Sepsis Pathophysiology, Chronic Critical Illness, and Persistent Inflammation-Immunosuppression and Catabolism Syndrome

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Objectives: To provide an appraisal of the evolving paradigms in the pathophysiology of sepsis and propose the evolution of a new phenotype of critically ill patients, its potential underlying mechanism, and its implications for the future of sepsis management and research.

Design: Literature search using PubMed, MEDLINE, EMBASE, and Google Scholar.

Measurements and Main Results: Sepsis remains one of the most debilitating and expensive illnesses, and its prevalence is not declining. What is changing is our definition(s), its clinical course, and how we manage the septic patient. Once thought to be predominantly a syndrome of over exuberant inflammation, sepsis is now recognized as a syndrome of aberrant host protective immunity. Earlier recognition and compliance with treatment bundles has fortunately led to a decline in multiple organ failure and in-hospital mortality. Unfortunately, more and more sepsis patients, especially the aged, are suffering chronic critical illness, rarely fully recover, and often experience an indolent death. Patients with chronic critical illness often exhibit "a persistent inflammation-immunosuppression and catabolism syndrome," and it is proposed here that this state of persisting inflammation, immunosuppression and catabolism contributes to many of these adverse clinical outcomes. The underlying cause of inflammation-immunosuppression and catabolism syndrome is currently unknown, but there is increasing evidence that altered myelopoiesis, reduced effector T-cell function, and expansion of immature myeloid-derived suppressor cells are all contributory.

Conclusions: Although newer therapeutic interventions are targeting the inflammatory, the immunosuppressive, and the protein catabolic responses individually, successful treatment of the septic patient with chronic critical illness and persistent inflammation-immunosuppression and catabolism syndrome may require a more complementary approach. (*Crit Care Med* 2017; 45:253–262)

Key Words: chronic critical illness; immunosuppression; inflammation; myeloid-derived suppressor cells; persistent inflammation-immunosuppression and catabolism syndrome; shock

The initial description of sepsis as a systemic inflammatory host response to a microbial pathogen came in the 1980s after the discovery and subsequent cloning of individual proinflammatory cytokines and their receptors. Landmark studies demonstrated that much of the early proinflammatory response to bacteremic shock could be reproduced by administration of several proinflammatory cytokines (1–4). The early definition of sepsis relied on a newly defined term, the "systemic inflammatory response syndrome" (SIRS), which provided a set of objective measures to quantify physiologic changes corresponding to the host's inflammatory response, regardless of etiology (5). Over the subsequent two decades, at least 150 clinical trials examined the efficacy of impeding individual mediators associated with severe sepsis without success (6).

In 2002, the "Surviving Sepsis Campaign" was established and provided evidence-based guidelines for the recognition and management of severe sepsis and septic shock (7, 8). Active endorsement and dissemination of these evidence-based guidelines have resulted in continuous improvements in both the management and outcomes of these patients. Improved compliance with these guidelines is independently associated with decreased in-hospital mortality (9–12). Levy et al (13) demonstrated that hospital and ICU length of stay decreased

by 4% for every 10% increase in compliance, and more importantly, in-hospital mortality risk decreased by 3–5%. However, poor compliance with these measures persists (9). Although recent studies report a decrease in "severe sepsis" in-hospital mortality from 30% in previous decades to 17% today (14–16), sepsis remains one of the most common indications for inpatient admission and continues to be a leading cause of death in the United States (14). As a result, the Center for Medicare and Medicaid Services (CMS) now requires demonstration of compliance with bundles for the identification and treatment of sepsis via Sepsis CMS Core Measure 1 (17). It is ironic that with the massive increase in our basic understanding of the science of sepsis and the billions of dollars spent to implement these basic science gains, it has been early recognition and the wide-spread integration of best clinical practices that have been primarily responsible for the progressive reduction of in-hospital mortality to sepsis.

NEW DEFINITIONS OF SEPSIS AND NEW APPROACHES TO ITS TREATMENT

In 2016, the third sepsis consensus conference published updated definitions for sepsis and septic shock that reflect our evolving understanding of sepsis pathobiology (**Table 1**) (18). Sepsis is now defined as a "dysregulated host response"

to infection, leading to "life-threatening organ dysfunction." Importantly, the foundation for this definition is no longer inflammation alone but rather a lack of immune homeostasis. Additionally, the urgency to treat (life-threatening) is promoted. Unfortunately, definitions frequently provide limited value clinically; thus, "Sepsis-3" recommends new clinical criteria for the rapid recognition of infected patients likely to suffer poor outcomes (ICU admission, prolonged length of stay, and increased mortality) characteristic of sepsis rather than uncomplicated infections. In its support, Seymour et al (19) demonstrate that a positive quick Sepsis-related Organ Failure Assessment score has an improved predictive validity for in-hospital mortality when compared with the SIRS criteria.

