Persistent inflammation and immunosuppression: A common syndrome and new horizon for surgical intensive care

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Surgical intensive care unit (ICU) stay of longer than 10 days is often described by the experienced intensivist as a “complicated clinical course” and is frequently attributed to persistent immune dysfunction. “Systemic inflammatory response syndrome” (SIRS) followed by “compensatory anti-inflammatory response syndrome” (CARS) is a conceptual framework to explain the immunologic trajectory that ICU patients with severe sepsis, trauma, or emergency surgery for abdominal infection often traverse, but the causes, mechanisms, and reasons for persistent immune dysfunction remain unexplained. Often involving multiple-organ failure (MOF) and death, improvements in surgical intensive care have altered its incidence, phenotype, and frequency and have increased the number of patients who survive initial sepsis or surgical events and progress to a persistent inflammation, immunosuppression, and catabolism syndrome (PICS). Often observed, but rarely reversible, these patients may survive to transfer to a long-term care facility only to return to the ICU, but rarely to self-sufficiency. We propose that PICS is the dominant pathophysiology and phenotype that has replaced late MOF and prolongs surgical ICU stay, usually with poor outcome. This review details the evolving epidemiology of MOF, the clinical presentation of PICS, and our understanding of how persistent inflammation and immunosuppression define the pathobiology of prolonged intensive care. Therapy for PICS will involve innovative interventions for immune system rebalance and nutritional support to regain physical function and wellbeing. (J Trauma Acute Care Surg. 2012;72: 1491–1501. Copyright © 2012 by Lippincott Williams & Wilkins)

KEY WORDS: Systemic inflammatory response syndrome; SIRS; compensatory anti-inflammatory response syndrome; CARS; persistent inflammation-immunosuppression catabolism syndrome; multiple-organ failure; surgical intensive care; acute care surgery.

Multiple-organ failure (MOF) emerged in the early 1970s as a result of advances in intensive care unit (ICU) technology that enabled patients to survive single-organ failure. Its epidemiology continues to change as our management strategies evolve from ongoing research (Fig. 1). In the late 1970s, reports by Polk, Eiseman, and Fry promoted the belief that MOF was the “fatal expression of uncontrolled infection” and focused research on infection-driven MOF. More than half of MOF cases were associated with intra-abdominal infection (IAI). Throughout the 1980s, IAI became less problematic due to advances in surgery and intensive care including: (a) better initial management of abdominal trauma and IAI, (b) more potent and appropriately dosed perioperative antibiotics, (c) earlier diagnosis of postoperative IAI with advanced computerized axial tomography, and (d) effective percutaneous abscess drainage using interventional radiology.

A series of reports from Europe by Faist et al., Nuytinck et al., and Waydhas et al. convincingly demonstrated that MOF was a frequent occurrence in blunt trauma patients without infection. The term sepsis syndrome became the vernacular to describe patients who appeared to be septic but had no obvious source of infection. The central question became, “What is the driving mechanism of this deleterious inflammation?” Given that shock was a consistent early event, whole-body ischemia-reperfusion was an attractive explanation. Alternatively, epidemiologic studies by Border et al. strongly implicated the gut as the occult source of bacteria that drove the sepsis syndrome. Indeed, prospective randomized controlled trials testing selective gut decontamination and early enteral nutrition found decreased rates of nosocomial infection (principally pneumonia) with these gut-directed therapies. These clinical observations were supported by the experimental work of Fukushima et al. that persuasively focused attention on bacterial translocation as a unifying mechanism that characterized noninfection-induced MOF.

In the late 1980s, Shoemaker et al. popularized an alternative hypothesis that “early unrecognized flow-dependent oxygen consumption” was a prime cause of noninfectious MOF. Pushing oxygen delivery to “supranormal” levels during initial resuscitation became a standard of care. Simultaneously, trauma system triage, advanced trauma life support, and “damage control” surgery were universally adopted. As a result, patients with severe injury were triaged to designated trauma centers, underwent damage control surgery, and in the ICU, received supranormal oxygen delivery resuscitation. Fewer
patients exsanguinated and more survived to ICU admission. Many developed abdominal compartment syndrome, which emerged as an epidemic in the mid 1990s and was subsequently shown to be another deadly MOF phenotype. By the mid 1990s, sepsis syndrome had evolved into the systemic inflammatory response syndrome (SIRS). SIRS was presumed to be inherently beneficial; however, if exaggerated or perpetuated, SIRS could precipitate early MOF independent of infection. It was not until the first decade of the new millennium that Matzinger provided an explanation for SIRS in absence of obvious microbial infection: the host responds to noninfectious insults and tissue injury by releasing endogenous mediators that are “danger signals.” Tissue damage, per se, releases “alarmins” and “damage-associated molecular pattern” (DAMP) molecules that can stimulate innate immunity through toll-like receptors (TLR) or other sensing systems. Thus, noninfectious insults can elicit exaggerated inflammation through the same pathway(s) as microbial pathogens and produce similar SIRS.

