Pathoanatomy and Clinical Correlates of the Immunoinflammatory Response Following Orthopaedic Trauma

Abstract

The natural inflammatory response to major trauma may be associated with the development of a systemic inflammatory state, remote multiorgan failure, and death. Although a controlled inflammatory response is beneficial, an exaggerated response can cause serious adverse systemic effects. Early identification of high-risk patients, based on inflammatory markers and genomic predisposition, should help direct intervention in terms of surgical stabilization and biologic response modification. Currently, two markers of immune reactivity, interleukin-6 and human leukocyte antigen–DR class II molecules, appear to have the most potential for regular use in predicting the clinical course and outcome in trauma patients; however, the ability to measure markers of inflammation is still limited at many hospitals. With improving technology and increasing research interest, understanding of the significance of the immunoinflammatory response system in injured patients will continue to evolve.

Inflammation is not itself considered to be a disease but a salutary operation ... but when it cannot accomplish that salutary purpose ... it does mischief.

John Hunter

For decades, the inflammatory response has been recognized as a physiologic reaction to injury. This complex response arises from the interplay between various mediators produced at the site of injury, including cytokines, growth factors, nitric oxide, and platelet-activating factors, and the activation of local and systemic polymorphonuclear neutrophils (PMNs), lymphocytes, and macrophages. In the acute period following major trauma, this endogenous response system mobilizes to initiate healing and acts as a barrier to injury propagation. Cytokines operate as the main regulators of the postinjury immune response. These mediators, which are produced by diverse cell types, exert their effects by binding to specific cellular receptors, regulating gene transcription, and modifying intracellular signaling pathways (Figure 1).

Typically, the amplitude of the inflammatory response is related to the severity of injury. When injury is dramatic, the local inflammatory response may propagate systemically, resulting in serious systemic disease, including acute respiratory distress syndrome and multiorgan failure. In addition to the initial injury, surgical...
reduction and fixation of fractures also stimulate the immunoinflammatory response. This may result in a second-hit phenomenon, in which a patient already in a hyperinflammatory physiologic state following serious injury (the first hit) is pushed into systemic inflammatory derangement by an ill-timed surgical procedure. The concept of limiting the second-hit insult inflicted by intensive surgical treatment originated in the field of thoracoabdominal surgery. Surgeons recognized that limiting primary surgery in the most critically injured patients to life-saving, stabilizing procedures rather than also performing definitive procedures provided patients the most optimal opportunity to recover from systemic inflammatory insult and, ultimately, improved survival. Subsequently, this approach has been applied to early care in the treatment of extremity trauma; the approach is referred to as damage control orthopaedics.

In damage control orthopaedics, emphasis is on the initial control of hemorrhage followed by rapid and temporary stabilization of fractures along with soft-tissue decompression and débridement. This is followed by staged, definitive fracture fixation following dissipation of the inflammatory response. In 1998, Tscherne et al helped solidify a framework for damage control orthopaedics by outlining basic principles of internal fixation in multi-trauma patients based on 20 years of treating multiply injured patients. In this framework, basic management of a multiply injured patient during the acute postinjury period (1 to 3 hours) is focused on the resolution of hemorrhage (including internal or external emergency stabilization of unstable pelvic ring injuries) and decompression of organ cavities. After achieving hemodynamic stability, orthopaedic emergencies are then assessed. The highest-priority injuries are open fractures, compartment syndromes, unstable pelvic injuries, and fractures with concomitant vascular injuries requiring stabilization. Immediate stabilization of closed fractures is the next priority; however, to limit systemic insult, the authors recommend restricting fracture care (eg, by using temporary fixation) in patients with serious associated injuries. Subsequent clinical decisions regarding the timing of surgical procedures are based on the general status of the patient (Table 1). Typically, the authors delayed any extensive orthopaedic procedure (ie, major pelvic or joint reconstruction) until 72 hours after injury.
Although guidelines provided by Tscherne et al\textsuperscript{6} offer a foundation on which to base clinical decisions regarding the appropriate timing and extent of surgical intervention in the multitrauma patient, there are no current standardized guidelines for implementing damage control orthopaedics. This is mostly because evaluation of the inflammatory response has proved to be difficult. Clinical parameters of organ system dysfunction are useful, but they are more beneficial in distinguishing patients with established organ injury than in identifying patients at risk for postsurgical inflammatory injury. Serum markers of inflammation may be more useful in examining the magnitude of the systemic inflammatory response. However, many of these markers have been shown to be non-specific and are unavailable in the clinical setting. There is a limited consensus regarding which markers may be the most useful for patient evaluation. With an improved understanding of the molecular basis of the inflammatory response, and by identifying relevant clinical markers of inflammation, surgeons can better manage the timing of surgical stabilization.