Although we have made important strides in in-hospital and 28-day mortality, long-term mortality remains prohibitively high, with recent studies reporting 2 and 3-year mortality among severe sepsis "survivors" at 45% and 71%, respectively (15, 20). As in-hospital mortality declines, sepsis is becoming a chronic illness with dismal long-term consequences. For example, the nationwide 30-day all cause readmission rate for "septicemia" admissions remains an undesirable 19% (14, 16). Additionally, these "survivors" are discharged to long-term acute care (LTAC) and skilled nursing facilities (SNF) in 35% of cases (14, 16). Furthermore, a sustained decline in physical

TABLE 1. Terminology and Definitions

Term	Definition	
Infection	Interaction between host and pathogen that promulgates a local or systemic host response[a]	
Sepsis	Life-threatening organ dysfunction secondary to a dysregulated host response to infection	
Sepsis onset	Evidence of new organ dysfunction remote from the site of infection	
Organ dysfunction	Acute change in total SOFA score > 2 points remote from the infection site[b]	
Septic shock	Profound metabolic, cellular, and circulatory derangements in a subset of sepsis associated with an increased risk of mortality[c]	
Rapid bedside organ dysfunction score—quick SOFA[d]—at least two of the following	Altered mental status—Glasgow Coma Scale score, ≤ 14 Systolic blood pressure, ≤ 100 mm Hg Respiratory rate > 22 breaths/min	
Persistent inflammation-immunosuppression and catabolism syndrome	Critically ill patient	Admission to the ICU > 14 d
	Persistent inflammation	C-reactive protein > 50 µg/dL Retinol binding protein < 1 mg/dL
	Immunosuppression	Total lymphocyte count < 0.80 × 10⁹/L
	Catabolic state	Serum albumin < 3.0 g/dL Creatinine height index < 80% Weight loss > 10% "or" body mass index < 18 during hospitalization

SOFA = Sepsis-related Organ Failure Assessment.

[a]Conventional definition, not redefined by the Sepsis-3 Task Force.
[b]Associated with > 10% in-hospital mortality.
[c]Associated with > 40% in-hospital mortality.
[d]Quick assessment to prompt further clinical investigation of organ dysfunction.
New consensus criteria for defining sepsis and septic shock (18). Although the Sepsis-related Organ Failure Assessment (SOFA) score provides the most robust predictive validity for outcomes, particularly in the ICU, the quick SOFA provides a rapid bedside assessment with readily available variables that promote further investigation and clinical intervention. Persistent inflammation-immunosuppression and catabolism syndrome (PICS) criteria are also defined here by surrogate markers of inflammation, immunosuppression, and catabolism that are readily available in most clinical settings (28). The use of these variables can aid in the identification of patients at risk of PICS. Reproduced with permission from Singer et al (18).

activity, exercise capacity, and muscle strength is often seen after sepsis (21). These patients are also at an increased risk of cardiovascular events, have long-term neurocognitive decline with an increased risk of developing dementia, and have increased functional limitations (22–24). Others imply that some patients should have disease-specific surveillance, such as septic patients with new-onset atrial fibrillation, as they have an increased long-term risk of heart failure, stroke, and death (25). Ultimately, the quality of life after sepsis is grim for most survivors (20, 26, 27).

PATHOPHYSIOLOGY OF SEPSIS

In the effort to identify the etiology and immunologic basis for sepsis-induced multiple organ failure, a number of paradigms have been established and discarded over the past three decades (28–31). The terms SIRS and "compensatory anti-inflammatory response syndrome" were first employed to describe phenomena that could explain the host's initial response to a variety of infectious and noninfectious conditions (28–31). These terms have generally been discarded as being overly simplistic of a much more complex host response.

Through improvements in early sepsis detection and acute ICU management, most patients now survive their initial septic insult. Many reestablish physiologic homeostasis and exhibit uncomplicated clinical trajectories. However, a significant number do not rapidly recover but are left to endure prolonged, complicated ICU stays, many ending with significant morbidity or mortality (32). The term "chronic critical illness" (CCI) has been used to describe patients (septic or otherwise) with a protracted and complex ICU course lasting for more than 7 days who suffer from recurrent infections, organ dysfunction, malnutrition, weakness, cognitive decline, and prolonged institutionalization; many fail to ever achieve functional independence and have poor long-term survival (33–35).