Also, in the mid 1990s, analysis of the Denver MOF database revealed that MOF occurred “early” or “late” in the surgical ICU course. Two different patterns of SIRS induced early MOF. The “one hit” model, i.e., a massive initial insult culminating in early fulminant SIRS and MOF; or the “two hit” model, i.e., resuscitating severely injured patients with SIRS followed by an early second inflammatory insult (e.g., pulmonary aspiration, blood transfusion, or early orthopedic intervention) amplifying SIRS to induce early MOF. This was believed due to priming and activation of innate immune response (principally polymorphonuclear leukocyte [PMN] mediated). SIRS was followed by delayed immunosuppression, often leading to late infection, which, in turn, appeared to precipitate late MOF after 7 days to 10 days.

By the early 2000s, ongoing research revealed that many time-honored ICU interventions (e.g., high tidal volume mechanical ventilation, high-volume crystalloid resuscitation, liberal blood transfusions, early total parenteral nutrition (TPN), intermittent hemodialysis) were actually promoting nosocomial infection and late MOF. Over the last decade, with more consistent delivery of evidence-based care to minimize these practices, abdominal compartment syndrome has become rare, death from traumatic shock-induced MOF has decreased substantially, and late MOF has disappeared.

However, this decrease in MOF incidence has not been observed with sepsis. Despite tremendous research efforts, sepsis remains a leading cause of MOF and prolonged ICU stay. With the advancing age of our population, the incidence of sepsis is increasing, and mortality rate remains prohibitively high (>40%) for patients who are allowed to progress into septic shock.

Early sepsis is often difficult to recognize, and for most patients presenting early sepsis, the initial diagnosis is delayed or missed. Many interventions are known to have an impact on outcome but are often administered in haphazard fashion. Optimal management strategies require assessment and implementation of current evidence-based standard operating procedures (SOPs). Such approaches have been successfully demonstrated by the recent “Glue Grant” experience, the “Surviving Sepsis Campaign,” ARDSNET, and other evidence-based guidelines (EBGs). A widely recognized challenge is bedside implementation of EBGs in daily intensive care of the individual patient. Recent audits have shown surprisingly low compliance with widely accepted EBGs, and substantial improvement in outcomes by strategies that only modestly improve compliance.

One approach that has consistently demonstrated improved implementation of evidence-based care and patient outcome is computerized clinical decision support (CCDS). With rule sets devised by the ICU clinician team, computerized protocol systems standardize clinical decision making, ensure high compliance, and consistently outperform expert ICU clinicians. EBG implementation not only improves outcome but also provides a more stable platform for multicenter prospective randomized clinical trials (PRCTs) because confounding effects of variable care are controlled and ongoing process improvement is stimulated.

Implementation of CCDS has resulted in a surprisingly large decrease in mortality rate from severe sepsis (Fig. 2A). Mortality rate from early fulminant SIRS has decreased significantly because intervention occurs before development of septic shock. Similar results were found with the Glue Grant experience for patients with severe blunt trauma using multivariate, consensus-derived, evidence-based SOPs. Glue Grant participants found modest compliance with agreed evidence-based SOPs to be associated with dramatic reduction of overall mortality rate from 22% before to 11% after SOP implementation.

However, there remain a large number of patients who linger in the ICU with manageable organ dysfunctions but who usually do not meet established criteria for late MOF. Their clinical course is characterized by ongoing protein catabolism with poor nutritional status, poor wound healing, immunosuppression, and recurrent infections. These patients are commonly discharged to long-term acute care (LTAC) facilities but, owing to excessive loss of lean body mass and prolonged immunosuppression, often develop secondary
nosocomial infections and rarely rehabilitate or return to functional life.

We propose that this “persistent inflammation-immunosuppression catabolism syndrome” (PICS) is the predominant phenotype that has replaced late occurring MOF in surgical ICU patients who fail to recover. Clinical management of these patients as they progress irreversibly toward indolent death is perhaps the most challenging problem currently confronting surgical intensive care.