### Systemic Inflammatory Response

Death resulting from traumatic injury occurs in a trimodal distribution. The first mode is death that directly results from the severity of the injury; this is typically associated with death at the scene of the injury. The second mode is early death because of hypoxia, hypovolemia, or head injury. The third type of mortality occurs in the days and weeks following injury and accounts for up to 45% of trauma-related deaths.\textsuperscript{7} Patients in this category typically die in the hospital as a result of head injury, acute respiratory distress syndrome (ARDS), or multiple organ failure syndrome (MOFS).\textsuperscript{7}

MOFS is characterized by a widespread state of inflammation with resulting tissue damage. Normally, the postinjury inflammatory response remains localized to the site of injury and is considered important for host recovery, resolving as the patient recovers. However, with serious traumatic events such as long-bone fracture, pelvic fracture, chest injury, tissue hypoxia, thoracic trauma, or head injury, an imbalance in proinflammatory mediators can develop, resulting in a generalized state of inflammation referred to as the systemic inflammatory response syndrome (SIRS).\textsuperscript{2} ARDS is also a syndrome of inflammation, one in which a diffuse inflammatory process results in increased lung permeability and refractory hypoxemia\textsuperscript{2} (Table 2). The development of SIRS, ARDS, and MOFS is considered a consequence of a hyperactive inflammatory response resulting in a state of systemic inflammation.\textsuperscript{3}

The entire pathophysiology of ARDS and MOFS is not fully understood.\textsuperscript{3} However, it appears that an increased production of cytokines and inflammatory mediators results in widespread fibrin deposition, leading to microvascular occlusion and tissue hypoxia, as well as a massive tissue sequestration of neutrophils\textsuperscript{2} (Figure 1). Activated PMNs in circulating blood bind to adhesion molecules on the surface of endothelial cells in organs remote from the initially injured tissue. At their binding sites, PMNs release proteolytic enzymes and oxygen metabolites from cytoplasmic granules, which cause damage to the endothelium. This results in endothelial barrier impairment, diffusely increased capillary permeability, and tissue paren-

### Table 1

<table>
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<tr>
<th>Criteria for Treatment of Fractures in Trauma Patients</th>
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<tr>
<td>Requirements for Clinical Status of Patients With Multiple Trauma Prior to Surgical Fixation</td>
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<tr>
<td>No evidence of increasing infiltration of lung parenchyma on chest radiograph (48 hr before surgery)</td>
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<tr>
<td>Balanced or negative fluid balance (48 hr before surgery)</td>
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<tr>
<td>PaO\textsubscript{2}/FiO\textsubscript{2} &gt;250 mm Hg within previous 24 hr</td>
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<tr>
<td>Pulmonary artery pressure &lt;24 mm Hg</td>
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<tr>
<td>Peak inspiratory pressure &lt;35 cm H\textsubscript{2}O</td>
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<tr>
<td>Platelet count &gt;95,000/mm\textsuperscript{3}</td>
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<tr>
<td>Leukocyte count &gt;2,000/mm\textsuperscript{3} and &lt;12,000/mm\textsuperscript{3} with no signs of sepsis</td>
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<tr>
<td>Intracranial pressure 15 cm H\textsubscript{2}O</td>
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<td>Computed tomography scan of the head stabilized with no increasing hygroma formation</td>
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<th>Conditions for Which Fracture Treatment Should Be Limited</th>
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<tr>
<td>Severe head injury with a Glasgow Coma Scale score &lt;8</td>
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<tr>
<td>Severe thoracic trauma/lung contusion with continuous intrabronchial bleeding or edema formation</td>
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<tr>
<td>Myocardial infarction</td>
</tr>
<tr>
<td>Significant clotting problems</td>
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<tr>
<td>Significant hypothermia (&lt;32°C)</td>
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chymal infiltration with plasma products and inflammatory mediators.\textsuperscript{2} If endothelial injury becomes widespread, the resulting diffuse fluid infiltration may result in the failure of multiple organs.\textsuperscript{3}