Unfortunately, without a consensus definition of CCI, benchmarking the natural history has been nearly impossible. Recently, the Research Triangle Institute commissioned by CMS defined CCI as patients remaining in the ICU for 8 or more days suffering from one or more of five eligible conditions (prolonged mechanical ventilation [> 96 continuous hours], tracheostomy, sepsis/severe infections, severe wounds, and multiple organ dysfunction) (36). In 2009, patients admitted to the ICU who developed CCI accounted for over $20 billion dollars in healthcare costs (33, 34). The majority of these patients (> 60%) were admitted with a sepsis diagnosis (34). Although only 20% of patients diagnosed with CCI were discharged home, more than 40% were discharged to SNFs or LTACs and about 30% died in the hospital (34). Over a third of these patients are older (> 65 yr old), and in the long-term, few return home to functional independence (10%) and have a 1-year survival estimated to be less than 50% (37–40). Most recently, Iwashyna et al (41) showed that while accounting for just 5% of ICU admissions, patients with CCI accounted for more than 30% of ICU bed days and more than 14% of hospital bed days, had higher mortality, and were less likely to be discharged home than the usual ICU patient.

Recently, we proposed a new syndrome for individuals who survive the initial sepsis event but become chronically critically ill—the "persistent inflammation-immunosuppression and catabolism syndrome" (PICS) (28). We hypothesize that it is PICS that mechanistically underlies a subset of CCI patients. This new syndrome is not to be confused with "post-ICU syndrome" that describes a series of conditions seen in survivors of ICU hospitalization, regardless of its etiology (42). We have defined PICS as ongoing inflammation, manageable organ failure, ongoing protein catabolism, and poor nutrition, leading to cachexia, poor wound healing, and immunosuppression with increased susceptibility to secondary infections (**Table 2**).

Using this definition, the prototypical PICS patient is one admitted to the ICU following devastating injury/infection and has a significant early inflammatory and immune suppressive response that later translates into ongoing organ injury, persistent inflammation and immune suppression with continued loss of lean muscle mass, and poor wound healing (**Fig. 1**). This in turn leads to poor functional outcomes, poor quality of life, and probable discharge to an LTAC, only to continue to decline and capitulate in an indolent death.

PATHOPHYSIOLOGY OF PICS: IS PICS A MYELODYSPLASTIC DISEASE?

The importance and value of defining PICS is that it proposes an overarching mechanism that can explain both the persistent low-grade inflammation and the adaptive immune suppression. PICS was never intended to explain all of the phenomena associated with CCI, including many of the cardiovascular and neurologic deficits that may also be explained by other mechanisms (43, 44). Rather, its intent was to explain the immunologic dyscrasia that now defines sepsis and pervades CCI.

In early sepsis or trauma, granulocytes in the bone marrow rapidly demarginate and follow chemokine gradients to the site of infection/injury creating niches in the bone marrow for the expansion of hematopoietic stem cells (HSCs). These new HSCs preferentially differentiate down myeloid pathways toward mature granulocytes, macrophages, and dendritic cells (45–47). This process occurs at the expense of both lymphopoiesis and erythropoiesis that are suppressed, contributing to the lymphopenia and anemia characteristic of this population. This rapid demargination and repopulation of the bone marrow with innate immune effector cells by HSCs and immature myeloid cells at a time of acute critical illness has been termed "emergency granulopoiesis/myelopoiesis" (48).

During emergency myelopoiesis, differentiation of immature myeloid cells into mature innate immune effectors is blocked, resulting in the expansion of a heterogeneous population of inducible immature myeloid cells with immunosuppressive and inflammatory properties, termed "myeloid-derived suppressor cells" (MDSCs) (49–52) (**Fig. 2**). In animals with chronic inflammatory states, MDSC infiltration of both secondary lymphoid and reticuloendothelial tissues is frequently observed (53–55). The immunosuppressive activity of MDSCs in these distant tissues and organs has been attributed to a number of mechanisms (49, 56–61). MDSCs

TABLE 2. Myeloid-Derived Suppressors Cells in Sepsis

Patient Cohort	12 hr	Day 1	Day 4	Day 7	Day 14	Day 21	Day 28
Healthy control—mean MDSC, %	11.7 (n = 18)						
Sepsis—mean MDSC, %	44.7[a] (n = 72)	37.8[a] (n = 70)	26.2[a] (n = 66)	25.6[a] (n = 51)	32.9[a] (n = 37)	34.9[a] (n = 24)	35.6[a] (n = 16)
Healthy control—mean granulocytic MDSC, %	26.6 (n = 18)						
Sepsis—mean granulocytic MDSC, %	71.0[a] (n = 72)	68.5[a] (n = 70)	58.6[a] (n = 66)	60.5[a] (n = 51)	66.4[a] (n = 37)	65.5[a] (n = 24)	67.5[a] (n = 16)
Septic patient with ICU length of stay < 14 d—mean MDSC, %	41.6 (n = 27)	34.8 (n = 26)	22.3 (n = 24)	19.3 (n = 16)	19.1 (n = 7)		
Septic patient with early mortality (< 14 d)—mean MDSC, %	63.0[b] (n = 6)	64.3[b] (n = 5)	38.0 (n = 4)	25.8 (n = 1)			

MDSC = myeloid-derived suppressor cells.

