The immune response to surgery and trauma: Implications for treatment

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BACKGROUND: Infection after surgery and trauma is a major cause of increased morbidity, mortality, and cost. Alterations of the hosts immune system following these insults is believed to be responsible for the increased risk of infection. The hosts' immune response to tissue injury is widely believed to follow a bimodal response, with the systemic inflammatory response syndrome (SIRS) followed by the compensated anti-inflammatory response syndrome (CARS). Recent data, however, suggests that his paradigm may not be correct.

METHODS: We reviewed the literature to describe the immunological changes following surgery and trauma and possible therapeutic interventions to limit this process.

RESULTS: Physical injury related to trauma and surgery increase the expression of T-helper 2 (Th2) lymphocytes which cause impaired cell mediated immunity (CMI). Activation of the hypothalamic-pituitary-adrenal (HPA) axis and sympathoadrenal system (SAS) with the release of cortisol and catecholamines appear to be responsible for altering the Th1/Th2 balance. Decreased expression and signalling of interleukin-12 (IL-12) and increased expression of T regulatory cells (Tregs) appear to play a central role in mediating this immune depression. Furthermore, Th2 cytokines increase the expression of arginase-1 (ARG1) in myeloid-derived suppressor cells (MDSC's) causing an arginine deficient state, which further impairs lymphocyte function. Immunomodulating diets (IMDs) containing supplemental arginine and omega-3 fatty acids have been demonstrated to restore the Th1/Th2 balance after surgical trauma and to reduce the risk of infectious complications. β-adrenergic receptor blockage reverses the Th-1 to Th2 shift and preliminary data suggests that such therapy may be beneficial.

CONCLUSION: Tissue injury following surgery and trauma results in depressed CMI leading to an increased risk of infections. The peri-operative use of IMDs appear to reverse this immunosuppression and decrease the risk of postoperative complications. While β-adrenoreceptor blockage may be beneficial in these patients, particularly when combined with a IMD, additional research is required. (*J Trauma Acute Care Surg*. 2012;73: 801–808. Copyright © 2012 by Lippincott Williams & Wilkins)

KEY WORDS: Surgery; trauma; immune response; T_H2 response; arginine.

Immune responses are regulated by antigen-presenting cells such as monocytes/macrophages and dendritic cells that are components of the innate immune system and T helper (T_H) and cytotoxic T lymphocytes that are components of acquired (adaptive) immunity. The innate immune system responds to pathogen-associated molecular patterns (PAMPs) predominantly via Toll-like receptor 2 (TLR2) and Toll-like receptor 4 (TLR4) to induce the expression of the nuclear transcription factors such as nuclear factor κβ (NF-κβ) and activator protein-1 (AP-1) with the subsequent production of proinflammatory cytokines, which include tumor necrosis factor α (TNF-α), interleukin 1 (IL-1), IL-6, IL-8, and IL-12.[1–3] Native $CD4^+$ T_H0 cells are bipotential and serve as precursors of T_H1 and T_H2 cells. T_H1 cells play an important role in killing intracellular pathogens, whereas T_H2 cells are important for antibody production and provide a defense against extracellular parasites. The T_H1 and T_H2 immune responses are dependent on the activation of transcription factors Stat4 and Stat6, respectively.[4] Among the factors known to influence the differentiation of these cells toward T_H1 or T_H2, cytokines produced by the innate immune system are the most important. IL-12 produced by activated monocyte/macrophages is the major inducer of T_H1 differentiation and hence cellular immunity.[5–7] T_H1 cells primarily secrete interferon γ (INF-γ), IL-2, and TNF-β, which promote cellular immunity, whereas T_H2 cells secrete a different set of cytokines (anti-inflammatory cytokines), primarily IL-4, IL-10, and IL-13, which promote humoral immunity and depress cell-mediated immunity.[5] Importantly, these T_H2 cytokines inhibit macrophage activation, T-cell proliferation, and the production of proinflammatory cytokines. T_H1 and T_H2 responses are mutually inhibitory. Homeostatic mechanisms ensure that the T_H1 and T_H2 responses are normally in balance; however, for patients with traumatic injuries and following surgery, this balance may become disturbed.