**SIRS, CARS, AND THEIR CURRENT RELEVANCE TO PICS**

Since the first identification of proinflammatory cytokines (e.g., interleukin 1 [IL-1] and tumor necrosis factor α [TNF-α]) in the 1980s,24,25 death from sepsis was presumed to be caused by an early overabundant innate immune response. Overproduction of multiple proinflammatory mediators, PMN activation, endothelial injury, inadequate perfusion and tissue damage caused early MOF and led to death.26-28 This process was driven by exposure to infectious products, such as pathogen-associated molecular patterns (PAMPs),29 or by endogenous danger signals (damage-associated molecular patterns [DAMP] and alarmins)11,12 acting through TLR or nucleotide-binding oligomerization domain (NOD) signaling pathways.30 The end results were similar, that is, the activation and overexpression of early response genes, driven in large part through nuclear factor κB (NF-κB) activation.31 There have been nearly 150 clinical trials of biologic response modifiers, most testing agents that attempt to block this early proinflammatory response.17,32 All but one of these studies failed to demonstrate efficacy.33 The only Food and Drug Administration–approved drug for severe sepsis-septic shock (Xigris, activated protein C, Eli Lilly and Co., Indianapolis, IN) was voluntarily withdrawn from the market in late 2011 due to failure of postmarketing clinical trials to confirm earlier outcome benefit.34

Anti-inflammatory approaches to sepsis have failed because of both conceptual and technical difficulties. Because of the rapid onset of the innate immune response, treatments initiated hours after the onset of symptoms have inevitably missed the early inflammatory mediator release and initiation of inflammatory cascades.35 In addition, redundancy of the early inflammatory mediator cascades has made success of monotherapies unlikely.35 Preclinical studies to investigate the efficacy of these drugs had a uniformly beneficial effect in rodent and primate models. Eichacker et al.36 performed an enlightening meta-analysis showing that the efficacy of anti-TNF-α in severe sepsis positively correlated with the mortality rate of the control group. Anti–TNF-α therapies were beneficial for the patients with most serious illness, but actually harmful in patients with lesser degree of illness.37

Concordantly, it was well known as early as the 1970s that severe trauma and sepsis were associated not only with exaggerated inflammation but also with an immunocompromised state.38 With the definition of SIRS, Bone39 described postinflammatory immunosuppression and coined the term *compensatory anti-inflammatory response syndrome* (CARS) (Fig. 3A). CARS was first described as an “anti-inflammatory response” characterized by increased appearance in the circulation of anti-inflammatory cytokines (e.g., IL-10 and IL-6) and cytokine antagonists (e.g., IL-1ra and sTNFRI).39 In animal models, the appearance of these cytokines was delayed when compared with early inflammatory mediators (i.e., TNF-α) after endotoxemia or Gram-negative bacteremia.40,41 In patients with critical illness, concentrations of these anti-inflammatory mediators were found to be increased for days and weeks, whereas

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**Figure 2.** Mortality rate for severe sepsis-septic shock and trauma—The Methodist Hospital (TMH), Surviving Sepsis Campaign and the Glue Grant experiences. (A) Yearly mortality rate (2006-2009) for patients treated for severe sepsis-septic shock in TMH Surgical ICU compared with Surviving Sepsis Campaign (SSC) guideline-based performance improvement initiative and National Surgical Quality Improvement Program (NSQIP) data. In 2006 (before initiation of sepsis protocol), mortality rate in TMH Surgical ICU was 34%. In 2007 (as sepsis screening and our sepsis protocol were implemented using a paper protocol [PP]), mortality rate decreased to 24%. In 2008 (using the PP), mortality rate was 23%. In 2009 (with implementation of computerized sepsis protocol [CP]), mortality rate decreased to 14%. For comparison, 31% mortality rate was reported in the eighth quarter of the SSC Pi initiative and 34% as reported in a recent NSQIP analysis. Reprinted with permission from McKinley et al.23 (B) The overall mortality rate for blunt trauma from the Glue Grant study cohort decreased during the study period from 22% in the first 2 years to 11% in the last 2 years (p < 0.01) as evidenced-based SOPs were implemented and compliance increased. Reprinted with permission from Cuschieri et al.16

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The early findings of Christou et al. from the 1970s showed that patients with critical illness could not mount a delayed type hypersensitivity response to common antigens and that T-cell proliferation was markedly suppressed. CARS had become the moniker for all the shared defects in adaptive immunity that accompany severe trauma and sepsis, including decreased antigen presentation, macrophage paralysis, depressed T-cell proliferative responses, increased lymphocyte and dendritic cell apoptosis, and shift from $T_{H1}$ to $T_{H2}$ lymphocyte phenotype (Table 1).

