the involvement of interleukin-10 in the differential deactivation of murine peritoneal macrophages by prostaglandin E2. *J Exp Med.* 1994;180:2365-2370.
59. Klava A, Windsor AC, Farmery SM, et al. Interleukin-10: a role in the development of postoperative immunosuppression. *Arch Surg.* 1997;132:425-429.
60. Ayala A, Meldrum DR, Perrin MM, Chaudry IH. The release of transforming growth factor-beta following haemorrhage: its role as a mediator of host immunosuppression. *Immunology.* 1993;79:479-484.
61. Hafez HM, Berwanger CS, Lintott P, et al. Endotoxemia during supraceliac aortic crossclamping is associated with suppression of the monocyte CD14 mechanism: possible role of transforming growth factor-beta1. *J Vasc Surg.* 2000;31:520-531.
62. Yadavalli GK, Auletta JJ, Gould MP, Salata RA, Lee JH, Heinzl FP. Deactivation of the innate cellular immune response following endotoxic and surgical injury. *Exp Mol Pathol.* 2001;71:209-221.
63. Dietz A, Heimlich F, Daniel V, Polarz H, Weidauer H, Maier H. Immunomodulating effects of surgical intervention in tumors of the head and neck. *Otolaryngol Head Neck Surg.* 2000;123:132-139.
64. Delogo G, Moretti S, Antonucci A, et al. Apoptosis and surgical trauma: dysregulated expression of death and survival factors on peripheral lymphocytes. *Arch Surg.* 2000;135:1141-1147.
65. Ertel W, Keel M, Bonaccio M, et al. Release of anti-inflammatory mediators after mechanical trauma correlates with severity of injury and clinical outcome. *J Trauma.* 1995;39:879-885.
66. Neidhardt R, Keel M, Steckholzer U, et al. Relationship of interleukin-10 plasma levels to severity of injury and clinical outcome in injured patients. *J Trauma.* 1997;42:863-870.
67. Angele MK, Faist E. Clinical review: immunodepression in the surgical patient and increased susceptibility to infection. *Crit Care.* 2002;6:298-305.
68. Klein HG. Immunomodulatory aspects of transfusion: a once and future risk? *Anesthesiology.* 1999;91:861-865.
69. Iwagaki H, Yagi T, Urushihara N, et al. Blood transfusion and postoperative plasma cytokine antagonist levels in colorectal cancer patients. *Hepatogastroenterology.* 2001;48:1351-1354.
70. Sietses C, Beelen RH, Meijer S, Cuesta MA. Immunological consequences of laparoscopic surgery, speculations on the cause and clinical implications. *Langenbecks Arch Surg.* 1999;384:250-258.
71. Brune IB, Wilke W, Hensler T, Holzmann B, Siewert JR. Downregulation of T helper type 1 immune response and altered pro-inflammatory and anti-inflammatory T cell cytokine balance following conventional but not laparoscopic surgery. *Am J Surg.* 1999;177:55-60.
72. Halevy A, Lin G, Gold-Deutsch R, et al. Comparison of serum C-reactive protein concentrations for laparoscopic vs open cholecystectomy. *Surg Endosc.* 1995;9:280-282.
73. Cho JM, LaPorta AJ, Clark JR, et al. Response of serum cytokines in patients undergoing laparoscopic cholecystectomy. *Surg Endosc.* 1994;8:1380-1384.
74. Karayiannakis AJ, Makri GG, Mantzioka A, Karousos A, Karatzas G. Postoperative pulmonary function after laparoscopic and open cholecystectomy. *Br J Anaesth.* 1996;77:448-452.
75. Schauer PR, Luna J, Ghlata AA, Glen ME, Warren JM, Sirinek KR. Pulmonary function after laparoscopic cholecystectomy. *Surgery.* 1993;114:389-399.
76. Hotokezaka M, Combs MJ, Schirmer BD. Recovery of gastrointestinal motility following open vs laparoscopic colon resection in dogs. *Dig Dis Sci.* 1996;41:705-710.
77. Hotokezaka M, Combs MJ, Mentis EP, Schirmer BD. Recovery of fasted and fed gastrointestinal motility after open vs laparoscopic cholecystectomy in dogs. *Ann Surg.* 1996;223:413-419.
78. Bohm B, Milsom JW, Fazio VW. Postoperative intestinal motility following conventional and laparoscopic intestinal surgery. *Arch Surg.* 1995;130:415-419.
79. Thaler W, Frey L, Marzoli GP, Messmer K. Assessment of splanchnic tissue oxygenation by gastric tonometry in patients undergoing laparoscopic and open cholecystectomy. *Br J Surg.* 1996;83:620-624.