The influence of circulating cytokines and inflammatory mediators on the development of SIRS has been demonstrated in an animal model in which an injection of inflammatory cytokines resulted in MOFS, whereas blockage of cytokines prevented organ injury and MOFS.\textsuperscript{8} In human patients who have died from ARDS, pulmonary samples contain large numbers of active PMNs and other activated inflammatory cells sequestered in microvascular tissue.\textsuperscript{8} Fracture fluid (hematoma combined with fracture-caused cellular debris) has also been shown to contain elevated levels of inflammatory mediators, including cytokine interleukin (IL)-8, which activates PMNs and initiates the release of oxidative mediators (respiratory burst).\textsuperscript{9} Advancing our understanding of each mediator’s role in the inflammatory process and its propensity to incite inflammation will help identify patients at risk for MOFS.

**Markers of Immune Reactivity**

Determining the magnitude of the inflammatory response in the traumatized patient has proved to be difficult. Traditionally used clinical parameters, including urinary output, blood gases, ventilation status, and basic vital signs, are useful but have limited sensitivity in screening for patients at risk of inflammatory injury. However, postinjury analysis of base deficit and lactate levels, which is commonly used to guide clinical resuscitation in patients with hemorrhagic shock, has shown utility in identifying patients at risk for inflammatory injury. Base deficit is used as a reliable indicator of blood loss, adequacy of resuscitation, and mortality in trauma patients, and it is a more sensitive marker of hypovolemia than are traditional vital signs.\textsuperscript{10} In addition, patients with evidence of considerable ischemic acidosis (ie, lower levels of base deficit and elevated lactate levels) in the initial 24 hours following major trauma are significantly more likely to develop ARDS in the first 4 days after injury.\textsuperscript{11}

A variety of inflammatory mediators has been implicated in the development of organ dysfunction. Serum markers of immune reactivity can be selectively grouped as markers of acute-phase reactants, mediator activity, or cellular activity (Table 3). The acute-phase response system is part of the innate arm of the immune system and consists of the first cells to arrive at the site of injury (eg, PMNs, lipopolysaccharide-activated macrophages). After arriving at the site of injury, PMNs generate and release numerous active substances, including proteolytic enzymes, reactive oxygen species, and vasoactive substances.\textsuperscript{7} The microvascular endothelium reacts to these substances with an increase in its permeability, resulting in interstitial edema, intravascular coagulation, and increased PMN adherence.\textsuperscript{7}

Markers of the acute-phase response include lipopolysaccharide-binding protein (LBP), C-reactive protein (CRP), and procalcitonin. LBP has been studied as a marker of sepsis, but serum levels have been reported as nonspecific for sepsis, and LBP response is not clearly correlated with severity of infection.\textsuperscript{21} CRP is an acute-phase protein produced by hepatocytes and is used extensively in the clinical setting as a marker for infection and inflammation. Although the synthesis of CRP is cytokine-dependent, clinical studies have shown CRP to be nonspecific for evaluating the immunoinflammatory response following trauma.\textsuperscript{12,21} Additionally, CRP serum levels do not correlate with severity of injury or predict survival in multi-