The scientific community came to conclude that the sequence of early proinflammation (SIRS) and later anti-inflammation (CARS) was responsible for adverse outcomes after severe trauma and sepsis (Fig. 3A). Just as MOF has evolved, this SIRS-CARS paradigm has been challenged on several fronts. The compensatory nature of CARS has been questioned in commonly used models of sepsis, including the cecal ligation and puncture and colon ascendens stent peritonitis. In these models of polymicrobial or abdominal sepsis, blocking early proinflammatory response had no effect on either anti-inflammatory responses or suppression of adaptive immunity. In addition, the concept that CARS is “delayed” relative to SIRS has been criticized and revised. Osuchowski et al. were first to report that production of anti- and proinflammatory cytokines occurs simultaneously in a polymicrobial sepsis model. More dramatically, Xiao et al. provided convincing evidence from genome-wide expression analysis of blood leukocytes after severe blunt trauma in humans that down-regulation of genes involved in T-cell responses and that antigen presentation and up-regulation of anti-inflammatory gene expression parallel increased expression of proinflammatory genes. The Glue Grant findings have generated a new model to replace the classic model of SIRS-CARS, in which induction of both responses occurs simultaneously (Fig. 3B).

Another component of the traditional SIRS-CARS paradigm is that proinflammation occurs early and is terminated by the development of CARS. This belies experimentadata suggesting that, in patients with critical illness and immunosuppression, inflammation is persistent but attenuated compared

![Modified SIRS-CARS Model to Accommodate Multiple Hits](image-url)

**Figure 3.** Evolution of SIRS-CARS model. (A) The traditionally accepted SIRS-CARS phenomenon holds that death from severe sepsis and injury is a consequence of an overabundant and dysregulated early innate immune response from the overproduction of proinflammatory mediators and cytokines, leading to endothelial injury, tissue damage, inadequate perfusion and MOF. For patients who survive this early SIRS event, a CARS response, including suppression of adaptive immunity, results. Additional insults such as nosocomial infection can cause a late “second-hit” that may lead to recurrent SIRS. (B) Recently, the Glue Grant results showed that, based on leukocyte genomic expression patterns, there is a simultaneous induction of innate (both proinflammatory and anti-inflammatory genes) and suppression of adaptive immunity genes, and that there is minimal genomic or clinical evidence for a “second-hit” phenomenon. Reprinted with permission from Xiao et al.

proinflammatory cytokines “disappeared.” The “compensatory” nature of this response was demonstrated in baboons and chimpanzees, and then in humans, by Van Zee et al. and van der Poll et al., who reported that blockade of the early inflammatory response with TNF-α inhibitors prevented appearance or release of anti-inflammatory cytokines and cytokine antagonists.

By the 1990s, it was well recognized that patients with severe sepsis not only exhibited an ongoing inflammatory response, but also exhibited multiple defects in adaptive immunity.
with the initial inflammatory event.\textsuperscript{50} This persistent inflammation is characterized by increased concentration of plasma IL-6, a persistent acute phase response, neutrophilia, with increased immature granulocyte count, anemia, lymphopenia, and, often, tachycardia. Although these patients are profoundly immunosuppressed, inflammation is ongoing. Importantly, this prolonged inflammation-immunosuppression process is consuming energy derived from fat and protein catabolism. Despite aggressive nutritional intervention, ongoing catabolism results in substantial loss of lean body mass and proportional decrease in functional status.

Modern ICUs are proficient with early recognition and treatment of SIRS. As a result, many patients survive their initial sepsis or emerge with surgical insult only to encounter prolonged, complicated ICU courses.\textsuperscript{51} In leading centers of expertise, emphasis is no longer targeting exaggerated proinflammation, but identifying mechanisms that drive prolonged immunosuppression, and searching for new therapies that prevent it or restore immune function.\textsuperscript{32}

**UNDERSTANDING THE BASIS FOR IMMUNOSUPPRESSION ASSOCIATED WITH CRITICAL ILLNESS**

Terminally differentiated macrophages (e.g., Kupffer cells and splenic macrophages), blood monocytes, and dendritic cells are key effector cells that remove pathogens and present antigens in innate immunity. Macrophage dysfunction is a significant contributor to both innate and adaptive immunosuppression.\textsuperscript{51} As bacterial clearance is decreased\textsuperscript{52} and capacity to present antigens and release proinflammatory cytokines is also decreased,\textsuperscript{51} the patient enters a state of "immune paralysis" and is vulnerable to secondary infection.\textsuperscript{28}

