Review

Clinical review: Immunodepression in the surgical patient and increased susceptibility to infection

Martin K Angele and Eugen Faist

Department of Surgery, Klinikum Grosshadern, Ludwig-Maximilians University, Munich, Germany

Correspondence: Eugen Faist, faist@gch.med.uni-muenchen.de

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Abstract

Several studies indicate that organ failure is the leading cause of death in surgical patients. An excessive inflammatory response followed by a dramatic paralysis of cell-mediated immunity following major surgery appears to be responsible for the increased susceptibility to subsequent sepsis. In view of this, most of the scientific and medical research has been directed towards measuring the progression and inter-relationship of mediators following major surgery. Furthermore, the effect of those mediators on cell-mediated immune responses has been studied. This article will focus on the effect of blood loss and surgical injury on cell-mediated immune responses in experimental studies utilizing models of trauma and hemorrhagic shock, which have defined effects on the immunoinflammatory response. Subsequently these findings will be correlated with data generated from surgical patients. The results of these studies may generate new approaches for the treatment of immunodepression following major surgery, thus reducing the susceptibility to infection and increasing the survival rate of the critical ill surgical patient.

Keywords: immunodepression, infection, surgery

Several studies indicate that organ failure is the leading cause of death in surgical patients [1]. Most cases of multiple organ dysfunction are precipitated by infection. Nonetheless, the outcome of organ dysfunction does not correlate well with the microbiology of multiple organ dysfunction syndrome [2]. Several studies indicate that a causal relationship exists between the surgical or traumatic injury and the predisposition of these patients to develop septic/infectious complications and/or multiple organ failure [3–5]. The excessive inflammatory response, together with a dramatic paralysis of cell-mediated immunity following major surgery [3,6], appears to be responsible for the increased susceptibility to subsequent sepsis.

In view of this, most of the scientific and medical research has been directed towards measuring the progression and inter-relationship of mediators that are activated or suppressed following major surgery. In most clinical studies alterations in immune parameters of patients following surgery have been assessed due to evaluation of peripheral blood cell function and plasma levels of various mediators. Therefore, animal models have been utilized that simulate the clinical conditions. This has allowed us to better define the pathophysiology of the immunoinflammatory response following surgical trauma, which reduces the patient's capability to resist subsequent life-threatening infectious complications.

This article will focus on the effect of blood loss and surgical injury on cell-mediated immune responses in experimental studies utilizing models of trauma and hemorrhagic shock, which have defined effects on the immunoinflammatory response. Subsequently each paragraph will discuss how the findings from these experimental studies correlate with data generated from surgical patients. The effect of surgeries on the susceptibility to polymicrobial sepsis and infection will then be illustrated. These studies may generate new approaches for the treatment of immunodepression following major surgery, thus reducing the susceptibility to infection and increasing the survival rate of the critical ill surgical patient.

APACHE = acute physiology and chronic health evaluation; ELISA = enzyme-linked immunosorbent assay; G-CSF = granulocyte colony stimulating factor; IFN = interferon; IL = interleukin; MHC = major histocompatibility complex; TGF = transforming growth factor; Th = T helper.

Macrophage function following surgery

Macrophage cytokine release

Altered host defense mechanisms after major surgery or trauma are considered important for the development of infectious complications and sepsis. Immune deterioration has also been reported in patients after trauma and surgery. In this respect, studies have shown areactivity of circulating monocytes towards stimulation with bacteria or endotoxin following surgical trauma [7]. This paralysis of monocyte cell function has been reported to persist for three to five days after trauma [8] and appears to be a potential risk factor for postoperative septic complications [7].

In contrast, other studies demonstrate an enhanced secretion of IL-1β and IL-10 by endotoxin-stimulated peripheral blood monocytes at different time points after surgery [9]. Differences in the severity of the surgical trauma might account for those divergent results.

In addition to cytokine release patterns, a high acute physiology and chronic health evaluation (APACHE) II score was associated with an increased number of proinflammatory CD14+ CD16+ monocytes [10]. Furthermore, high levels of CD14+ CD16+ monocytes remained in patients with persistently high APACHE II scores [10].