80. Allendorf JD, Bessler M, Kayton ML, et al. Increased tumor establishment and growth after laparotomy vs laparoscopy in a murine model. *Arch Surg.* 1995;130:649-653.
81. Wildbrett P, Oh A, Carter JJ, et al. Increased rates of pulmonary metastases following sham laparotomy compared to CO2 pneumoperitoneum and the inhibition of metastases utilizing perioperative immunomodulation and a tumor vaccine. *Surg Endosc.* 2002;16:1162-1169.
82. Bone RC, Balk RA, Fein AM, et al; E5 Sepsis Study Group. A second large controlled clinical study of E5, a monoclonal antibody to endotoxin: results of a prospective, multicenter, randomized, controlled trial. *Crit Care Med.* 1995;23:994-1006.
83. Abraham E, Wunderink R, Silverman H, et al; TNF-alpha MAb Sepsis Study Group. Efficacy and safety of monoclonal antibody to human tumor necrosis factor  $\alpha$  in patients with sepsis syndrome: a randomized, controlled, double-blind, multicenter, clinical trial. *JAMA.* 1995;273:934-941.
84. Cohen J, Carlet J; International Sepsis Trial Study Group. INTERSEPT: an in-



- ternational, multicenter, placebo-controlled trial of monoclonal antibody to tumor necrosis factor- $\alpha$  in patients with sepsis. *Crit Care Med*. 1996;24:1431-1440.
85. Fisher CJ Jr, Agosti JM, Opal SM, et al; Soluble TNF Receptor Sepsis Study Group. Treatment of septic shock with the tumor necrosis factor receptor:Fc fusion protein. *N Engl J Med*. 1996;334:1697-1702.
  86. Abraham E, Glauser MP, Butler T, et al; Ro 45-2081 Study Group. p55 Tumor necrosis factor receptor fusion protein in the treatment of patients with severe sepsis and septic shock: a randomized controlled multicenter trial. *JAMA*. 1997;277:1531-1538.
  87. Opal SM, Fischer CJ Jr, Dhainaut 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, multicenter trial. *Crit Care Med*. 1997;25:1115-1124.
  88. Hartung T, Docke WD, Gantner F, et al. Effect of granulocyte colony-stimulating factor treatment on ex vivo blood cytokine response in human volunteers. *Blood*. 1995;85:2482-2489.
  89. Hershman MJ, Sonnenfeld G, Mays BW, Fleming F, Trachtenberg LS, Polk HC Jr. Effects of interferon-gamma treatment on surgically simulated wound infection in mice. *Microb Pathog*. 1988;4:165-168.
  90. Gennari R, Alexander JW, Eaves-Pyles T. IFN- $\gamma$  decreases translocation and improves survival following transfusion and thermal injury. *J Surg Res*. 1994;56:530-536.
  91. Ertel W, Morrison MH, Ayala A, Dean RE, Chaudry IH. Interferon- $\gamma$  attenuates hemorrhage-induced suppression of macrophage and splenocyte functions and decreases susceptibility to sepsis. *Surgery*. 1992;111:177-187.
  92. Hoffmann H, Markewitz A, Kreuzer E, Reichert K, Jochum M, Faist E. Pentoxifylline decreases the incidence of multiple organ failure in patients after major cardio-thoracic surgery. *Shock*. 1998;9:235-240.
  93. Bacher A, Mayer N, Klimscha W, Dismuller C, Steltzer H, Hammerle A. Effects of pentoxifylline on hemodynamics and oxygenation in septic and nonseptic patients. *Crit Care Med*. 1997;25:795-800.
  94. Staubach KH, Schroder J, Stuber F, Gehrke K, Traumann E, Zabel P. Effect of pentoxifylline in severe sepsis: results of a randomized, double-blind, placebo-controlled study. *Arch Surg*. 1998;133:94-100.
  95. Faist E, Markewitz A, Fuchs D, et al. Immunomodulatory therapy with thymopentin and indomethacin: successful restoration of interleukin-2 synthesis in patients undergoing major surgery. *Ann Surg*. 1991;214:264-273.
  96. Markewitz A, Faist E, Lang S, Endres S, Fuchs D, Reichart B. Successful restoration of cell-mediated immune response after cardiopulmonary bypass by immunomodulation. *J Thorac Cardiovasc Surg*. 1993;105:15-24.
  97. Rasmussen LA, Nielsen HJ, Sorenson S, et al. Ranitidine reduces postoperative interleukin-6 induced C-reactive protein synthesis. *J Am Coll Surg*. 1995;181:138-144.