Small studies testing immunostimulatory therapies to reverse monocyte deactivation indicate that these may be successful treatments of sepsis-induced immunosuppression.\textsuperscript{62,63} Doek et al.\textsuperscript{63} tested administration of interferon-γ in septic patients and found marked improvement in monocyte HLA-DR expression. Meisel et al.\textsuperscript{64} administered granulocyte-macrophage colony-stimulating factor (GM-CSF) to septic patients with immunosuppression identified by decreased monocyte HLA-DR receptor expression. They showed that GM-CSF was effective in restoring macrophage immunocompetence and was associated with decreased ICU length of stay and duration of mechanical ventilation.\textsuperscript{64} These reports indicate that, in refractory sepsis, the immune system is so severely compromised that immunostimulatory therapy does not unbridge the proinflammatory response seen in early sepsis.\textsuperscript{17}

Another facet of sepsis-induced immunosuppression involves defective T-cell lymphocytes, including apoptotic depletion,\textsuperscript{53,65} decreased proliferation,\textsuperscript{66} and T\textsubscript{H}2 polarization.\textsuperscript{66,67} Programmed death 1 (PD-1) protein (a negative costimulatory molecule expressed on a number of immune cells) prevents T-cell proliferation, causes T cells to become nonresponsive, and increases monocyte production of IL-10.\textsuperscript{17,68} The PD-1: programmed death ligand (PD-L) pathway is thought to be critical in chronic infections such as HIV, but its role in innate and adaptive immunity after sepsis has yet to be elucidated.\textsuperscript{68,69} Recently, Huang et al.\textsuperscript{68} showed that absence of PD-1 increases survival rate after polymicrobial sepsis in PD-1 knockout mice. In addition to effects on T-cell effector function, increased expression of PD-1 on macrophages and monocytes during sepsis is associated with their functional decline, indicating that this survival advantage may be secondary to a macrophage effect.\textsuperscript{68} Similarly, Brahmandam et al.\textsuperscript{70} showed that, when using a PD-1 receptor antibody initiated 24 hours after the onset of polymicrobial sepsis in mice, survival rate increased. When examining septic patients, these investigators found that T lymphocytes in the spleen and lung had increased expression of PD-1 and splenic capillary endothelial cells had increased expression of PD-L1.\textsuperscript{71} Recently, Said et al.\textsuperscript{69} showed that PD-1 impairs immunity via increased production of IL-10. They found that, in HIV-positive patients, PD-1 activation results in increased IL-10 secretion from monocytes and that, when the PD-1: PD-L1 receptor interaction is blocked, PD-1–induced inhibition of CD4 T cells was reversed.\textsuperscript{17,69} Other inhibitory peptides that may be involved in adaptive immunosuppression during sepsis and trauma include cytotoxic T-lymphocyte antigen-4 (CTLA-4), B and T lymphocyte attenuator (BTLA), and herpes virus entry mediator (HVEM).\textsuperscript{55–57}

The antiapoptotic cytokine IL-15 may be another novel therapeutic agent to target both innate and adaptive immunity. IL-15 has a broad range of functions. It acts as an antiapoptotic cytokine and augments interferon γ expression, which may help reverse monocyte dysfunction in sepsis and, therefore, is an intriguing immunostimulatory cytokine.\textsuperscript{72} In a murine model of polymicrobial sepsis, Inoue et al.\textsuperscript{73} showed decreased splenic cell apoptosis in septic mice treated with IL-15 and, in mice with polymicrobial sepsis treated postoperatively with IL-15, threefold improvement in survival rate. Similarly, improved survival rate was found in mice undergoing the Pseudomonas aeruginosa pneumonia model.\textsuperscript{73} Treating sepsis with IL-15 has not been attempted in human clinical trials, but IL-7, an immunostimulatory cytokine with effects similar to IL-15, is currently being used as a therapy for patients with hepatitis C, HIV, or cancer.\textsuperscript{17}

