Critical Illness–Induced Immune Suppression: Current State of the Science

By Kristin C. Greathouse, MS, CPNP-AC, and Mark W. Hall, MD

Abstract
Critical illness comprises a heterogeneous group of serious medical conditions that typically involve an initial proinflammatory process. A compensatory anti-inflammatory response may occur that, if severe and persistent, places the patient at high risk for adverse outcomes including secondary infection and death. Monitoring strategies can identify these patients through measurement of innate and adaptive immune function. Reductions in monocyte HLA-DR expression, reduced cytokine production capacity, increased inhibitory cell surface molecule expression, and lymphopenia have all been associated with this immune-suppressed state. Intriguing data suggest that critical illness–induced immune suppression may be reversible with agents such as interferon-γ, granulocyte macrophage colony-stimulating factor, interleukin 7, or anti–programmed death-1 therapy. Future approaches for characterization of patient-specific immune derangements and individualized treatment could revolutionize how we recognize and prevent complications in critically ill patients. (American Journal of Critical Care. 2016;25:85-92)

The immune system plays a major role in the acute phase of critical illness, as well as late manifestations that result in morbidity and mortality. It comprises a complex network of barriers, cells, and mediators that are activated upon injury or cellular stress and functions to detect and destroy pathogens. Once activated, several cellular and molecular events ensue that involve the innate and adaptive immune systems. These systems have separate functions, yet are intricately interconnected. Innate immune cells respond rapidly and serve to identify broad classes of pathogens, ingest and kill them, and digest them into antigenic peptides for display on antigen-presenting molecules. In addition, innate immune cells produce cytokines and chemokines to make the local environment favorable for fighting infection and to recruit other immune cells to the area. These cells include neutrophils, dendritic cells, natural killer (NK) cells, monocytes, and macrophages.

The adaptive immune response is generated by lymphocytes, including T cells, which are responsible for cytokine production and cytotoxic activity, and B cells, which are responsible for antibody production. These cells have highly antigen-specific receptors and typically require presentation of that antigen by a member of the innate immune system in order to become activated. Lymphocytes can persist for life, providing immunologic memory and the capacity for rapid response in the event of reexposure to the same pathogen. The first response of a naïve lymphocyte to a pathogen, however, can take days to manifest fully. Accordingly, the initial immunologic response to critical illness is often mediated by the innate immune system with the adaptive response most likely being more prevalent in the subacute phase of illness.

Many diagnoses that require intensive care unit (ICU) support involve an acute injury that results in...
Critical illness–induced immune suppression is most likely a multifactorial process.

an overwhelming systemic inflammatory response syndrome (SIRS). This syndrome is characterized by the release of proinflammatory mediators into the systemic circulation and manifests clinically as the classic symptoms of fever, vasodilation, tachypnea, and tachycardia. Indeed, high levels of proinflammatory mediators such as interleukin (IL)-6 and IL-8 have long been associated with increased risks for adverse outcomes from adult and pediatric critical illness.1-3

The compensatory anti-inflammatory response syndrome (CARS) has evolved to serve as a counter-regulatory mechanism in the face of systemic inflammation. This syndrome involves the elaboration of anti-inflammatory mediators such as IL-10, which serves to down-regulate the proinflammatory response and inhibit leukocyte function. If the CARS state is severe and persistent, it represents a form of secondary immune deficiency that can profoundly affect both innate and adaptive immune function (Figure 1).

Critical illness–induced immune suppression has been demonstrated in children and adults with a variety of diagnoses, including trauma,4,5 sepsis,6-8 pancreatitis,9,10 severe viral infections,11,12 and following cardiopulmonary bypass.13,14 The clinical consequences of immune suppression in the ICU setting include increased risk of multiple organ dysfunction syndrome,15 increased susceptibility to secondary bacterial infections,4,7,16 reactivation of latent viruses,17 susceptibility to opportunistic organisms,18,19 and increased risk of death.6,7,20 Now that most critically ill patients are surviving the acute phase of their illness as the result of advances in supportive care, many patients are facing the subacute or chronic phases of their illness bearing the additional burden of secondary immune suppression.

What Causes Critical Illness–Induced Immune Suppression?

Critical illness–induced immune suppression is likely a multifactorial process. Overall, 3 broad categories of factors appear to contribute to its incidence and severity: patient-related factors, illness-related factors, and treatment-related factors.