Macrophage antigen presentation following major surgery

Antigen presentation is defined as a process whereby a cell expresses antigen on its surface in a form capable of being recognized by a T cell. The proteinaceous antigen typically undergoes some form of processing in which it is degraded into small peptides that are capable of associating with MHC class II antigen for presentation to helper T lymphocytes or in association with MHC class I antigen to become a target for cytotoxic T lymphocytes [11]. However, for competent antigen presentation to take place, the antigen-presenting macrophage must provide a second costimulatory signal, in the form of a membrane and/or soluble factor. Impaired monocyte function and disruption of monocyte/T cell interaction have been shown to be crucial for the development of septic complications in surgical patients [12]. It this respect, human leukocyte antigen (HLA-DR) receptor expression is depressed in some surgical patients and correlates with sepsis severity and outcome [12]. Furthermore, a significant shift toward Fc receptor monocyte subsets can be found. This subpopulation resembles activated macrophages characterized by high proinflammatory cytokine synthesis and suppressed antigen presentation. Similarly, Wakefield *et al.* demonstrated that an earlier recovery of the depressed HLA-DR expression was associated with a lower rate of septic complications [13].

It should be noted that a normal or enhanced capacity of peripheral blood monocytes to present bacterial superantigens and to stimulate T cell proliferation after surgery has been found despite decreased HLA-DR antigen presentation [9]. These changes were evident despite a significant loss of cell surface HLA-DR molecules. Thus, the level of MHC class II protein expression does not necessarily predict the antigen-presenting capacity of monocytes obtained from surgical patients with uneventful postoperative recovery [9].

Moreover, MacLean *et al.* [14] and Christou *et al*. [15] have reported that the outcome of trauma patients is worsened when they exhibit a depressed, delayed-type hypersensitivity reaction (which is antigen specific). Thus, depressed cell-mediated immunity in patients following injury or major surgery, which is associated with an increased mortality from subsequent sepsis [16,17] is probably due, in part, to decreased antigen-presenting capacity by macrophages.

These above findings collectively suggest that the depression of macrophage antigen presentation capacity following injury or major surgery is an important contributory factor to the depression of cell-mediated immunity, thereby, increasing subsequent susceptibility to infection. Interestingly, multiple factors (which include decreased metabolic activity, anti-inflammatory cytokines, prostaglandins and nitric oxide) appear to be responsible for the depression of macrophage antigen-presenting capacity.

These changes in macrophage function appear to be irreversible. Therefore, we treated patients undergoing major surgery with 15 μg granulocyte colony stimulating factor (G-CSF) perioperatively, which reduced the acute inflammatory response. This anti-inflammatory effect of G-CSF might contribute to the normalization of the depressed lipopolysaccharide-induced cytokine release by monocytes following major surgery. Moreover, administration of G-CSF normalized the depressed HLA-DR expression in surgical patients. It is our hypothesis, that G-CSF induces the release of new, unaltered monocytes postoperatively, thereby preventing immunosuppression. Whether these effects of G-CSF result in a decreased infection rate following major surgery remains to be determined in a larger clinical trial.

Lymphocyte function following hemorrhagic shock

Both experimental and clinical studies indicate that a wide range of traumatic injuries alter the ability of T lymphocytes to respond to mitogenic activation (by concanavalin A and phytohemagglutinin) [18–23]. These studies demonstrate decreased mitogenic response of lymphocytes in patients following general surgery, blunt trauma, and thermal injury [20–24]. Interestingly the degree of lymphocyte depression correlated with the complexity of the surgery. Similarly, following trauma-hemorrhage decreased splenocyte proliferative capacity in response to the T cell mitogen, concanavalin A, has been demonstrated extensively in our laboratory [18,19,25,26]. In addition, Hensler *et al*. showed a severe defect of T lymphocyte proliferation and cytokine secretion *in vitro* following major surgery. In these studies, reduced

cytokine secretion by T lymphocytes was observed for IL-2, IFN-γ, and tumor necrosis factor α (TNF-α) during the early postoperative course [9]. Monocyte functions, however, were not altered, suggesting a predominant defect in the T cell response rather than an impaired monocyte antigen-presenting capacity. Thus, suppression of T-cell effector functions during the early phase of the postoperative course may define a state of impaired defense against pathogens and increased susceptibility to infection and septic complications.