[a] $p < 0.05$ when compared with healthy control subjects.

[b] $p < 0.05$ when compared with patients with ICU length of stay < 14 d.

Circulating MDSCs in patients with severe sepsis and septic shock are significantly elevated at all time points in the first 28 d after onset of sepsis when compared with those in healthy controls. In particularly, the primary MDSC phenotype is granulocytic. For the first 24 hr, patients with early mortality (< 14 d) have significantly more MDSCs than do patients with an ICU course < 14 d. Although there is a trend for elevated MDSCs thereafter, these are no longer statistically significant.

can also contribute to the persistent inflammation, through their ability to produce inflammatory mediators, nitric oxide and reactive oxygen species (53, 62).

We and others have now demonstrated that MDSC populations expand dramatically in patients with sepsis and remain elevated for weeks, as long as patients remain critically ill (63, 64). These immature myeloid cells are predominantly granulocytic, have profound suppressive properties, and at the transcriptional level, are proinflammatory and poor antigen presenters (64) (Table 2). Importantly, patients who had the greatest elevation in MDSCs had either early mortality or prolonged hospitalizations; rapid resolution of MDSC numbers was associated with early discharge from the ICU (64).

IS PICS THE CAUSE OF MORBIDITY ASSOCIATED WITH CCI?

It is reasonable to question whether PICS is itself the cause of increased morbidity and long-term mortality in CCI patients or is merely a reflection of the long-term consequences of CCI. Association studies can go only so far in demonstrating causality although components of PICS are directly related to adverse outcomes in the critically ill. For example, frailty and sarcopenia have been associated with discharge to nonhome location, increased in-hospital and long-term mortality, and increased readmission and resource utilization (65–67). Similarly, long-term cognitive impairment and functional impairment after sepsis are associated with increased resource utilization and increased mortality (23). Additionally, viral reactivation in the critically ill has been associated with increased morbidity and mortality (68–70).

In most cases, direct causality can only be shown by intervention studies, and efforts to intervene in MDSC expansion and the development of PICS are limited. Although few of these studies exist in sepsis, expansion of MDSCs and PICS is also associated with metastatic or advanced cancer where direct causality between MDSCs, immunosuppression, inflammation, and poor outcomes has been shown (71, 72). It is well accepted that cancer patients who are cachectic (73), are immunosuppressed (74), and have chronic inflammation (75) have lower life expectancies than those who do not. More specifically, blockade of MDSC expansion in patients with advanced cancer has not only improved T-cell function and immunotherapy in cancer but also improved outcome. For example, gemcitabine, 5-fluorouracil, and axitinib have been shown to decrease MDSCs while increasing antitumor activity of CD8^{+} T cells in tumor-bearing mice (76–78). Additionally, blockade of C-X-C motif chemokine receptor 2-mediated MDSC trafficking has been shown to enhance anti-programmed death 1 signaling efficacy in a murine model (79). In renal cell cancer, patients treated with sunitinib saw a reduction in the proportion of MDSCs and improved the type 1 helper T-cell antigen specific response (80). In addition, all-trans-retinoic acid has been shown to stimulate myeloid cell differentiation, as well as dendritic cell and antigen-specific T-cell function (81). We have shown that blocking MDSC expansion in murine cancer improves survival to sepsis and endotoxicosis (82). Although these findings have been limited to cancer only, similar approaches are now being considered for sepsis. For example, anti–programmed death ligand (PD-L1) is in phase II clinical trials for sepsis as a means to block the adaptive immune suppression seen in this population (NCT02576457).