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<td>Clinical Criteria for Diagnosis of Acute Respiratory Distress and Systemic Inflammatory Response Syndromes</td>
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<tr>
<td><strong>Acute Respiratory Distress Syndrome</strong></td>
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<tr>
<td>Acute onset</td>
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<tr>
<td>Predisposing condition</td>
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<tr>
<td>Diffuse bilateral infiltrates on chest radiograph</td>
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<tr>
<td>Refractory hypoxemia: $\text{PaO}_2/\text{FiO}_2 &lt; 200 \text{ mm Hg}$ regardless of positive end-expiratory pressure level</td>
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<tr>
<td>No evidence of left-heart failure; wedge pressure $\leq 18 \text{ mm Hg}$</td>
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<tr>
<td><strong>Systemic Inflammatory Response Syndrome</strong></td>
</tr>
<tr>
<td>Any two or more of the following:</td>
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<tr>
<td>Body temperature $&lt;36^\circ \text{C}$ or $&gt;38^\circ \text{C}$</td>
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<tr>
<td>Heart rate $&gt;90 \text{ beats per minute}$</td>
</tr>
<tr>
<td>Respiratory rate $&gt;20 \text{ breaths per minute}$</td>
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<tr>
<td>Hyperventilation</td>
</tr>
<tr>
<td>White blood cell count $&lt;4,000/\text{mm}^3$ or $&gt;12,000/\text{mm}^3$</td>
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<tr>
<td>Immature neutrophils $&gt;10%$</td>
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trauma patients. Serum levels of procalcitonin have been shown to correlate with the severity of sepsis, but the prognostic value of procalcitonin levels in the trauma population has not been established.

Important serum markers of mediator activity include tumor necrosis factor (TNF)-α and IL-1, -6, -8, and -10. TNF-α is produced by a variety of cells and acts to increase the permeability of endothelial cells and the expression of adhesion molecules. However, investigations into the use of TNF-α as a clinical marker of inflammation have been equivocal, and this marker is not currently used clinically. IL-1 and -10 also have been studied as possible clinical markers of the inflammatory response, but mixed reports regarding their clinical utility have limited their use. In contrast, a direct relationship has been confirmed between elevated levels of IL-6 and -8 and degree of injury. IL-6 has also been shown to be a reliable marker of the magnitude of systemic inflammation. In a study evaluating clinical outcome in children following blunt trauma, serum IL-8 level at admission was identified as the most important determinant of postinjury mortality. Another clinical investigation found that patients who died of sepsis had significantly higher levels of IL-6 than did those who survived. Gebhard et al found that IL-6 levels increased immediately following trauma, that patients with the most severe injuries had the highest plasma IL-6 levels, and that systemic IL-6 plasma concentrations correlated with Injury Severity Score values at hospital admission. Additionally, serum level of IL-6 is readily measurable and is less transient than is that of IL-1 or TNF-α.

Markers of cellular activity include endothelial adhesion molecules intercellular adhesion molecule-1 and E-selectin, leukocyte CD11b receptor, and human leukocyte antigen (HLA) molecules. HLA-DR class II molecules, which mediate the processing of antigens for cellular immunity, have shown the most promise for clinical utility. Serum levels of HLA-DR class II molecules are considered a reliable marker of clinical infection and act as an independent predictor of mortality in patients with septic shock; diminished HLA-DR levels in burn-injured patients have been associated with the development of septic complications and mortality. HLA-DR is also considered to be the most reliable marker of immune reactivity and correlates with mortality and morbidity following trauma. In a study examining the expression of HLA-DR with monocytes and T cells in patients who sustained blunt trauma, reduced serum levels of HLA-DR were found in patients who subsequently developed severe sepsis relative to levels in those who did not. Improving the clinical availability of testing for markers of immune reactivity may help guide clinical decisions for trauma patients.

### Table 3

<table>
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<tr>
<th>Clinical Utility of Important Markers of Immune Reactivity</th>
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<tr>
<td><strong>Markers of Acute-phase Reactants</strong></td>
</tr>
<tr>
<td>Lipopolysaccharide-binding protein: serum levels are nonspecific for sepsis</td>
</tr>
<tr>
<td>C-reactive protein level: nonspecific; does not correlate to severity of injury or predict survival in multiply traumatized patients</td>
</tr>
<tr>
<td>Procalcitonin: correlates with the severity of sepsis, but nonestablished prognostic value</td>
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<tr>
<td><strong>Markers of Mediator Activity</strong></td>
</tr>
<tr>
<td>Tumor necrosis factor-α: equivocal utility as a clinical marker of inflammation</td>
</tr>
<tr>
<td>IL-1/IL-10: equivocal clinical utility</td>
</tr>
<tr>
<td>IL-6: reliable marker of the severity of injury, magnitude of systemic inflammation, and mortality rate</td>
</tr>
<tr>
<td>IL-8 serum levels are an important determinant of postinjury mortality in pediatric blunt-trauma patients</td>
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<tr>
<td><strong>Markers of Cellular Activity</strong></td>
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<tr>
<td>Human leukocyte antigen: reliable marker of clinical infection and an independent predictor of mortality in patients with septic shock; most reliable marker of immune reactivity mortality and morbidity following trauma</td>
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### Clinical Basis of Surgical Stabilization