Similarly, the release of Th1 lymphokines (i.e. IL-2, IFN-γ) by splenocytes has been shown to be significantly depressed as early as two hours following experimental trauma and hemorrhagic shock, simulating surgical trauma [18,19,25,26] and this depression persists for up to five days following trauma-hemorrhage [26]. In contrast to Th1 lymphokines, the release of the anti-inflammatory Th2 lymphokine, IL-10, has been shown to be increased after trauma-hemorrhage in mice [18]. Neutralizing IL-10 by the addition of anti-IL-10 monoclonal antibodies to the culture media restored the depressed splenocyte proliferative capacity in splenocytes harvested from traumatized animals [18]. Moreover, early anti-IL-10 treatment following burn injury prevented T cell immunosuppression and improved the survival rate following subsequent sepsis [27]. Thus, IL-10 following trauma-hemorrhage might contribute to the depressed splenocyte Th1 lymphokine release following trauma and injury. In contrast, van der Poll *et al.* demonstrated in a model of endotoxemia an increased mortality rate following anti-IL-10 treatment, suggesting protective effects of IL-10 following lipopolysaccharide injection [28]. Depending on the model and the time of administration, anti-IL-10 might exhibit divergent effects on immune responses.

In addition to release patterns, T lymphocyte subsets have been determined in patients with acute illness [29]. These studies indicate that following major surgery, both cell populations decrease. Patients that develop septic complications, however, display a predominant decrease in CD4+cells [30].

Moreover, changes in B cell function have also been reported following surgical trauma. The capacity of splenic B cells to produce antibodies is significantly decreased following trauma and blood loss [31,32]. In this regard, a decrease in overall serum levels of immunoglobulin was seen for up to three days after surgical trauma and blood loss [31,32]. The decreased IL-2 production by T lymphocytes has been suggested to be responsible for the downregulation of antibody production by B cells following severe injury, since T cell lymphokines are a prerequisite for adequate B cell proliferation and immunoglobulin secretion [3]. Whether restoration of T cell function following severe injury and major surgery, however, restores the depressed B cell function remains to be determined.

Circulatory inflammatory mediators

The observed immunodeficiency in trauma victims and patients following major surgery has been found to be associated with enhanced concentrations of inflammatory cytokines, reflecting activated immunocompetent cells in the patient [33]. Thus, it appears that the depressed cell-mediated immune responses *in vitro* discussed in the above paragraphs reflect hyporesponsiveness to a second stimulus following massive activation *in vivo* [34].

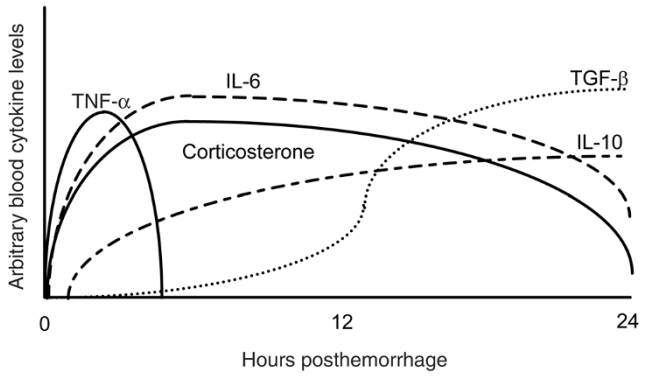
In this respect, elevated levels of TNF-α, IL-1 and IL-6 in the plasma have been well described in both animal experiments [3,35,36] and patient studies [5,37–40] following trauma, severe blood loss, and sepsis. The sequence of cytokine release following trauma and hemorrhagic shock includes an increase of plasma TNF-α as early as 30 min after the onset of injury, peak TNF-α levels by two hours post trauma and hemorrhage, and a return towards baseline values at 24 hours [3,35] (Fig. 1). In contrast to measurements using a bioassay [35], elevated plasma TNF-α levels were detectable at 24 hours post trauma and blood loss with the ELISA (enzyme-linked immunosorbent assay) technique [41]. This suggests that TNF-α detected 24 hours after injury might not be biologically active. In this regard, soluble TNF-α receptors that might neutralize the biological activity of circulating TNF-α have been isolated from the plasma [42]. Unlike TNF-α, plasma IL-6 levels are not significantly elevated until two hours post hemorrhage, and the levels remain elevated up to 24 hours after the induction of hemorrhage [43].

Since *in vivo* administration of IL-1, IL-6, and TNF-α [44–47] induces a shock-like syndrome, similar to that observed following severe blood loss and sepsis, it has been suggested that these cytokines may play a role in initiating the cascade of events that can lead to the development of multiple organ dysfunction following severe hemorrhagic shock.