CLINICAL IMPLICATIONS OF PICS, MDSCS, AND CCI

Based on this proposed model for the development and propagation of CCI and PICS in sepsis survivors, successful treatment options are likely to be multifactorial and complex. Clearly, the ligands responsible for the initial sepsis event are
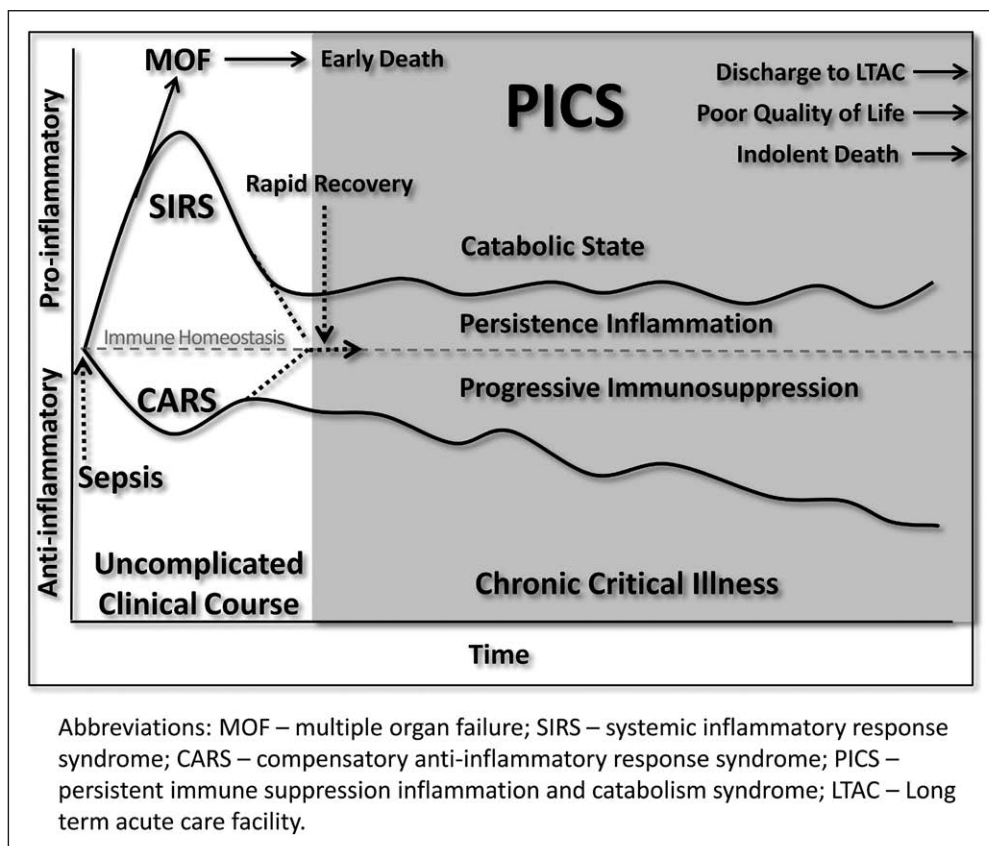
Figure 1. Model of persistent inflammation-immunosuppression and catabolism syndrome (PICS). Early deaths from acute multiple organ failure (MOF) secondary to the acute hyperinflammatory phase of sepsis have declined with implementation of best clinical practice guidelines, primarily early detection, and rapid initiation of supportive care (9–12). Following the simultaneous inflammatory and immunosuppressive responses, patient may return to a homeostatic immune state, leading to a rapid recovery, or develop chronic critical illness and PICS, resulting from protein catabolism, cachexia, and secondary infections. Following a prolonged hospitalization, 35% of patients are sent to skilled nursing and long-term acute care facilities (14, 16). A multitude of these patients fails to ever recover and suffer an indolent death with 3-yr mortality of 71% (20, 28). CARS = compensatory anti-inflammatory response syndrome, LTAC = long-term acute care, SIRS = systemic inflammatory response syndrome. Reproduced with permission from Gentile et al (28).

damaged tissue and organ injury (83, 84). Increased concentrations of many of these endogenous compounds are commonly reported in sepsis survivors and the chronic critically ill (85, 86).

The source of these alarmins is likely the organs and tissues injured during the early sepsis event and have ongoing injurious or inflammatory processes. Most likely, these include the kidney, lungs, and intestines of patients with CCI. Even modest increases in acute kidney injury are associated with significantly worsened outcomes in sepsis and surgical trauma, and the failure of full kidney recovery is another independent predictor of adverse outcome (87, 88). Lung injury associated with mechanical ventilation is well described, but the inflammatory properties of muscle atrophy have not received the appreciation they generally deserve (89). Patients on mechanical ventilation lose dramatic amounts of diaphragmatic tissue mass over the first week (90). Surprisingly, this loss is often associated with a local and systemic inflammatory response, and more importantly, therapeutic efforts to reduce this muscle wasting are often associated with reduced inflammatory responses (91).

likely different than those responsible for the persistent inflammation and immune suppression seen in many patients with CCI, as appropriate source control and antimicrobial coverage are employed. There is surely a subset of these patients in whom obvious sources of ongoing infection can be identified and are likely contributing to the persistent processes. However, there remains a large subset of sepsis survivors residing in the ICU who continue to exhibit PICS without an obvious source of infection.