Understanding of the complexities and physiologic consequences of immunologic alterations that occur after orthopaedic trauma has increased considerably in recent years. However, clinical application of these findings continues to evolve. One important area lacking a definitive standard of care is the timing and method of surgical intervention in patients who require orthopaedic fixation.

Skeletal stabilization is clearly important for the mobilization and restoration of function in seriously injured multitrauma patients, and early fixation of femoral fractures has been shown to reduce the incidence of ARDS and MOFS. In addition, early definitive fixation avoids complications associated with staged procedures (eg, external fixation pin site infection) and allows for the immediate mobilization of extremities. However, subsequent surgical procedures in the severely injured pa-
tient have been shown to result in the release of proinflammatory mediators, to prime circulating PMNs, and to cause changes in the fibrinolytic and coagulatory cascades independent of the initial traumatic injury. The second-hit concept acknowledges that postinjury surgical procedures have the potential to induce a second inflammatory insult in addition to the initial trauma. An ill-timed surgical procedure before restoration of physiologic balance may result in a hyperinflammatory state with the potential to cause systemic disease, including SIRS, ARDS, and MOFS (Figure 2). This understanding has led to a cautious approach in early total care for patients with severe injuries.

The goal with damage-control orthopaedics is to avoid early morbidity in the multitrauma patient caused by overly aggressive treatment of injury combined with a lack of attention to the underlying physiologic state of the victim. Currently, most of the literature analyzing damage-control orthopaedics focuses on evaluation of the initial stabilization of femur fractures and on the subsequent inflammatory response and outcome in multiply injured patients. In a 2007 multicenter intervention study, Pape et al randomized 165 blunt trauma patients with femur fractures and an Injury Severity Score >16 points into either initial definitive stabilization of femoral shaft fractures with intramedullary (IM) nailing or initial placement of external fixation, followed later by definitive fixation. Patients were graded as either stable or borderline based on their risk of systemic complications (eg, higher trauma index, Injury Severity Scores, Combined Thoracic Index). The authors found the odds of developing acute lung injury to be 6.69 times greater in borderline patients who underwent initial IM nailing compared with borderline patients who underwent initial placement of an external fixator. The authors concluded that, in stable patients, primary femoral nailing is safe. However, in borderline patients, initial definitive fracture fixation with IM nailing is associated with a higher incidence of lung dysfunction; the preoperative condition of the patient should guide clinical decisions.

In another prospective study, Pape et al examined serum levels of IL-6 and -8 in 35 patients with lower extremity long-bone fracture with an associated Injury Severity Score >16 points. The authors found significantly elevated levels of serum IL-6 ($P = 0.03$) and IL-8 ($P < 0.05$) in the initial 24 hours following injury in patients who underwent stabilization with IM nailing compared with patients treated with initial external fixation. No association was found, however, between serum inflammatory markers and postoperative clinical complications.

In contrast, several studies have reported inflammatory disease after major trauma with early definitive treatment. In one study, 38% of trauma patients who underwent major secondary reconstructive surgery (ie, facial reconstruction; osteosynthesis of the pelvic girdle, long bones, or spine) within 3 days after admission developed MOFS. Patients who developed MOFS had significantly higher preoperative levels of PMN elastase-α1 proteinase inhibitor complex and CRP than did those who did not develop MOFS. The authors concluded that the initial degree of inflammatory system priming was a major factor in the subsequent development of MOFS after surgery. Another clinical study reported a fourfold increase in the incidence of ARDS in patients with chest injury who underwent definitive femoral fracture fixation within 24 hours of admission compared with patients who underwent fracture repair any time after the first day of admission. Ideally, advancing the ability to analyze immunoinflammatory molecular markers will improve our understanding of the appropriate timing for surgical intervention in high-risk patients.
Reamed Intramedullary Nailing and the Immunoinflammatory Response