The immunosuppressed state that characterizes severe trauma or sepsis is also associated with increased suppressor cell populations. The best described are CD4\textsuperscript{+} and CD8\textsuperscript{+} T regulatory cell (Treg) populations, popularized by Sakaguchi et al.\textsuperscript{74} Evidence now suggests that naturally occurring Tregs play a major role in suppressing immunoreactivity in many diseases.\textsuperscript{75} In addition to naturally occurring Tregs, there are inducible populations that have immunoregulatory functions, including TGF-β producing T\textsubscript{H}3 cells involved in oral tolerance, and IL-10 producing Treg type 1 (T\textsubscript{H}1) cells.\textsuperscript{74} Many cell surface molecules serve as markers that are coexpressed on Tregs, including glucocorticoid-induced TNF receptor (GITR) and intracellular CTLA-4.\textsuperscript{55–57} Other factors contribute to development and activity of regulatory cells, such as the forkhead box transcription factor, Foxp3, and TLRs, which recognize PAMPs or can augment Treg function or proliferation.\textsuperscript{76} Treatment of mice with an agonist antibody to GITR has been shown to both suppress Treg function and to stimulate T effector cell function, resulting in increased polymicrobial sepsis survival rate.\textsuperscript{66}
Monneret et al. was the first to report that sepsis increases the relative number of Tregs in the blood of septic patients. We reported a relative increase in Tregs in a murine model of polymicrobial sepsis and that their suppressor activity was markedly increased. Their importance to outcome remains controversial. Scumpia et al. and Wisnoski et al. have not shown any impact on outcome when these populations were deleted in sepsis, but Chen et al. reported improved survival rate in septic mice when Tregs were depleted. Recently, Nascimento et al. showed increased presence of Tregs in thymus and spleen after polymicrobial sepsis, and that this increased presence was associated with decreased proliferation of CD4+ T cells. The sepsis surviving mice were subjected to secondary infection with a nonlethal dose of Legionella pneumophila at 15 and 30 days after sepsis. The mice did not survive, thus leading to the conclusion that the sepsis surviving mice had immune dysfunction. This effect was reversed by treatment with an agonist GITR antibody.

After decades of failure of clinical trials of therapies to quell early proinflammation induced by sepsis or SIRS, there is intriguing evidence that therapies to restore immunocompetence by targeting reversal of macrophage and T-cell dysfunction may offer an attractive alternative approach. Only clinical trials will show whether adaptive immunity stimulants for the treatment of immunosuppression have more success than anti-inflammatory approaches.

**EMERGENCY MYELOPOIESIS DRIVES PERSISTENT IMMUNOSUPPRESSION AND INFLAMMATION**

The concept that the early inflammatory (SIRS) response to severe trauma or systemic infection is short lived and transient is fallacious. We now recognize that, in patients with severe trauma and sepsis, inflammation and immunosuppression are proceeding concurrently for prolonged periods. After the initial insult, granulocytes in the bone marrow rapidly marginate and follow chemokine gradients to sites of infection or injury. Emptying the bone marrow, combined with dramatic lymphocyte apoptosis in secondary lymphoid organs, creates space for hematopoietic progenitor production, and production is skewed toward myelopoietic precursors that can differentiate into mature granulocytes, macrophages, or dendritic cells (Fig. 4). This is a well conserved response to inflammation and has been termed emergency myelopoiesis-granulopoiesis. Mediators that may drive this response include growth factors (e.g., G/GM-CSF) and cytokines (e.g., IL-6 and IL-17) produced during the early SIRS response.

One of the surprising results of emergency myelopoiesis is the emergence of myeloid-derived suppressor cells (MDSCs) in bone marrow, secondary lymphoid organs, and even in organs of the reticuloendothelial system. MDSCs, originally noted for their immunosuppressive functions, including ability to suppress T-cell responses via increased production of inducible nitric oxide synthase (iNOS), arginase (ARG), and reactive oxygen species (ROS), are a heterogeneous population of activated immature myeloid cells with immunosuppressive functions. We have shown that the increased expansion of MDSC populations is proportional to the severity of the inflammatory insult. Moderate trauma (midline laparotomy) induces a transient increase that persists for days, and more-severe insult models (sepsis and burn) cause increase of MDSC population that persist for weeks to months.

The role of MDSCs in sepsis is controversial, although we think that they play a central, but still unproven role in the persistent inflammation of human sepsis, trauma, and the development of PICS. MDSCs, unlike terminally differentiated macrophages, express low concentrations of major histocompatibility class II (MHC-II) and CD80/CD86, making them poor antigen presenting cells. However, these MDSCs, unlike terminally differentiated macrophages and monocytes after sepsis or trauma, produce large amounts of IL-10, TNF-α, Regulation upon Activation, Normal T cell Expressed and Secreted (RANTES), monocyte chemotactic protein-1 (MCP1), stroma-derived factor-1 (SDF-1) and macrophage inflammatory protein-1α (MIP1α). These cells also consume large quantities of arginine, producing NO, ROS, and peroxynitrites that are both proinflammatory and immunosuppressive. Murine models have shown dramatic MDSC proliferation in bone marrow, spleen, and lymph nodes of mice surviving more than 3 days and 10 days after onset of sepsis, marked splenomegaly, and 40% of spleen and 90% of bone marrow cells are MDSCs with persistence beyond 12 weeks. Failure to expand the MDSC population was associated with worsened outcomes. Surprisingly, prevention of expansion of the MDSC population has been shown to be detrimental to survival from sepsis and burn injury. MDSCs appear to be critical for maintenance of innate immunity and inflammatory responses to secondary infection.