Furthermore, the marked increase in the release of proinflammatory cytokines by Kupffer cells following trauma and blood loss in experimental studies has been reported to be associated with depressed immune functions [3]. This suggests that proinflammatory cytokines produced by Kupffer cells following hemorrhage act in an autocrine as well as a paracrine fashion to downregulate Kupffer cell and other macrophage populations. Furthermore, Kupffer cells, which represent the largest pool of macrophages in the body, were found to release increased amounts of IL-1, IL-6, and TNF-α following shock [44] and the selective reduction of this macrophage population by injection of gadolinium chloride significantly reduced plasma IL-6 levels following hemorrhage [48]. This leads to the conclusion that Kupffer cells are a significant source of the increased plasma levels of proinflammatory cytokines following trauma and hemorrhage, and these cytokines can act to depress macrophage function. Whether or not Kupffer cells are the only contributors to the enhanced proinflammatory plasma levels following severe injury and major surgery remains to be determined.

In contrast to the early increase of proinflammatory cytokines in the plasma following trauma and shock, elevated plasma

Figure 1



Arbitrary blood cytokine levels during the first 24 hours following trauma and hemorrhagic shock. Levels of tumor necrosis factor α (TNF-α), IL-6, and transforming growth factor β (TGF-β) were determined by specific bioassay. IL-10 was measured by ELISA and corticosterone was measured by radioimmunoassay.

levels of the anti-inflammatory cytokine, transforming growth factor (TGF)-β, are not detectable until 24 hours after the insult [49]. Furthermore, this elevation in plasma TGF-β persisted until 72 hours after trauma and hemorrhage [49]. Neutralization of TGF-β antibodies restored the depressed antigen presentation to normal levels [49]. These results, along with the studies by Miller-Graziano *et al*. [50] indicate that the enhanced release of TGF-β is an additional factor responsible for the prolonged suppression of macrophage function following hemorrhagic shock.

In addition to pro- and anti-inflammatory cytokines, numerous other mediators in the plasma have been reported to contribute to the depression of cell-mediated immune response following trauma and shock. In this respect, eicosanoids have been extensively studied as agents involved in immunological responses [51–53]. Two hours after shock, an increased release of prostaglandins and leukotrienes by macrophages occurs leading to elevated plasma levels of eicosanoids [3,54]. Moreover, prostaglandin E_2 has been shown to inhibit cell-mediated immune function [55,56]. Conversely, administration of ibuprofen (an inhibitor of cyclooxygenase) to animals following severe blood loss prevented the depression of macrophage functions [57]. Ayala *et al.* [58] have also demonstrated that rodents that were pre-fed a fish oil diet high in omega-3-fatty acids (known to inhibit the synthesis of prostaglandin E_2 via inhibition of arachidonic acid metabolism) had normal macrophage functions following hemorrhage.

Increased levels of circulating cytokines have also been reported following a variety of tissue insults in patients, including trauma, sepsis, thermal injury, and surgery [5,40,59,60]. In this regard, increased plasma IL-6 levels in patients have been observed during the first week following trauma [40]. Interestingly, levels of proinflammatory cytokines have been shown to be higher in trauma patients with severe blood loss compared to patients with trauma alone [5]. Moreover, in septic patients the increase of the proinflammatory cytokines IL-6 and TNF-α has been found to be much higher than in trauma victims without septic complications [40]. These findings suggest additive effects of trauma, blood loss, and septic complications on the immunoinflammatory response. Furthermore, proinflammatory cytokine levels, as well as the duration of elevation, appear to correlate with the severity of the insult. In addition, elevated cytokine levels have been shown to persist for five days after gastrectomy, compared to three days after mastectomy [60]. Furthermore, several clinical studies have shown an association between elevated plasma levels of proinflammatory cytokines, increased infectious complications, and higher mortality rates [5,37,61–65]. In this respect, Molloy *et al.* reported a progressive decline in TNF-α levels in survivors of septic shock, whereas TNF-α levels remained persistently elevated after initial diagnosis and attempted treatment in nonsurvivors from septic shock [66].

The above studies suggest the important contribution of proinflammatory cytokines to the pathophysiological changes seen in surgical patients and trauma victims. Therefore, determination of proinflammatory cytokine levels might become important for clinicians who encounter a trauma patient in the intensive care unit. Knowledge of the patient's cytokine levels may give him/her some indicator of the intracellular milieu, and possibly insight into cellular changes taking place. This information might give the clinician a better understanding of how to treat such a critically ill trauma patient. More refinements towards the rapid and online measurements of cytokines are needed, however, before the full benefits of such information can be effectively translated to better management of trauma patients. Although various cytokine therapies in septic patients so far have not yielded satisfactory results, the lack of beneficial effects might be related to the timing and dose of anti-cytokine administration. It is our hypothesis that total blockade/neutralization of cytokines will not be helpful to the host. Instead, modulation of cytokine production/release by immune cells (i.e. macrophages, T cells) leading to the restoration of cellular homeostasis might be a better approach for decreasing the susceptibility of trauma victims and patients following major surgery to subsequent sepsis and infection.