Patient-Related Factors

It has been convincingly demonstrated in family studies that the predisposition to a pronounced CARS response is indeed a heritable trait.21 The identification of specific genotypes or polymorphisms that confer this risk, however, has been difficult so far. It also appears that epigenetic factors may play an important role in promoting the immune-suppressed phenotype. Specific histone methylation patterns, for example, have been

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Evidence strongly suggests that critical illness–induced immune suppression has the potential to be reversed.

Associated with severe immune suppression following cardiopulmonary bypass in children. The degree to which a patient is at risk for critical illness–induced immune suppression may well be influenced by other patient factors including age, sex, and race, although large-scale evaluation of these factors has not yet been undertaken.

Illness-Related Factors
It has been observed across multiple diagnostic categories that the degree of initial inflammation observed with a critical illness or injury often correlates with the severity of subsequent immune suppression. In the case of traumatic injury, the severity of the initial injury is often associated with the development of impaired immune function in the ICU. Moreover, certain types of injury are prone to greater degrees of immune suppression. Brain injury, for example, has long been known to severely impair host defense, most likely through neurohormonal mechanisms. Reductions in the production of proinflammatory cytokines, such as tumor necrosis factor (TNF)-α, while maintaining production of anti-inflammatory mediators are commonly elevated at the same time. White blood cell gene expression data in critically ill patients have suggested upregulation of innate immune signaling and suppressed adaptive immune signaling in several studies, although this finding has not been universally observed. Functional immune monitoring offers an opportunity to quantify the degree of immune compromise in ICU patients. Although many of these tests are not currently available in the clinical laboratory in the United States, they have the potential to inform our understanding of the immunobiology of critical illness in the research setting (Table 1).

Innate Immune Monitoring
Monocytes display antigens on their cell surfaces via human leukocyte antigen (HLA)-DR molecules. HLA-DR expression can be easily measured by flow cytometry. More than 90% of healthy monocytes express HLA-DR, and they do so at a density of more than 8000 molecules per cell. Suppressed monocytes internalize their HLA-DR molecules. If less than 30% of monocytes strongly express HLA-DR, or if the expression level is fewer than 8000 molecules per cell, multiple investigators have demonstrated increased risks for adverse outcomes from critical illness.

Healthy innate immune cells should also produce robust amounts of proinflammatory cytokines when stimulated ex vivo with lipopolysaccharide. In the setting of immune suppression, these cells will be unable to respond to this new challenge and will produce low amounts of cytokine. Indeed, reduced whole blood ex vivo lipopolysaccharide-induced tumor necrosis factor (TNF)-α production capacity has been associated with increased risks for secondary infection and death in sepsis, critical viral infections, trauma, and cardio pulmonary bypass.

Adaptive Immune Monitoring
Perhaps the most readily available marker of adaptive immune function in critical illness is the absolute lymphocyte count. Lymphocyte apoptosis, with resultant lymphopenia and cellular dropout in lymphoid organs, has been repeatedly associated with immune suppression.
with mortality and secondary infection risk in adults and children with sepsis. The function of the remaining T cells is poor in some circumstances, with the degree of T-cell dysfunction predictive of adverse outcomes.

Lymphocytes can also express high levels of negative costimulatory cell surface molecules, such as programmed death (PD)-1, in critical illness. These molecules, when ligated, promote apoptosis or cellular deactivation. Patients with sepsis whose cells demonstrate increased cell surface inhibitory molecule expression are at increased risk for secondary infections and mortality, providing evidence for another distinguishing marker of immune suppression.

Last, regulatory T cells are a highly immunosuppressive subset of T cells that are known to produce large quantities of anti-inflammatory cytokines. They appear to be resistant to apoptosis and can predominate in the subacute phase of sepsis in adults although this has not been seen in children.

**Treatment of Critical Illness–Induced Immune Suppression**

Recent evidence strongly suggests that critical illness–induced immune suppression has the potential to be reversed through agents known to stimulate either innate or adaptive immune function. Table 2 provides a summary of the evidence available from human trials.