The systemic effects of IM reaming compared with unreamed nailing or fracture plating have led to controversy focusing on the potential influence on the immune response system. During the reaming process, transient pulmonary vascular changes (including increased pulmonary artery pressure and pulmonary vascular resistance) have been shown to occur without pulmonary injury. In the presence of pulmonary injury, reamed nailing has been shown to cause permanent pulmonary microvascular damage. Reamed nailing of intact femurs in sheep during a shock state with lung contusion caused an elevation in the cardiac index, impaired liver function, and a decrease in creatinine clearance for 10 days following injury. Additionally, reamed nailing in both a baboon model and in human trials is associated with a higher degree of fat embolization and level of inflammatory response compared with unreamed nailing.

Serum markers of inflammation have also been shown to be elevated following reamed nailing, and IL-6 concentrations are significantly elevated in the femoral canal following fracture. Significantly increased serum levels of IL-6 and elastase have been found in patients following reamed IM nailing of femoral shaft fractures. However, the general use of reamed nailing has not shown any significant difference in systemic complications compared with other definitive fixation techniques. In one study examining reamed and unreamed nailing and plate fixation of femoral shaft fractures in sheep with lung contusion, none of the surgical interventions, including reamed nailing, altered the pulmonary hemodynamic response (pulmonary arterial pressure), even in the presence of thoracic injury. Bosse et al found no difference in the rate of ARDS, pulmonary embolus, MOFS, pneumonia, or death in patients who underwent open plating or reamed IM nailing of femoral shaft fractures. In addition, animal studies have demonstrated no difference in pulmonary function in animals undergoing reamed or unreamed IM nailing. Additional clinical trials are needed to better understand the safety of reamed IM nailing and the influence on the inflammatory response system in multiply injured patients.

Improving Outcome: Future Treatments and Genetic Variation

An improved understanding of the immunoinflammatory response to injury and its response to surgical intervention is an important component of directing appropriate patient care after traumatic injury. In addition to modifying the timing and extent of surgery based on the inflammatory state of the patient, pharmacologic treatment directed specifically at controlling the inflammatory response is another potential intervention. Agents such as TNF-neutralizing antibodies, soluble TNF receptors, and IL-1 receptor antagonists have been used successfully to treat patients with chronic inflammatory diseases such as rheumatoid arthritis and inflammatory bowel disease. However, studies investigating the use of cytokine antagonists in the acute trauma setting are limited.

Pharmacologic agents with antioxidant properties have shown promise for controlling the inflammatory response. One such agent is N-acetylcysteine (NAC), a potent antioxidant commonly used clinically to treat hepatic toxicity from acetaminophen overdose. Experimentally, NAC has been shown to reduce nuclear factor-κB and IL-8 in patients with sepsis, attenuate the production of IL-8 in patients with early septic shock, and protect against endotoxin-derived microcirculatory disturbances. In a 2004 study, Timlin et al demonstrated that a single dose of NAC administered to rats immediately following bilateral femoral fracture with fixation significantly attenuated measures of postfracture lung injury (ie, bronchoalveolar lavage protein, lung tissue myeloperoxidase levels) seen in untreated animals. Cyclooxygenase (COX)-2 inhibitors are another type of pharmacotherapeutic intervention that may help modulate the inflammatory response. COX-2 is the inducible isof orm of the COX enzyme, which is produced by macrophages and expressed at sites of inflammation and injury. COX-2 contributes to the production of prostaglandin E2, which is one of the earliest mediators of inflammation released after injury and which has been shown to be increased in inflammatory conditions such as injury and burns. Mice administered selective COX-2 inhibitors within 24 hours after single femur fracture and significant hemorrhage (40% blood volume) demonstrated suppressed prostaglandin E2 levels, decreased IL-6 levels, and improved survival to postinjury (7 days after injury) septic challenge (cecal ligation and puncture) compared with controls. Additional large, clinical trials are needed to fully assess the clinical utility of these compounds; however, they do exemplify potential therapeutic interventions that, in the future, may be used to modulate the acute inflammatory response.