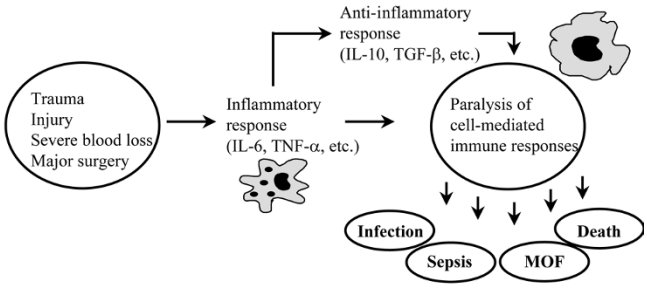
Increased susceptibility to infection

The studies mentioned above indicate depressed immunoresponsiveness after trauma and hemorrhage, which persists despite fluid resuscitation. To determine whether these observations translate into an actual reduction in the capacity of these traumatized animals to ward off infection of a clinically relevant nature, additional studies were conducted by Stephan *et al.* in which sepsis was induced 3 days after hemorrhagic shock [19]. The results demonstrate an increased susceptibility of hemorrhaged animals to polymicrobial

sepsis, as evidenced by an increased mortality rate of hemorrhaged animals following subsequent sepsis (mortality of hemorrhaged animals following subsequent sepsis 100% compared to 50% in sham animals subjected to sepsis) [19,67]. Similarly, Zapata-Sirvent *et al.* have indicated that the mortality rate in response to a septic challenge was increased in mice [68]. Interestingly, restoration of the depressed immune responses following trauma and severe blood loss with immunomodulatory agents, such as flutamide (an androgen receptor blocker), was associated with increased survival rates following subsequent sepsis [67].

An association between the loss of immunocompetence (paralysis of the cell-mediated immunity) in patients following traumatic injury, and the development of sepsis and late death has been reported [16,17] (Fig. 2). Furthermore, alterations in the levels of circulating E-selectin adhesion molecules after trauma and resuscitation have been found to be associated with an increased risk for infections complications, organ failure, and death [69]. In summary, these studies suggest that the immunodepression following injury and major surgery leads to an increased susceptibility to polymicrobial sepsis. Therefore, attempts to modulate the depressed immune responses in trauma victims might decrease the development of septic complications and multiple organ failure in those patients.

Figure 2



Hypothesis of the cascade of events following major surgery that lead to the development of depressed immune responses and increased susceptibility to sepsis. TGF-β, transforming growth factor β; TNF-α, tumor necrosis factor α.

Gender-specific immune responses following trauma, injury, and blood loss

Despite the fact that gender differences in the susceptibility to, and morbidity from, sepsis have been observed in several clinical and epidemiological studies [70–73], little attention has been paid to gender when studying immune responses in surgical and trauma patients. Furthermore, experimental studies investigating alterations in immune functions following trauma have used predominantly male laboratory animals. Recent studies initiated by Zellweger *et al*. [74], however, examined immune functions in female rodents following the induction of sepsis by cecal ligation and puncture. The results demonstrated maintenance of splenocyte function in females when they were in the proestrus stage of the estrus cycle, as opposed to depression of splenocyte function in males following cecal ligation and puncture [74]. Furthermore, the preservation of immune responses in females was also associated with higher survival rates following the induction of sepsis [74]. Subsequently, further studies were conducted investigating the effect of gender on cell-mediated immunity following injury and blood loss. In particular, females in the proestrus state showed enhanced IL-1 and IL-6 release by splenic and peritoneal macrophages, and splenocyte IL-2 and IL-3 release, as opposed to depressed macrophage and splenocyte functions in males under such conditions [75]. Higher plasma estradiol and/or higher plasma prolactin levels in proestrus females might contribute to the enhanced immune responses following hemorrhage in proestrus females. Furthermore, administration of estrogen to castrated male mice that were supplemented with testosterone improved the depressed immune responses in those animals [76]. In addition, treatment of male mice with estradiol normalized the depressed immune responses after trauma and hemorrhage and improved the survival rate following subsequent sepsis [77]. Since estradiol replacement therapy is associated with an increased rate of thromboembolism, this therapy is not useful in surgical patients [78]. Such complications, however, have not been reported with regard to the steroid hormone dehydroepiandrosterone, which has been reported to display estrogenic effects [79]. Moreover, treatment of male mice following trauma and blood loss prevented immunosuppression [80]. Since dehydroepiandrosterone is used clinically as a long-term immunoenhancing drug in humans, this hormone might represent a useful therapy for preventing immunodepression in surgical patients.