### Innate Immune-Stimulating Agents

**Granulocyte Macrophage Colony-Stimulating Factor (GM-CSF).** GM-CSF is a cytokine that accelerates the production of neutrophils and monocytes from the bone marrow and enhances the activity of these cells in circulation and in tissues. GM-CSF is approved by the Food and Drug Administration for bone marrow reconstitution following chemotherapy and bone marrow transplant and has been used off-label for immunomodulation in critically ill adults and children. Taken as a whole, these studies suggest that GM-CSF can promote restoration of monocyte HLA-DR expression, improve neutrophil function, and increase TNF-α production capacity. Potential clinical benefits include resolution of infection, prevention of nosocomial infection, and shorter durations of mechanical ventilation, ICU stays, and hospital stays, although these outcomes have yet to be evaluated in large trials. Of note, no serious adverse events were ascribed to GM-CSF in any of these studies, nor did GM-CSF therapy result in increased systemic inflammation as measured by plasma IL-6 levels.

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**Table 1**

<table>
<thead>
<tr>
<th>Innate immunity</th>
<th>Consequence</th>
</tr>
</thead>
<tbody>
<tr>
<td>↓ Monocyte HLA-DR expression</td>
<td>↓ Antigen-presenting capacity</td>
</tr>
<tr>
<td>↓ Capacity to produce proinflammatory cytokines, such as TNF-α, when whole</td>
<td>↓ Ability of innate immune cells to respond to a new challenge, such as</td>
</tr>
<tr>
<td>blood or isolated monocytes are stimulated ex vivo with LPS or other</td>
<td>nosocomial infection</td>
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<tr>
<td>stimulants</td>
<td></td>
</tr>
<tr>
<td>↑ Cell-surface expression of inhibitory, negative costimulatory molecule</td>
<td>Active inhibition of lymphocytes</td>
</tr>
<tr>
<td>ligands such as PD-L1 and PD-L2 on antigen-presenting cells</td>
<td></td>
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<table>
<thead>
<tr>
<th>Adaptive immunity</th>
<th>Consequence</th>
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</thead>
<tbody>
<tr>
<td>Lymphocyte apoptosis resulting in lymphopenia and depletion of lymphoid organs</td>
<td>↓ Ability to sustain an immune response to pathogens</td>
</tr>
<tr>
<td>(eg, spleen)</td>
<td></td>
</tr>
<tr>
<td>↓ Capacity to produce proinflammatory cytokines, such as IFN-γ, when whole</td>
<td>↓ Ability of lymphocytes to respond to a new challenge, such as nosocomial</td>
</tr>
<tr>
<td>blood or isolated lymphocytes are stimulated ex vivo with PHA or other</td>
<td>infection</td>
</tr>
<tr>
<td>stimulants</td>
<td></td>
</tr>
<tr>
<td>↑ Cell surface expression of inhibitory, negative co-stimulatory molecules</td>
<td>Promotion of lymphocyte apoptosis or deactivation</td>
</tr>
<tr>
<td>on lymphocytes including PD-1, CTLA-4, and BTLA</td>
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</tr>
<tr>
<td>↑ Proportion of inhibitory regulatory T cells</td>
<td>↑ Expression of anti-inflammatory cytokines and direct deactivation of</td>
</tr>
<tr>
<td></td>
<td>lymphocytes</td>
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<table>
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<tr>
<th>Plasma biomarkers</th>
<th>Consequence</th>
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<tbody>
<tr>
<td>↑ Plasma IL-10 levels</td>
<td>Deactivation of innate and adaptive immune cells</td>
</tr>
<tr>
<td>↑ Plasma TGF-β levels</td>
<td>Deactivation of innate and adaptive immune cells</td>
</tr>
</tbody>
</table>

Abbreviations: BTLA, B- and T-lymphocyte attenuator; CTLA, cytotoxic T-lymphocyte-associated protein; HLA, human leukocyte antigen; IFN, interferon; LPS, lipopolysaccharide; PD, programmed death; PHA, phytohemagglutinin; TNF, tumor necrosis factor; TGF, transforming growth factor.
Interferon Gamma (IFN-γ). IFN-γ is a cytokine that plays a major role in activating lymphocytes, NK cells, monocytes, and macrophages. It has therefore been identified as a candidate drug to stimulate innate and adaptive immune function in critical illness. Use of IFN-γ has been associated with improvements in both monocyte HLA-DR expression and cytokine production capacity and was associated with lower incidence of ventilator-associated infection after severe trauma and improved clearance of invasive infections in fungal sep sis in several small studies. In 1 large randomized controlled trial (RCT) of 416 injured adults, IFN-γ or placebo was given for 21 days or until hospital discharge, with those in the IFN-γ group demonstrating a "Table 2"