  98. Moesgaard F, Jensen LS, Christiansen PM, et al. The effect of ranitidine on postoperative infectious complications following emergency colorectal surgery: a randomized, placebo-controlled, double-blind trial. *Inflamm Res*. 1998;47:12-17.
  99. Yarwood GD, Ross RJM, Medbak S, Coakley J, Hinds CJ. Administration of human recombinant insulin-like growth factor-I in critically ill patients. *Crit Care Med*. 1997;25:1352-1361.
  100. Minard G, Kudsk KA. Nutritional support and infection: does the route matter? *World J Surg*. 1998;22:213-219.
  101. Alexander JW, Ogle CK, Nelson JL. Diets and infection: composition and consequences. *World J Surg*. 1998;22:209-212.
  102. Atkinson S, Sieffert E, Bihari D. A prospective, randomized, double-blind, controlled clinical trial of enteral immunonutrition in the critically ill. *Crit Care Med*. 1998;26:1164-1172.
  103. Bower RH, Cerra FB, Bershadsky B, et al. Early enteral administration of a formula (Impact) supplemented with arginine, nucleotides, and fish oil in intensive care unit patients: results of a multicenter, prospective, randomized, clinical trial. *Crit Care Med*. 1995;23:436-449.
  104. Garcia-de-Lorenzo A, Ortiz-Leyba C, Planas M, et al. Parenteral administration of different amounts of branched-chain amino acids in septic patients: clinical and metabolic aspects. *Crit Care Med*. 1997;25:418-424.
  105. Griffiths RD, Jones C, Palmer TE. Six-month outcome of critically ill patients given glutamine-supplemented parenteral nutrition. *Nutrition*. 1997;13:295-302.
  106. Pearce FJ, Lyons WS. Logistics of parenteral fluids in battlefield resuscitation. *Mil Med*. 1999;164:653-655.
  107. Nakayama S, Sibley L, Gunther RA, Holcroft JW, Kramer GC. Small-volume resuscitation with hypertonic saline (2400 mOsm/liter) during hemorrhagic shock. *Circ Shock*. 1984;13:149-159.
  108. Velasco IT, Pontieri V, Rocha e Silva M Jr, Lopes OU. Hyperosmotic NaCl and severe hemorrhagic shock. *Am J Physiol*. 1980;239:H664-H673.
  109. Mattox KL, Maningas PA, Moore EE, et al. Prehospital hypertonic saline/dextran infusion for post-traumatic hypotension: the USA Multicenter Trial. *Ann Surg*. 1991;213:482-491.
  110. Coimbra R, Hoyt DB, Junger WG, et al. Hypertonic saline resuscitation decreases susceptibility to sepsis after hemorrhagic shock. *J Trauma*. 1997;42:602-607.
  111. Junger WG, Hoyt DB, Davis RE, et al. Hypertonicity regulates the function of human neutrophils by modulating chemoattractant receptor signaling and activating mitogen-activated protein kinase p38. *J Clin Invest*. 1998;101:2768-2779.
  112. Younes RN, Aun F, Ching CT, et al. Prognostic factors to predict outcome following 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 resuscitation 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 adhesion by various resuscitation fluids. *Crit Care Med*. 2000;28:74-78.
  115. Hampton MB, Chambers ST, Vissers MC, Winterbourn CC. Bacterial killing by neutrophils in hypertonic environments. *J Infect Dis*. 1994;169:839-846.
  116. Rizoli SB, Kapus A, Fan J, Li YH, Marshall JC, Rotstein OD. Immunomodulatory effects of hypertonic resuscitation on the development of lung inflammation following hemorrhagic shock. *J Immunol*. 1998;161:6288-6296.
  117. Ciesla DJ, Moore EE, Zallen G, Biffi WL, Silliman CC. Hypertonic saline attenuation of polymorphonuclear neutrophil cytotoxicity: timing is everything. *J Trauma*. 2000;48:388-395.
  118. Angle N, Cabello-Passini R, Hoyt DB, et al. Hypertonic saline infusion: can it regulate human neutrophil function? *Shock*. 2000;14:503-508.
  119. Pascual JL, Khwaja KA, Chaudhury P, Christou NV. Hypertonic saline and the microcirculation. *J Trauma*. 2003;54:S133-S140.
  120. Pascual JL, Khwaja KA, Ferri LE, et al. Hypertonic saline resuscitation attenuates neutrophil lung sequestration and transmigration by diminishing leukocyte-endothelial interactions in a two-hit model of hemorrhagic shock and infection. *J Trauma*. 2003;54:121-130.