In addition to female sex steroids, the lower levels of male hormones in female animals compared to males might also contribute to the divergent immunoresponsiveness following injury and blood loss. Support for the importance of male sex hormones in producing the immune depression in males following hemorrhage comes from recent studies indicating that castration of male mice two weeks prior to hemorrhage prevented the depression of splenic and peritoneal macrophages following the hemorrhagic insult [76,81]. Moreover, depletion of testosterone by castration prior to hemorrhage normalized the IL-6 release by Kupffer cells following hemorrhage [76,81]. In attempting to address whether testosterone per se is responsible for the depressed macrophage functions following hemorrhage in males, studies were conducted in which castrated male mice were treated with 5α-dihydrotestosterone prior to trauma-hemorrhage [76]. The results demonstrated that castrated male mice treated with testosterone (which had higher plasma testosterone levels than intact males) displayed similar immune responses to hemorrhage to those shown by intact males, namely depression of splenic and peritoneal macrophage function [76]. Similarly, treatment of female mice

with 5α-dihydrotestosterone also depressed splenic and peritoneal macrophage function as well as splenocyte responses [25,82]. In addition, gender-specific immune responses have also been demonstrated in the thymus, the primary location of T cell lymphopoiesis [83]. The exact mechanism, however, for the immunomodulatory properties of male and female sex steroids following trauma-hemorrhage remains unknown.

Similar observations have been obtained in clinical trials following sepsis, surgery, or trauma and blood loss. In this regard, Bone demonstrated, in a retrospective study incorporating four major sepsis studies, a preponderance of morbidity and mortality in males compared to females [70]. McGowan *et al.* also reported a significantly higher incidence of bacteremic infections in males than in females [72]. A recent prospective study by Schröder *et al*. confirms that gender differences were observed in human sepsis, with a significantly better prognosis for women [73]. Hospital-mortality rate in this study was 70% for male compared to 26% for female patients following the induction of sepsis. Similarly, following injury, male gender has been shown to be a risk factor for the development of septic complications and pneumonia [84–86].

In summary the above studies suggest that gender, as well as the state of the estrus cycle in females, should be taken into consideration in designing not only experimental but also clinical studies concerning immune responses following trauma and shock. Moreover, the results of these studies suggest that administration of sex steroids or treatment with their specific blockers should be considered as a novel and useful approach for modulating the immune responses in those patients.

Conclusion

The above studies indicate that injury, trauma, and blood loss produce a marked suppression in cell-mediated immunity and an increased susceptibility to subsequent sepsis and wound infection. Furthermore, global as well as differential effects can be observed on macrophages that are dependent on their anatomical location. The use of a variety of immunomodulatory agents (e.g. dilitiazem, chloroquine, ibuprofen, IFN-γ, prolactin, metclopramide, and flutamide) have been shown to be helpful for the normalization of the altered immune responses following trauma and hemorrhage in experimental studies. The success in the use of immunomodulatory agents following hemorrhage in rodent models appears to be promising in the development of new therapeutic concepts for the treatment of immunosuppression and for decreasing the mortality from subsequent sepsis in humans. However, careful evaluation of both the benefits and potential adverse effects of therapy is needed before widespread clinical use can be envisioned. Recently, administration of G-CSF perioperatively has been shown to prevent immunosuppression following major surgery. The enhanced release of new, unaltered monocytes appears to be responsible for the immunoenhancing effects of G-CSF. Larger clinical trials should be initiated to verify that the immunoprotective effects of G-CSF are associated with a decreased susceptibility of surgical patients to infectious complications, thereby decreasing the mortality rate.

The immunoinflammatory response, and subsequent sepsis, is still one of the major causes of morbidity and mortality following major surgery. While significant advances have been made, it is important to further define the pathophysiology and identify the precise mechanisms responsible for the depression of the cell-mediated immunity using experimental animal models. However, these animal models should take into consideration the various manipulations that the patient receives as well as the effect of gender, nutritional status, pre-existing conditions etc. Effective treatment regimes for patients can only be developed when models of injury begin to consider these factors.

Competing interests

None declared.

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