The hosts' response to surgery and injury is widely believed to follow a bimodal response.[8,9] The current paradigm suggests that tissue injury results in a systemic inflammatory response syndrome (SIRS) with "unbridled inflammation," which after a few days or weeks, evolves into the compensated anti-inflammatory response syndrome.[8–12] The initial SIRS response has been presumed to be similar to the inflammatory response associated with sepsis. However, studies performed during the last two decades suggest that this paradigm is not correct. Bacterial infection involves engagement of both the innate and adaptive immune response with bacterial antigens with production of proinflammatory mediators by macrophages and dendritic cells and the activation of T_H1 lymphocytes with the production of T_H1 cytokines. These mediators stimulate the synthesis of nitric oxide (NO) and other inflammatory mediators that result in a systemic inflammatory response. Clearly, bacterial sepsis and surgical trauma are quite different processes. However, the hosts' immune response to tissue injury and surgery is complex and poorly understood. When assessing the host response to a noxious insult, it is important to determine the balance between the proinflammatory and anti-inflammatory pathways (T_H1/T_H2) and to quantitate these changes over time. Many studies have measured proinflammatory cytokines alone and assumed that surgery/trauma results in a proinflammatory state (SIRS).[11–14] However, it has been well established that surgery and trauma cause selective suppression of T_H1 function, a shift toward a T_H2 cytokine pattern with cell-mediated immune suppression.[15–22] The depression of T_H1 immunity has been reported to increase the risk of infectious complications, most notably pneumonia, wound infections, and septicemia.[15–19] Multiple reports during the last two decades have indicated that the proliferative response to T-cell mitogens is significantly impaired for patients and experimental animals immediately after traumatic or thermal injury.[15–19] The T-cell dysfunction after traumatic stress is characterized by a decrease in T-cell proliferation, an aberrant cytokine profile, decreased T-cell monocyte interactions, and attenuated expression of the T-cell receptor complex. Furthermore, surgical stress induces a shift in the T_H1/T_H2 balance resulting in impaired cell-mediated immunity.[20–22] While the T_H1 cytokines may be increased following trauma and surgery, these cytokines do not reach the levels seen for patients with sepsis, and unlike patients with

sepsis, the T_H2 response predominates. O'Sullivan et al.[21] demonstrated that serious injury resulted in diminished production of IL-12 by peripheral mononuclear cells and a shift to the T_H2 phenotype with increased production of IL-4 and IL-10. Spolarics et al.[22] demonstrated depressed IL-12 production by monocytes following severe traumatic injury. In this study, a significant inverse correlation was found between the number of IL-12–producing monocytes and IL-4–producing $CD4^+$ cells. In addition, the depressed capacity for IL-12 production correlated with the development of multiorgan failure. Similarly, Franke et al.[23] demonstrated that HLA-DR expression, IL-12 release, and the synthesis of INF-γ were significantly reduced following cardiac surgery. Furthermore, a number of authors have demonstrated that the ability of monocytes to produce proinflammatory mediators (T_H1) in response to endotoxin is significantly reduced after severe multiple injuries.[24] Kirchhoff et al.[25] demonstrated that the capacity of circulating monocytes to produce proinflammatory mediators (TNF-α, IL-1β, IL-6, and IL-8) de novo was significantly diminished very early after trauma, reaching a nadir 24 hours after severe injury followed by a recovery during the next 48 hours. In this study, there was a significant correlation between the development of multiple-organ failure and the ex vivo cytokine response. Duggan et al.[26] studied the level of gene expression of the