As shown in **Figure 3**, our proposal is that PICS and CCI can be understood as a vicious self-stimulating cycle in which infection drives aberrant myelopoiesis, inducing the suppression of adaptive and innate immunity while increasing protein wasting, ultimately leading to poor long-term outcomes and/or an indolent death. There has been considerable speculation about what drives this persistent inflammation in the absence of microbial pathogens and their pathogen-associated molecular patterns. The persistent inflammation of hospitalized patients with CCI could be attributed to the increased release of damage-associated molecular patterns or endogenous alarmins from

All of these inflammatory processes lead to continued suppression of adaptive immunity. Anergy, reductions in absolute lymphocyte counts, and reactivation of latent viral infections are all indicative of this suppressed protective immunity. With this suppression of protective immunity and protein malnutrition, changes in the microbiota and increased loss of barrier functions, increased incidence of nosocomial infections, and reactivation of latent viral and bacterial infections all lead to reinfection and frequently readmission to acute care facilities. Once infection has reestablished, inflammation is amplified, myelopoiesis is further affected, and additional wasting of lean tissue and suppression of adaptive immunity occur.

Pharmacologic interventions meant to interrupt the cycle of inflammation, immunosuppression, and protein catabolism leading to reinfection, induced frailty, and indolent outcomes become critically important. Although anti-inflammatory approaches have failed in the setting of the early inflammatory response, they have not been evaluated in the context of persistent low-grade inflammation associated with CCI and
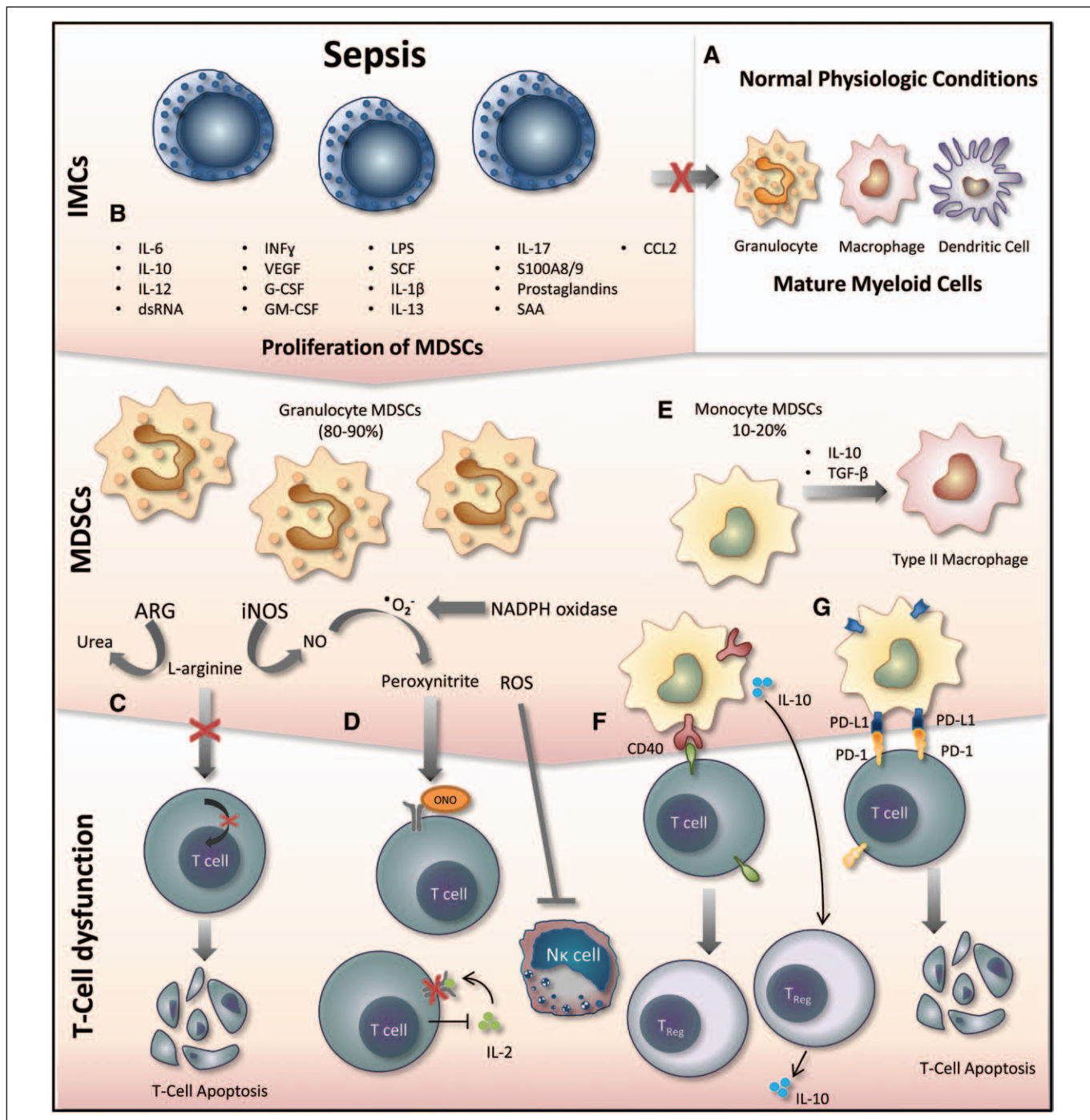
Figure 2. Role of myeloid-derived suppressor cells (MDSCs) in severe sepsis/septic shock patients. **A**, Under normal physiologic conditions, immature myeloid cells (IMCs) differentiate into granulocytes, monocytes/macrophages, and dendritic cells; however, in the septic patient, the inflammatory milieu is altered, and maturation is impaired. **B**, Severe sepsis/septic shock results in a cascade of signaling molecules, including but not limited to interleukin (IL)-6, IL-10, IL-12, double-stranded RNA (dsRNA), interferon (INF)-γ, vascular endothelial growth factor (VEGF), granulocyte-colony stimulating factor (G-CSF), granulocyte macrophage colony-stimulating factor (GM-CSF), lipopolysaccharide (LPS), stem cell factor (SCF), IL-1β, IL-13, IL-17, S100A8/9, prostaglandins, serum amyloid A (SAA), and C-C motif chemokine ligand 2 (CCL2) (49, 50, 101, 102). As a result, IMCs remain as MDSCs at the expense of differentiation into mature myeloid