Targeting treatment modalities at specific components of the inflammatory pathway molecular cascade may
help to modify the hyperinflammatory response. One such potential target are toll-like receptors (TLRs), a class of membrane-spanning, pattern-recognition receptors found on leukocytes that recognize microbe-derived molecules and endogenous ligands that signal host injury43 (Figure 3). One of these receptors, TLR4, has been isolated as a major driver of the immune response in sterile inflammatory settings. IRF-3 = interferon regulatory factor-3, TRAM = TRIF-related adaptor molecule, TRIF = toll/IL-1 receptor domain-containing adaptor-inducing interferon-β

Mechanism of action of toll-like receptors (TLRs). Using the intracellular complex TRIF/TRAM, these transmembrane proteins trigger intracellular signaling pathways, resulting in the release of inflammatory cytokines via either the nuclear factor-κB (NF-κB) pathway or the release of interferons. The receptor TLR4 has been isolated as a major driver of the immune response in sterile inflammatory settings. IRF-3 = interferon regulatory factor-3, TRAM = TRIF-related adaptor molecule, TRIF = toll/IL-1 receptor domain-containing adaptor-inducing interferon-β

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In an animal study by Levy et al,44 TLR4 knockout mice subjected to bilateral femur fracture had reduced systemic and hepatic inflammatory responses compared with wild-type mice. The authors concluded that TLR4 is critical for the initiation of systemic inflammation and subsequent development of remote organ injury following isolated extremity trauma.

Another protein that appears to be highly involved in the initiation of systemic inflammation is the high-mobility group box-1 (HMGB1), which is a DNA-binding protein present within the nuclei of most eukaryotic cells. HMGB1 proteins display proinflammatory cytokine-like properties through interactions with TLR4. In a recent study, mice subjected to bilateral femur fractures following neutralizing antibody treatment to HMGB1 produced lower serum IL-6 and -10 levels, as well as diminished systemic inflammation and end-organ injury compared with immunoglobulin G (IgG) antibody–treated controls.45 Both TLR4 receptors and the TLR4-HMGB1 pathway may play important roles in cellular recognition and response to injury and provide an encouraging target for future molecular modification of the inflammatory response.

Genetic variation likely contributes to discrepancies among individual inflammatory responses, making some individuals more prone to develop an exaggerated inflammatory reaction to injury. In a study by Stüber et al,46 biologic variation and genetic predisposition were shown to contribute to variations in the mortality rate of patients who developed postoperative sepsis. In addition, polymorphism has been reported in levels of HLA-DR expression, cytokine genomic profiles of TNF-α, IL-6, IL-10, and receptors for interferon-γ, and neutrophil receptors for IgG.8 The possibility of delineating individual genomic profiles in the future may ultimately offer the opportunity to measure specific immune responses for each patient and then tailor subsequent clinical decisions to meet each individual’s needs.

Along with genetic differences, alcohol use, substance abuse, and the use of prescription medications may also alter the normal inflammatory response to trauma. Alcohol intoxication, present in 25% to 40% of trauma patients with orthopaedic injuries, has been shown to alter the immunoinflammatory pathway.7,48 However, the significance of alcohol intoxication on the inflammatory response following trauma is not well understood. It is known that both
acute and chronic alcohol intake independently influence aspects of the inflammatory response and may cause different inflammatory profiles following serious injury. Alcohol intake on a substantial basis is associated with immunosuppressive effects. However, patients with chronic alcohol-induced liver injury have increased production of inflammatory markers, including hepatic levels of IL-8 and macrophage inflammatory protein-1, and serum levels of IL-6, -8, and -10. In addition, chronic alcohol abuse is associated with altered endothelial cells and alveolar-capillary barrier function, an independent risk factor for the development of ARDS, and is associated with higher incidence of ARDS and severity of MOFS in critically ill patients.