Importantly, expansion of the MDSC population in sepsis can also explain some of the immunosuppression seen in...
patients with PICS. MDSCs also play a widely recognized role in T-cell suppression, in part through nitrosylation of the T-cell receptor and depletion of intracellular arginine, and in promotion of Treg cell production (Table 2). As a result, the role that MDSCs have in sepsis is neither simple nor clear-cut. Although MDSCs are a component of emergency myelopoiesis and contribute to immune surveillance against secondary infections, their presence in the septic host may also be detrimental by promoting adaptive immunosuppression and persistent inflammation.

**DESIGNATION OF PICS**

With patterns of MOF evolving, our traditional definitions of immunologic status are becoming obsolete. Successful management of SIRS in ICUs has increased numbers of patients who reside in ICUs for weeks with a syndrome of moderate organ dysfunction, secondary infection, requirement for life support, and progressive protein catabolism, commonly resulting in loss of lean body mass and failure to regain strength. Successful management of these patients is commonly defined as discharge to a LTAC facility, rather than return to a functional life. As fewer patients are developing late MOF, we now observe the emergence of this new syndrome, PICS, and are presented with the challenge of managing simultaneous chronic inflammation and adaptive immunosuppression, protecting against secondary nosocomial infection, and preventing severe protein catabolism (Fig. 5). The designation of PICS acknowledges the presence of multiple immunologic and physiologic defects that occur simultaneously and that likely require multimodal therapy.

Patients with PICS can be identified in the critically ill surgical intensive care population with prolonged stay time and routine ICU and clinical laboratory measurements. As shown in Table 3, a patient meets PICS criteria if he or she is residing in the ICU for at least 10 days and is having persistent inflammation defined by C-reactive protein (CRP) concentration more than 150 µg/dL and retinol binding protein concentrations less than 1mg/dL, immunosuppression crudely defined by a total lymphocyte count less than 0.80 × 10⁹/L, and a catabolic state defined by serum albumin concentrations less than 3.0 g/dL, creatinine height index less than 80%, and weight loss more than 10% or body mass index less than 18 during the current hospitalization. Although these clinical markers are not direct measurements of inflammation, immunosuppression, or protein catabolism, they can serve as surrogates that are readily available in most critical care settings.

Fortunately, research approaches to better characterize the immunosuppression and chronic inflammation associated with critical illness are becoming more and more routine. Rapid enzyme-linked immunosorbent assay (ELISA) and Luminex techniques are making plasma protein, including cytokines such as IL-6, IL-10, IL-1ra, and sTNFRI, routine assessments for the inflammatory status of the patients. Procalcitonin analysis is in regular clinical use in Europe and is becoming more popular in the United States. Flow cytometric analyses, which were once limited exclusively to large research laboratories are now being used in critical care settings, allowing for simultaneous characterization of cell populations much more routine. Characterization of the “paralyzed monocyte” by looking at HLA-DR or CD80/CD86 expression on CD4+ cells is now routine, as is identification of T-cell suppressor molecules, PD-1, CTLA-4, BTLA, and HVEM on CD4+ and CD8+ cell populations. Even description of the elusive human MDSC is becoming possible with cell sorting techniques that can isolate sufficient cells for not only ARGI and

**TABLE 2. Functional Properties of MDSCs**

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<th>Pathologic Process</th>
<th>Mechanism/Function</th>
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<td>Inducible nitric oxide synthetase</td>
<td>Cancer, inflammation; immunosuppression</td>
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<tr>
<td>NADPH oxidase</td>
<td>Cancer, inflammation; chemokine, iNOS</td>
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<tr>
<td>M-CSFR (CD115) Cancer</td>
<td>Cancer, Inflammation; chemokine</td>
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<td>IL-4ra (CD124) Cancer</td>
<td>Cancer, T&lt;sub&gt;H&lt;/sub&gt;2 skewing and associated with suppressive activity</td>
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<td>Cancer, IL-10 and TCR activation</td>
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Arginase, Arginase; M-CSFR, monocyte colony stimulating factor receptor; LTA4H, leukotriene A<sub>4</sub> hydrolase; MIP-1β, macrophage inflammatory protein-1 beta; TRC, T regulatory cell. MDSCs are known to be pluripotent, affecting both innate and adaptive immunity through direct contact and the secretion of various soluble factors (including iNOS, ROS, and cytokines). These properties are responsible for both the immunosuppressive function of MDSCs and as their protective role against primary and secondary infection.

Modified with permission from Cuenca et al.
NOS2 expression, but also antigen-specific cell suppression assays. The Glue Grant effort has shown the ability to perform genome-wide expression routinely on enriched subsets of leukocyte populations and determine genomic expression patterns associated with different clinical outcomes.