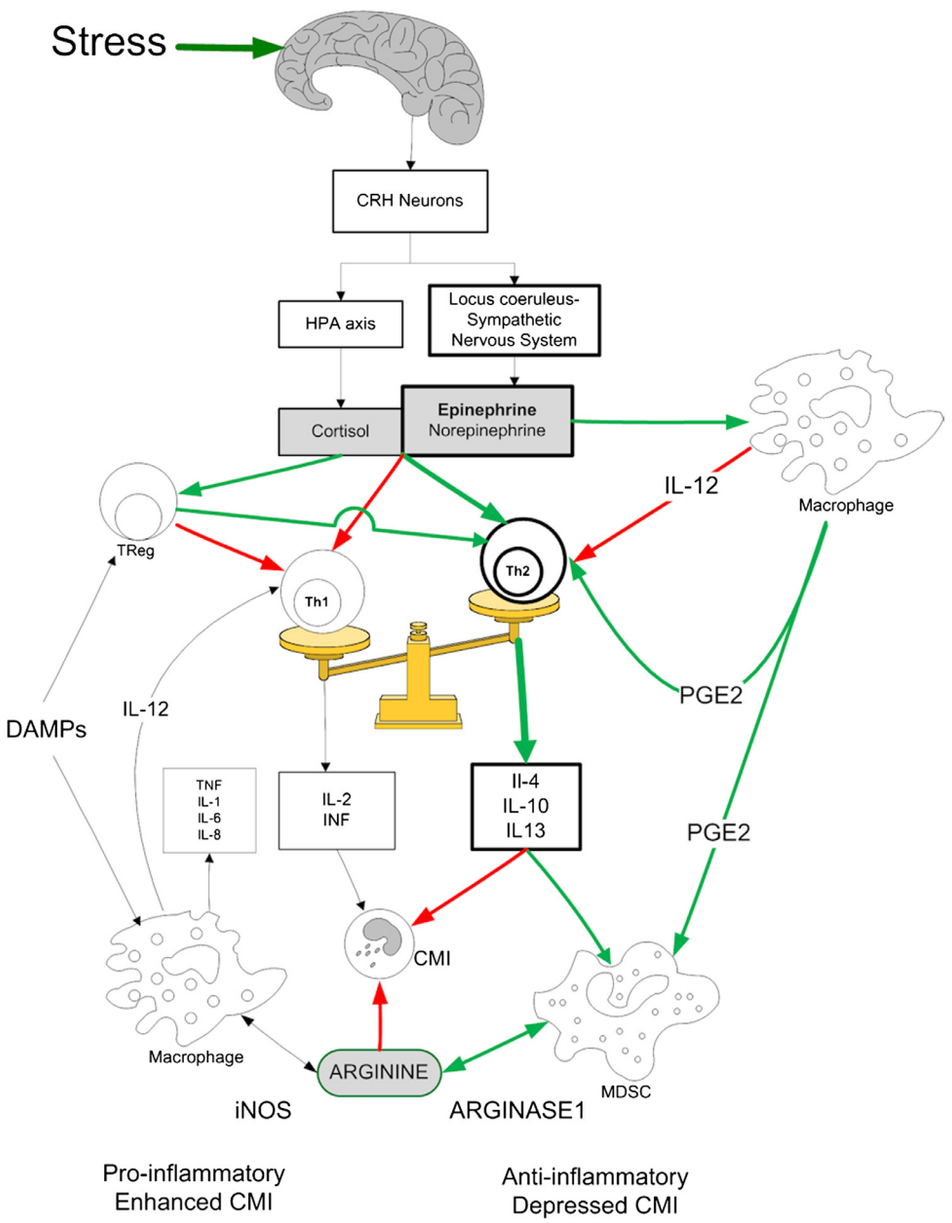

Figure 1. Postulated mechanism involved in T_H2 pathways and arginine deficiency after physical trauma. CMI, cell-mediated immunity; CRH, corticotrophin-releasing hormone; HPA, hypothalamic-pituitary-adrenal axis.

proinflammatory and anti-inflammatory cytokines TNF-α and IL-10 for patients undergoing cardiac surgery. These authors reported increased expression of IL-10 with an increased IL-10/TNF-α ratio.

A number of pathogenic pathways have recently been explored to explain activation of T_H1 cytokine-producing mononuclear cells after trauma and surgery. Tissue ischemia-reperfusion is believed to play an important role in activating the release of proinflammatory mediators following trauma.[27] Ischemia-reperfusion injury results in the production of reactive oxygen species through mitochondrial electron transport mechanisms, activation of the purine/xanthine oxidase system, and NADPH oxidase activation.[28] There is increasing evidence showing that TLR4 can transduce proinflammatory signals produced by reactive oxygen species.[28] This results in activation of NF-κβ with the production of proinflammatory cytokines. In addition to the recognition of PAMPs, TLR2 and TLR4 have been shown to recognize endogenous ligands, which have been termed *danger-associated molecular patterns* (DAMPs).[1,29,30] Tissue injury and hemorrhage following trauma induce the release of DAMPs.[1] Free heme and fragments of hyaluronic acid, a major extracellular matrix glycosaminoglycan, have been shown to activate TLR4 signaling pathways.[31–33] High-mobility group box 1 protein (HMGB1) is a nuclear-binding protein that binds nucleosomes and promotes DNA binding.[34] When cells die in a nonprogramed way, HMGB1 is released in the extracellular medium; in contrast, apoptotic cells modify their chromatin so that HMGB1 binds irreversibly and thus is not released.[34] HMGB1 levels are increased within hours after accidental trauma in humans.[35] HMGB1 has proinflammatory effects that seem to be mediated by NF-κβ transcription through TLR2 and TLR4.[34,36,37] Similarly, heat shock proteins are released extracellularly after trauma and have been shown to increase transcription of proinflammatory mediators through TLR2 and TLR4.[1,38] In addition, cellular disruption by trauma releases mitochondrial DAMPs into the circulation.[39] These DAMPs have evolutionarily conserved similarities to bacterial PAMPs and activate innate immune pathways via TLR9. DAMPs have also been demonstrated to activate inflammasomes in animal models.[40,41] Inflammasomes are intracellular multiprotein complexes that mediate the autoactivation of caspase 1. IL-1β and IL-18 are related cytokines that are produced as cytosolic precursors and require caspase 1–mediated cleavage for full activation and secretion.[42]