Alternatively, acute alcohol administration has been shown to suppress the injury-induced mRNA induction of inflammatory markers, including IL-6, IL-12, and INF-α, and to attenuate the in vitro production of toxic superoxide by neutrophils. Acute alcohol administration before septic shock is associated with suppressed lung proinflammatory cytokine expression. However, in burn injury, acute alcohol ingestion causes increased levels of lung inflammation and neutrophil infiltration and is associated with impairment of neuroendocrine counter-regulation and hemodynamic stability following hemorrhage.

Thus, it appears likely that alcohol and other pharmacologic compounds common in the trauma population do alter the inflammatory response. Further elucidation of the effects that these substances have on the inflammatory response to injury is important to help identify patients who are at heightened risk for developing adverse immunoinflammatory reactions following serious injury.

**Recommendations**

Management of the multitrauma patient with orthopaedic injuries starts with an open line of communication with all services active in patient care, including the general trauma service and the critical care management team. Patients at heightened risk for postinjury inflammatory complications should be rapidly assessed and sufficiently resuscitated, with urgent management of any hemorrhage. After appropriate acute resuscitation, reassessment of the general status of the patient should be conducted using hemodynamic parameters, oxygenation, vital signs, base deficit, lactate levels, and blood gas readings. If available, markers of inflammation, including IL-6, CRP, and HLA-DR, may be used to guide clinical decisions.

At our institution, the goal is to provide early total care to all multiply injured patients. Surgical decisions are based on continual reassessment of the patient’s general status. Orthopaedic emergencies are managed as rapidly as possible, with consideration given to limiting surgical time. When possible, multiple surgical teams can work jointly to minimize the length of surgical time.

Management of long-bone fractures follows emergencies in priority of treatment. If a deteriorating clinical picture prevents definitive fixation, long-bone fractures may be managed acutely by means of external fixation or placement of skeletal traction until the physiologic status of the patient allows for definitive care. For patients able to proceed with IM nailing, our institution uses reamed nailing because of the biomechanical advantages reaming offers, including the insertion of larger and stiffer nails, improved cortical contact, and better fracture healing. Reaming has not been shown to increase mortality or diminish pulmonary function clinically. However, in all multiply injured patients, our institution limits the reaming passes and allows a slightly smaller nail than that which would normally be used. When the patient remains stable following reassessment, complete fracture management, including pelvis fixation, may proceed. Thus, in the seriously injured patient, surgical timing and degree of intervention may need to be adjusted based on the general status of the patient.

**Summary**

Traumatic orthopaedic injury is associated with mobilization of the immunoinflammatory response system. With serious injury, the immunoinflammatory response system may be stimulated to an extent that it overwhelms the threshold of local response, leading to a systemic inflammatory reaction with the potential to cause local and remote organ injury. The inflammatory burden from secondary surgical procedures and fracture fixation contributes to the overall magnitude of the immunoinflammatory response. The damage control philosophy aims to avoid morbidity in the trauma patient caused by overly aggressive treatment of injury combined with lack of attention to the underlying physiologic state of the victim.

Although the evaluation of the preoperative inflammatory response has traditionally proved to be challenging, several specific markers of inflammation show promise for clinical use, including IL-6, which is a reliable marker of severity of injury and magnitude of systemic inflammation, and HLA–DR class II, which has been shown to be an independent predictor of mortality following trauma. Reamed IM nailing in the seriously injured patient is controvers-
sial because it results in an increased inflammatory response and increased serum levels of IL-6. However, reamed nailing has not been associated with a significantly greater number of systemic complications compared with other definitive fixation techniques.

Clarification of the biologic basis of the inflammatory response and the identification of associated clinical markers will improve the utility of the perioperative analysis of multiply injured patients. Ultimately, evaluation of the extent of the immunoinflammatory response following acute trauma will help guide clinical decisions regarding the timing and spectrum of surgical stabilization.

References

Evidence-based Medicine: References 5, 6, 9, 11, 12, 17-20, 22, 24-26, 28, 30-33, 35-46, 50, 52-56, and 58-60 are level I or level II studies. References 7, 10, 13, 15, 21, 23, 27, 29, 34, 48, 49, 51, and 57 are level III or level IV case-control studies or case series. References 2, 3, 4, 6, and 36 are expert opinion.

Citation numbers printed in bold type indicate references published within the past 5 years.