**CLINICAL RELEVANCE AND MEDICAL MANAGEMENT**

Combating MOF has been a major ICU challenge for the past 40 years. Management strategies have continued to evolve to address different MOF phenotypes and prevent or minimize their fatal expression. Through improved, aggressive initial care, today’s patients survive previously lethal insults, be it severe sepsis, trauma, or surgical intervention, do not develop late MOF, and do not die in the ICU. Unfortunately, many who survive their initial ICU days do not progress to normal recovery but, for undetermined reasons, persist with manageable organ dysfunctions, catabolism, poor nutritional status, and recurrent infections, only to be discharged to a LTAC facility, subsequent ICU readmission, or indolent death. We think that this syndrome, termed PICS, is the predominant pathology that prolongs intensive care, and is the new phenotype that has replaced late appearing MOF.

When PICS is recognized, course correction is difficult, and rehabilitation of these patients into a functional state is rare. The major challenges for this new paradigm are: (1) to identify PICS early in its course, (2) to understand its underlying pathophysiology, and (3) to initiate appropriate multimodal therapies that target specific components of the syndrome. We believe that the identification of PICS and the development of therapeutic interventions will be best performed from a platform of optimized care derived from EBGs for patient management, available with CCDS.

Medical care resource consumption associated with PICS has yet to be measured, but is likely to be a large multiple of the costs associated with the short-term treatment of trauma, severe sepsis and septic shock. The incidence of PICS is likely to increase as our population ages and our technology improves. Characterization and management of PICS will require new strategies.

**TABLE 3. PICS Criteria**

<table>
<thead>
<tr>
<th>Clinical Determinants of PICS</th>
<th>Measurements</th>
</tr>
</thead>
<tbody>
<tr>
<td>Persistent Prolonged ICU stay</td>
<td>&gt;10 d</td>
</tr>
<tr>
<td>Inflammation C-reactive protein</td>
<td>&gt;150 μg/dL</td>
</tr>
<tr>
<td>Immunosuppression Total lymphocyte count</td>
<td>&lt;0.80 × 10^9/L</td>
</tr>
<tr>
<td>Catabolism Weight loss</td>
<td>&gt;10% during hospitalization or body mass index &lt;18</td>
</tr>
<tr>
<td>Creatinine height index &lt;80%</td>
<td></td>
</tr>
<tr>
<td>Albumin level</td>
<td>&lt;3.0 g/dL</td>
</tr>
<tr>
<td>Prealbumin level</td>
<td>&lt;10 mg/dL</td>
</tr>
<tr>
<td>Retinol binding protein level</td>
<td>&lt;10 μg/dL</td>
</tr>
</tbody>
</table>

**Research or Laboratory Methodologies**

<table>
<thead>
<tr>
<th>Inflammation</th>
<th>Luminesx for cytokine concentrations: IL-6, IL-10, IL-1ra, and procalcitonin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Leukocyte genome expression patterns, e.g., ARG1, NOS2, IL-1RA, SILR2, MMP8, MMP9, MMP2</td>
<td></td>
</tr>
<tr>
<td>Immunosuppression Paralyzed monocyte</td>
<td>Reduced ex vivo cytokine production</td>
</tr>
<tr>
<td>Reduced HLA-DR expression</td>
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<tr>
<td>Reduced phagocytosis</td>
<td></td>
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<tr>
<td>Anergy or exhausted T cell</td>
<td>Expression of suppressor molecules, e.g., PDL-1, CTLA-4, BTLA, and HVEM</td>
</tr>
<tr>
<td>Reduced T-cell proliferation</td>
<td></td>
</tr>
<tr>
<td>Treg polarization</td>
<td></td>
</tr>
<tr>
<td>Increased Treg numbers and suppressor activity</td>
<td></td>
</tr>
</tbody>
</table>

*Medical care resource consumption associated with PICS has yet to be measured, but is likely to be a large multiple of the costs associated with the short-term treatment of trauma, severe sepsis and septic shock. The incidence of PICS is likely to increase as our population ages and our technology improves. Characterization and management of PICS will require new strategies.*
technologies for direct monitoring and modulation of the patient's individual nutritional status and immune responses. Management of PICS should capitalize on available EBGs and computerized protocol technology to implement guidelines at the bedside. PRCTs in well-characterized patient populations with current evidence-based and optimized care will require multiple collaborating clinical centers of expertise. We suggest that PICS is the new horizon for surgical intensive care.

AUTHORSHIP
F.A.M., L.L.M., and B.A.M. conceived of and designed this work. All authors participated in the composition, drafting, and editing of the manuscript.

DISCLOSURE
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