### Selected human studies evaluating drugs targeting innate and adaptive immune suppression in critical illness

<table>
<thead>
<tr>
<th>Study</th>
<th>Design</th>
<th>Population</th>
<th>N</th>
<th>Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Drugs targeting innate immune suppression</strong></td>
<td></td>
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<tr>
<td>INF-γ</td>
<td></td>
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<td></td>
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<tr>
<td>Polk et al, 1992</td>
<td>RCT</td>
<td>Severely injured adults</td>
<td>193</td>
<td>↑ mHLA-DR expression in treated group.</td>
</tr>
<tr>
<td>Dries et al, 1994</td>
<td>RCT</td>
<td>Severely injured adults</td>
<td>416</td>
<td>↓ Incidence of infection-related mortality in treated group</td>
</tr>
<tr>
<td>Döcke et al, 1997</td>
<td>Nonrandomized, interventional</td>
<td>Adults with sepsis, low mHLA-DR expression</td>
<td>9</td>
<td>↑ mHLA-DR expression and TNF-α production capacity after treatment</td>
</tr>
<tr>
<td>Wasserman et al, 1998</td>
<td>RCT</td>
<td>Adults with severe burn injury</td>
<td>216</td>
<td>No differences in infection-related mortality</td>
</tr>
<tr>
<td>Nakos et al, 2002</td>
<td>RCT (inhaled IFN-γ)</td>
<td>Severely injured adults</td>
<td>52</td>
<td>↑ alveolar macrophage HLA-DR expression and lower rates of ventilator pneumonia in treated group</td>
</tr>
<tr>
<td>Delsing et al, 2014</td>
<td>Nonrandomized, interventional</td>
<td>Adults with severe invasive fungal sepsis</td>
<td>8</td>
<td>Increased mHLA-DR expression and enhanced anti-fungal pro-inflammatory cytokine production</td>
</tr>
<tr>
<td><strong>GM-CSF</strong></td>
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<tr>
<td>Bilgin et al, 2001</td>
<td>RCT</td>
<td>Neonates with sepsis and neutropenia</td>
<td>60</td>
<td>↓ Mortality in treatment group</td>
</tr>
<tr>
<td>Drossou-Agakidou et al, 2002</td>
<td>RCT</td>
<td>Neonates with sepsis</td>
<td>56</td>
<td>↑ mHLA-DR in GM-CSF treated group compared to G-CSF or placebo</td>
</tr>
<tr>
<td>Presneill et al, 2002</td>
<td>RCT</td>
<td>Adults with sepsis, pulmonary dysfunction</td>
<td>18</td>
<td>↑ Neutrophil function and improved oxygenation in treated group</td>
</tr>
<tr>
<td>Nierhaus et al, 2003</td>
<td>Nonrandomized, interventional</td>
<td>Adults with sepsis, low mHLA-DR expression</td>
<td>9</td>
<td>↑ mHLA-DR expression and TNF-α production capacity after treatment</td>
</tr>
<tr>
<td>Rosenbloom et al, 2005</td>
<td>RCT</td>
<td>Adults with sepsis</td>
<td>33</td>
<td>↑ mHLA-DR expression and faster resolution of infection in treated group</td>
</tr>
<tr>
<td>Orozco et al, 2006</td>
<td>RCT</td>
<td>Adults with abdominal sepsis</td>
<td>58</td>
<td>↓ Hospital stay and ↓ infectious complications in treated group</td>
</tr>
<tr>
<td>Meisel et al, 2009</td>
<td>RCT</td>
<td>Adults with sepsis and low mHLA-DR</td>
<td>38</td>
<td>↑ mHLA-DR expression and ↓ durations of mechanical ventilation and ICU stay in treated group</td>
</tr>
<tr>
<td>Hall et al, 2011</td>
<td>RCT</td>
<td>Children with MODS and low TNF-α production capacity</td>
<td>14</td>
<td>Enhanced TNF-α production capacity and lower incidence of nosocomial infection in treated group.</td>
</tr>
<tr>
<td>Paine et al, 2012</td>
<td>RCT</td>
<td>Adults with ALI/ARDS</td>
<td>132</td>
<td>No difference in ventilator-free days</td>
</tr>
<tr>
<td><strong>Drugs targeting adaptive immune suppression</strong></td>
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<tr>
<td><strong>IL-7</strong></td>
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<tr>
<td>Venet et al, 2012</td>
<td>Ex vivo (cell culture)</td>
<td>Adults with septic shock</td>
<td>10</td>
<td>↑ Lymphocyte proliferation and INF-γ production</td>
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<tr>
<td><strong>Anti-PD-1 antibodies</strong></td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chang et al, 2014</td>
<td>Ex vivo (cell culture)</td>
<td>Adults with sepsis</td>
<td>43</td>
<td>↑ INF-γ production and decreased lymphocyte apoptosis</td>
</tr>
</tbody>
</table>