cell populations. Although this causes a decreased number of mature myeloid cells, it more importantly leads to the production of large numbers of MDSCs, which act through several mechanisms to promote inflammation and global suppression of adaptive immune function. **C**, MDSCs deplete L-arginine via *ARG1* and inducible nitric oxide (NO) synthase (iNOS) (56, 57). In the absence of adequate L-arginine, T-cell function is altered, intracellular signaling is impaired, and T cells undergo apoptosis (57). **D**, MDSCs produce increased reactive oxygen species (ROS), which combine with the byproduct of iNOS, NO, to produce peroxynitrites (49). The resulting peroxynitrite nitrosylates several cell surface proteins, including the z-chain of T-cell receptors, resulting in decreased T-cell responsiveness (103). Nitrosylation of cysteine residues results in altered IL-2 signaling (104). Additionally, IL-2 mRNA stability is affected by NO (104). **E**, Monocytic MDSCs cause polarization of macrophages toward a type II phenotype via IL-10 and transforming growth factor (TGF-β) production (53). Additionally, natural killer (NK) cell suppression is mediated by ROS (105). **F**, Direct contact of monocytic MDSCs via CD40 receptors results in induction of T_reg cells (106). Production of IL-10 by MDSCs has been associated with induction of T_reg cells that produce IL-10 (58). **G**, Upregulation of anti–programmed death ligand-1 (PD-L1) and other checkpoint inhibitors in MDSC leads to T-cell apoptosis (100).
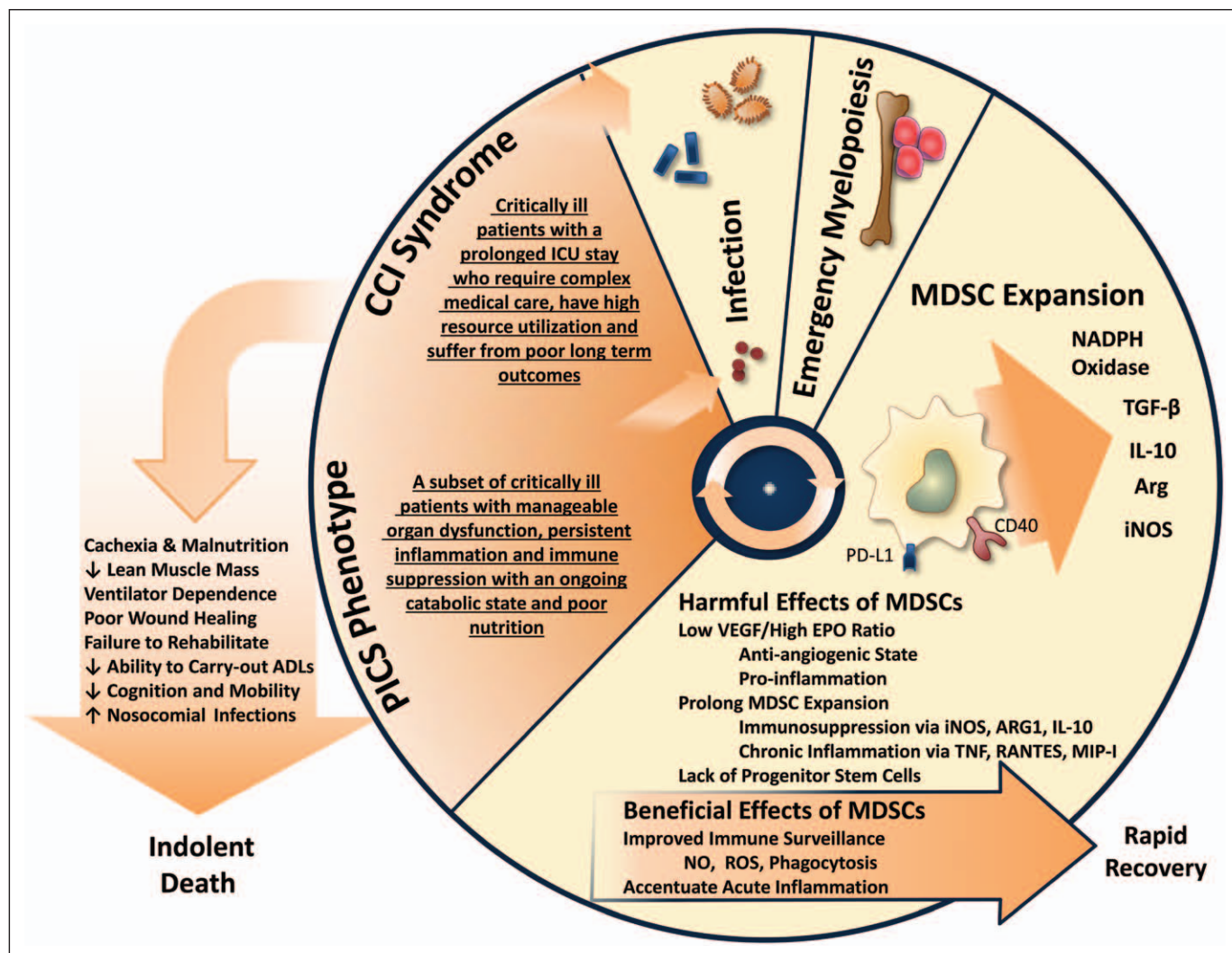
Figure 3. Sepsis, emergency myelopoiesis, myeloid-derived suppressor cell (MDSC) expansion, and the development of chronic critical illness (CCI) and persistent inflammation-immunosuppression and catabolism syndrome (PICS). Sepsis results in a self-stimulating cycle. Initially, sepsis leads to emergency myelopoiesis and MDSC expansion (52). Although MDSC expansion has proven to be of early benefit, prolonged MDSC expansion leads to immunosuppression, chronic inflammation, and features of CCI (61). These patients advance to PICS suffering from manageable organ failure, ongoing protein catabolism, poor nutrition, cachexia, and poor wound healing in addition to persistent inflammation and immune suppression (28). Patients with CCI and PICS have increased susceptibility to secondary or nosocomial infections, which reestablish inflammation, and the cycle repeats. ADL = activities of daily living, Arg = arginine, EPO = erythropoietin, IL = interleukin, iNOS = nitric oxide synthase, MIP-I = macrophage inhibitory protein-1, NO = nitric oxide, RANTES = regulated on activation, normal T cell expressed and secreted, ROS = reactive oxygen species, TGF-β = transforming growth factor-β, TNF = tumor necrosis factor, VEGF = vascular endothelial growth factor.