How does one explain the early T_H1-to-T_H2 shift and depression of cell-mediated immunity, which follows surgery and traumatic injuries? Elenkov,[7] Elenkov et al.,[43] Elenkov and Chrousos[44] have suggested that activation of the hypothalamic-pituitary-adrenal axis and sympathoadrenal system are responsible for the T_H1/T_H2 imbalance that occurs following tissue damage and trauma. Furthermore, Ochoa et al.[45–49] have demonstrated the fine induction of arginase 1 (ARG1) in myeloid-derived suppressor cells (MDSCs) following surgery and trauma. Increased expression of ARG1 results in an arginine deficiency state. Arginine is required for lymphocyte proliferation and the formation of the T-cell receptor. The arginine deficiency compounds the immune depression caused by T_H2 cytokines.[45,49] We believe these mechanisms provide a working hypothesis to explain the derangements of the immune system following surgery and tissue injury.

As part of the "general adaptation syndrome" or stress response, surgery and trauma result in activation of the hypothalamic-pituitary-adrenal axis and sympathoadrenal system with the release of cortisol and catecholamines.[50,51] Epinephrine released predominantly by the adrenal medulla and norepinephrine released by the postganglionic nerve terminals act synergistically with glucocorticoids to induce a T_H2 shift (Fig. 1).[25] Glucocorticoids shift the T_H1/T_H2 balance by decreasing the synthesis of Type 1 cytokines and increasing the synthesis of Type 2 cytokines, by acting directly on $CD4^+$ T-cells and indirectly by inhibiting IL-12 production by monocytes.[6] Furthermore, glucocorticoids down-regulate the expression of IL-12 receptors on T-cells and natural killer cells.[29] Since IL-12 is extremely potent in enhancing INF-γ and inhibiting IL-4 synthesis by T-cells, the inhibition of IL-12 production by macrophages/monocytes may represent the major mechanism by which glucocorticoids affect the T_H1/T_H2 balance.[7] In addition, glucocorticoids inhibit IL-12–activated cellular pathways. Glucocorticoids markedly inhibit IL-12–induced phosphorylation of Stat4, while IL-4–induced Stat6 phosphorylation is unaffected.[4] Catecholamines drive a T_H2 shift at the level of both macrophages/monocytes and T_H1 cells. Epinephrine and norepinephrine inhibit the production of IL-12 and enhance the production of IL-10. These effects are mediated by stimulation of β-adrenergic receptors.[7] Elenkov et al.[52] have demonstrated that the order of potency of stress hormones to inhibit IL-12 production ex vivo was epinephrine, followed by norepinephrine, and then cortisol. Catecholamines also inhibit the production of the proinflammatory cytokines. Sympathetic activation following traumatic brain injury and stroke have been demonstrated to increase IL-10 release and shift the T_H1/T_H2 balance toward T_H2 cytokine production.[53,54] Prostaglandin E2 (PGE2) produced in increased quantities by macrophages after tissue injury increase T_H2 cytokine production while decreasing T_H1 cytokine production.[28] Cortisol and PGE2 have been shown to synergistically cause immunosuppression after trauma.[29] Increased expression of cylooxygenase 2, the inducible form of cylooxygenase, has been demonstrated following trauma and surgery.[30,31]

It is important to emphasize that glucocorticoids act on the immune system by both suppressing and stimulating a large number of proinflammatory or anti-inflammatory mediators.

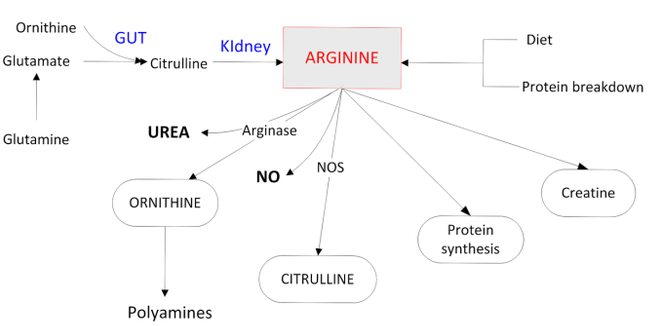

Figure 2. Arginine metabolic pathways.