Abbreviations: ALI, acute lung injury; ARDS, acute respiratory distress syndrome; G-CSF, granulocyte colony-stimulating factor; GM-CSF, granulocyte macrophage colony-stimulating factor; IFN-γ, interferon gamma; IL, interleukin; mHLA-DR, monocyte HLA-DR expression, MODS, multiple organ dysfunction syndrome; PD, programed death; RCT, randomized controlled trial; TNF, tumor necrosis factor.
lower rate of infection-related mortality. In a similar study of 216 critically ill adult burn patients, IFN-γ administration was associated with no difference in outcomes. To date, no large RCTs using IFN-γ in critical illness have been performed in sepsis.

**Adaptive Immune Stimulating Agents**

*Interleukin-7.* IL-7 is a lymphocyte-stimulating cytokine required for T-cell development and for maintenance and restoration of mature T cells. Recombinant human IL-7 (rhIL-7) therapy has been evaluated in preclinical sepsis models, and data suggest beneficial effects, including increased cytokine production capacity, T-cell proliferation, prevention of lymphocyte apoptosis, and improved survival. Ex vivo treatment of lymphocytes from patients with sepsis with IL-7 significantly improved T-cell proliferation, up-regulation of anti-apoptotic proteins, and IFN-γ production capacity. Whereas rhIL-7 is currently being evaluated in patients with chronic viral infection and cancer, to date it remains unstudied in vivo in the setting of critical illness.

*PD-1 and CTLA-4 Blocking Antibodies.* In addition to immunostimulatory cytokine therapy, an alternative approach to restore adaptive immune function involves blocking inhibitory molecules such as PD-1 or cytotoxic T-lymphocyte-associated protein (CTLA)-4. Preclinical studies have shown improved lymphocyte survival, cytokine production capacity and improved survival in murine models of bacterial and fungal sepsis that eliminate or block PD-1 or CTLA-4. Both anti-PD-1 and anti-CTLA-4 antibody therapy have been studied in vivo in humans as adjuvant therapies for malignant neoplasia and may have a role in future clinical trials in sepsis.

**Future Directions in Diagnosis and Treatment of Critical Illness–Induced Immune Suppression**

Given the heterogeneity of conditions and the complexity of the immunologic response to critical illness, each patient will be different in presenting characteristics and response to treatment. It is therefore likely that different approaches will be necessary, with the same patient potentially requiring different treatments at various points in time.

It is similarly likely that multiple diagnostic approaches will need to be employed in the ICU. Such an immune monitoring regimen could include an initial risk assessment with genetic and epigenetic determinants, once identified, being evaluated upon admission (Figure 2). Serial measurement of innate and adaptive immune function using a combination of cell surface marker analysis and stimulation studies could inform the use and timing of immunostimulatory agents. Patients with clearly identified innate and/or adaptive immune dys- function would then be appropriately stratified into treatment groups based on their individual immunologic deficits. Furthermore, the patient’s individual response to treatment would be longitudinally monitored and adjustments to immunomodulatory therapies made accordingly. Throughout, attention would be paid to avoid immunosuppressive therapies in at-risk patients in favor of an immune-friendly treatment plan. This comprehensive and highly dynamic

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**Figure 2** A future paradigm for the diagnosis and management of critical illness–induced immune suppression. After the onset of critical illness, patients would undergo a risk assessment including genetic and epigenetic screening, followed by prospective, comprehensive immune function monitoring. Should immune suppression be detected, the patient would receive immunostimulatory therapy specifically tailored to treat the detected deficit. Immune-friendly supportive care would be provided throughout.
approach to immune function has the potential to provide patient-specific immunomodulation to improve outcomes in critical illness.

FINANCIAL DISCLOSURES
None reported.

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