PICS. Similarly, there is a strong theoretical basis for the use of immune adjuvants in patients with CCI who manifest symptoms of immunosuppression similar to those patients with advanced malignancies (92, 93). Treatment with inhibitors of T-cell apoptosis, lymphopoietic agents, such as interleukin (IL)-7 and IL-15, and blockade of checkpoint inhibition (anti–cytotoxic T-lymphocyte–associated protein or anti–programmed death ligand-1/PD-1) have all improved survival and demonstrated a key role for the adaptive immune system in murine models of sepsis (94–100).

CONCLUSIONS

The last two decades have seen remarkable advances in our understanding of the pathophysiology of sepsis. CCI and long-term outcomes in sepsis have become more important as more patients are surviving sepsis. To better understand the underlying pathologic consequences of CCI in patients surviving sepsis or severe injury, we have described a subpopulation of patients with a PICS phenotype. The PICS definition is primarily a tool to provide the foundation for rational treatment strategies of this chronic critically ill population. Driven by the continuous exposure to endogenous danger–associated and pathogen-associated products resulting from organ injury, opportunistic infections, and/or viral reactivation, these patients are trapped in a vicious cycle of inflammation, immunosuppression, and protein catabolism. Without successful intervention and interruption, these patients are committed to a pathway that has only a single indolent, adverse outcome. A combination of therapies including anti-inflammatory agents, immune adjuvants, and nutritional and physical support is likely to be required for optimal outcomes. CCI and PICS will require a long-term and multipronged commitment for a sustainable recovery.

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