The balance between these apposing effects is dose dependent.[55] It would seem that the role of glucocorticoids as part of the stress response is to enhance the local clearance of foreign antigens, toxins, microorganisms, and dead cells while at the same time preventing an overexuberant proinflammatory response.[56] Glucocorticoids enhance opsonization and macrophage phagocytotic ability. Macrophage inhibitory factor (MIF) is an important proinflammatory cytokine whose secretion is enhanced by glucocorticoids. TLR4 expression is increased by MIF, which underscores the role of MIF in the macrophage response to endotoxins and gram-negative bacteria.[57]

A subpopulation of $CD4^+$ T-cells that constitutively express the α chain of the IL-2 receptor (CD25) has been identified as playing a critical role in immune responses.[58,59] These $CD4^+$ $CD25^+$ cells are designated as T regulatory cells (Tregs). Tregs highly express the FoxP3 transcriptional factor, which seems to be a key factor that controls the development and function of these cells. Tregs help control inappropriate T-cell responses by actively suppressing $CD4^+$ T-cell reactivity to self or nonself antigens. Tregs suppress T_H1 immune responses and promote a shift toward a T_H2 response. MacConmara et al.[60] demonstrated a significant increase in Tregs by Day 7 in a cohort of trauma patients. These cells were the primary source of the T_H2 cytokines, and depletion of these cells restored T_H1 cytokine responsiveness. The factors that lead to an increase in Tregs following trauma is unclear. However, Tregs may be activated by DAMPs such as heat shock protein or HMGB1.[61] Furthermore, glucocorticoids increase FoxP3 mRNA expression and have been shown to increase the induction of Tregs.[62–64]

A decrease in circulating arginine is evident within a few hours after physical injury.[45,65,66] This rapid fall in arginine suggests that the arginine deficiency does not develop from lack of intake but rather through increased metabolism.[45] Arginine is metabolized predominantly by two competing pathways, namely inducible NO synthetase (iNOS) to NO and by arginase as part of the urea cycle (Fig. 2). ARG1 is found in the cytosol of hepatocytes and white blood cells while ARG2 is found in the mitochondria of many cells. Both ARG1 and iNOS are inducible enzymes in myeloid cells, with ARG1 being induced by T_H2 cytokines and iNOS by T_H1 cytokines. ARG1 is induced by trauma while iNOS expression is increased in patients with sepsis.[45,67,68] Consequently, NO metabolites are reported to be increased in patients with sepsis and SIRS and decreased in patients with physical trauma.[69] It is noteworthy that patients with physical injury who subsequently develop sepsis have markedly reduced level of NO metabolites compared with those without physical injury.[69] Makarenkova et al.[70] have demonstrated that within hours of physical injury, large number of ARG1 expressing immature myeloid cells (IMCs) accumulate in the spleen and other lymphoid tissue. These cells are called myeloid-derived suppressor cells (MDSC). When placed in culture with T lymphocytes, MDSC inhibit T lymphocyte growth and function.[49] MDSCs are a heterogenous population of myeloid progenitor cells and IMCs. In healthy individuals, IMCs are generated in the bone marrow and quickly differentiate into mature granulocytes, macrophages, or dendritic cells. By contrast, in pathologic conditions such as cancer, trauma, and some autoimmune diseases, a partial block in the differentiation of IMCs into mature myeloid cells result in the expansion of this population.[71] T_H2 cytokines, catecholamines, and PGE2 induce the expression of MDSC and act synergistically to increase the expression of ARG1 in these cells.[72–74] From the forgoing information, it seems that activation of the stress response with the release of cortisol and catecholamines together with the release of PGE2 result in a T_H1/T_H2 switch with the release of T_H2 cytokines. The T_H2 cytokines induce the expression of ARG1, which depletes cellular arginine resulting in further impairment of T-cell proliferative responses. Finally, increased expression of Tregs compounds the depression of T-cell function, at a time when the stress response may have already abated.

The goal of clinicians managing trauma and postoperative patients is to minimize the immunosuppression following these insults to reduce the risk of secondary infections and to promote healing and tissue repair. The degree of immunosuppression can potentially be reduced by a number of interventions. The most obvious intervention is to reduce the degree of activation of the "stress-response." This can be achieved by laparoscopic as opposed to open surgery, as well as the adjunctive use of liberal analgesia or spinal anesthesia. Such interventions have been demonstrated to reduce the degree of T_H2-mediated immunosuppression.[75,76] Recently, much attention has been focused on reversing the immunosuppression following surgery and trauma with the use of an immunomodulating diet (IMD) containing supplemental arginine, omega 3 fatty acids and antioxidants. Tissue injury following surgery and trauma results in an arginine-deficient state that could potentially be treated with arginine supplementation. In experimental studies, L-arginine has improved wound healing, restored postoperative depressed macrophage function and lymphocyte responsiveness, and augmented resistance to infection.[77–79] Tepaske et al.[80] demonstrated that patients treated preoperatively with an arginine containing immunomodulating formula had increased expression of HLA-DR and an improved delayed hypersensitivity response to recall antigens, which persisted until hospital discharge. Omega 3 fatty acids that are metabolized preferentially to PGE3 (and not PGE2) may decrease T_H2 cytokine production and induction of ARG1. In both human and murine experiments, Mizota et al.[81] demonstrated that a diet high in omega 3 fatty acids induced a shift in the T_H1/T_H2 balance toward a T_H1 lymphocyte response. While the effect of omega 3 fatty acids on Treg cell function is complex, Yessoufou et al.[82] reported that docosahexaenoic acid deceased Treg suppressive function by reducing their migratory abilities via ERK1/2 and Akt pathways and acetylation/deacetylation of nuclear histones. In addition to their effect on T-cell function, omega 3 fatty acids increase the production of resolvins and protectins, which enhance tissue repair.[83] Matsuda et al.[84] and Suzuki et al.[85] have demonstrated that preoperative nutritional supplementation with an IMD containing arginine and omega 3 fatty acids decreased the production of T_H2 cytokines, maintained the T_H1/T_H2 balance, and significantly reduced the rate of infectious complications following elective surgery. A number of randomized controlled trials have been conducted, which have examined the benefit of an IMD for patients undergoing elective surgery. We recently published a systematic

review and meta-analysis to evaluate the benefit of IMDs in patient's undergoing elective surgery.[86] We demonstrated that immunonutrition significantly reduced the risk of acquired infections (odds ratio [OR], 0.49; 95% confidence interval [CI], 0.39–0.62; $p < 0.0001$), wound complications (OR, 0.60; 95% CI, 0.40–0.91; $p = 0.02$) and length of stay (OR, −3.03 days; 95% CI, −3.43 to −2.64 days; $p < 0.0001$).

As β-adrenergic receptor activation following the release of catecholamines plays a major role in the development of immunodepression after injury, it would seem logical that β-adrenergic receptor blockade would be beneficial.[87] Elenkov et al.[43] demonstrated that the effects of epinephrine and norepinephrine on IL-12 and IL-10 secretion and the T_H1-to-T_H2 shift were blocked completely by propranolol. In a rat model of acute brain injury, Woiciechowsky et al.[53] demonstrated that the β-receptor antagonist propranolol prevented the increase in IL-10 plasma levels. Similarly, in a stroke model, Prass et al.[54] demonstrated that propranolol prevented most of the stroke-induced immunosuppressive effects and drastically reduced mortality. Furthermore, β-adrenoreceptor blockage has been demonstrated to decrease macrophage ARG1 activity following trauma.[73] While the role of β-adrenoreceptor blockage for patients undergoing surgery is controversial,[88,89] cohort studies on patients with traumatic injuries including those with head injuries have demonstrated that β-blockade was independently associated with improved survival.[90–93]

In summary, tissue injury following surgery and trauma results in depressed cell-mediated immunity leading to an increased risk of infectious complications. While our understanding of the cellular pathways leading to T-cell dysfunction in these patients has increased enormously during the last two decades, many questions remained unanswered. Nevertheless, the perioperative use of IMDs containing arginine and omega 3 fatty acids seems to reverse this immunosuppression and decrease the risk of postoperative complications. While β-adrenoreceptor blockage may be beneficial for these patients, particularly when combined with an IMD, additional research is required.

AUTHORSHIP

This article was conceived by P.E.M. and M.F. Both the authors reviewed the literature and were responsible for writing the article. P.E.M. is responsible for creating the figures. Both authors have reviewed the final version of the article and approve it for publication.

DISCLOSURE

The authors declare no conflicts of interest.

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